ABOUT THE USE OF ANTIBIOTICS IN A COUNTY HOSPITAL. A ROMANIAN PERSPECTIVE (I)

Cristina Brinzeu¹, Leonard Mada², Andrei Brinzeu², Antoniu Brinzeu²

REZUMAT

Prescripția de antibiotice reprezintă o parte importantă din bugetul farmaceutic al spitalelor, cu impact direct asupra morbidității și mortalității. De aceea, o politică a antibioticelor pentru ca obiectivele de calitate în îngrijirea pacientului, de securitate și sănătate să se regăsească în posibilitățile economice, devine o necesitate pentru un spital județean. Cele mai bune metode pentru a pune în practică acestea doare să încep cu educarea și informarea continuă asupra studiilor, conferințelor de consens și protocolelor din alte centre. Prezentarea noastră cuprinde mai multe capitole începând cu antibioticopatia chirurgicală, motivatie și protocoluri, terapia infecțiilor intraabdominale cu rețrecere în revistă a entităților clinice, clasificarea lor și prezentarea antibioterapiei pe fundalul studiilor recente și creșterii rezistenței bacteriene la antibiotice cu elaborarea unor recomandări în prescripția de antibiotic. Vorn trece în revistă proiecțiile medicale în străinătate într-un capitol separat, datorită riscului crescut de infecte urmat de un diagnostic foarte rezervat; analizăm datele actuale privind profilaxia antibiotică și terapia postoperatorie. Vorn continua demersul nostru cu prezentarea în numărul viitor a infecțiilor pulmonare, urinare și a altor infectii în terapie intensivă (TI).

ABSTRACT

Antibiotherapy has a great impact on morbidity and mortality. At the same time it accounts for a significant proportion of hospital costs. An antibiotic policy becomes necessary to ensure adequate treatment while minimizing the development of bacterial resistance and keeping treatment costs at an affordable level. There are various means to implement and endorse a successful antibiotic policy. Proven methods include the continuous education of the personnel, regular presentations of new study results, consensus conferences, guidelines and treatment protocols. This review, divided into several parts, starts by presenting the anti-infectious prophylaxis in surgery, explaining the reasons and the currently recommended regimens. We shift then the focus to intra-abdominal infections describing the various disease entities and classification schemes needed to better understand the treatment strategies. Antibiotic regimens will be presented in the light of current evidence and increasing resistance trends, followed by recommendations for antibiotic use in the local county hospital. Necrotizing pancreatitis is presented separately because of the high risk of infectious complications, which portend an unfavorable outcome. The evidence supporting anti-infectious prophylaxis and therapy of infected pancreatic necrosis is presented thereafter. The remaining infections, including but not limited to pulmonary and urinary tract infections will be presented in a subsequent article.

1. INTRODUCTION

Antibiotherapy has a great impact on morbidity and mortality accounting for a significant proportion of health-care resources. The emergence of bacterial resistance further complicates this problem, as more expensive therapies are required for the resolution of infectious diseases. Numerous studies have tried to tackle the problem of rising resistance and the impact on treatment costs, cost-effectiveness of various regimens and impact on health-care.

Total costs for anti-infection exceeded in 1997 US$ 17 billion worldwide. In 2003 the costs in the US alone were $10 billion for expenditures on antibiotics in the intensive care units (ICU). The corresponding costs in Canada reached $0.2 billion, while the antibiotic costs in the County Hospital in Timisoara summed up at $1.5 million. Half of this was spent on the surgical wards and 25% went to the ICU.

Twenty percent of the roughly 14,000 surgical patients treated in the County Hospital developed an infection. Furthermore, a considerable amount of antibiotics was used for the prophylaxis of surgical infections in patients.

The costs of antibiotic prophylaxis exceeded $100,000 only taking into account the patients admitted to the ICU. Using the protocols from well-accepted guidelines (Sanford Guide, Société Française d’Anesthésie et de Réanimation), these costs should have stayed below $10,000. We estimate that the total costs for antibiotic prophylaxis using a correct,
internationally-accepted protocol would add up to less than $42,000 per year for the entire County Hospital.

An evaluation of the adequacy of antibiotic treatment in the ICU during the same time frame concluded that only one third of the antibiotics were prescribed on sound medical grounds.

Infections on the ICU are more difficult to treat and are the cause of higher costs, precluding a more detailed analysis of medical practices and treatment strategies in the ICU. A cost-analysis in the ICU is more difficult to perform but is urgently needed to guide a more appropriate distribution of health care resources.

The increased costs of treating patients with infection in the ICU are partly due to the fact that these patients have for the most part severe underlying conditions and are at risk for acquiring nosocomial infections.

Nosocomial infections are defined as those infections, which are acquired during the patient’s hospitalization. This means that these infections were neither present nor in the incubation phase at the patient’s admission.

The risk to acquire a nosocomial infection is higher in the intensive care units (ICU) than in other departments, this being explained by the invasiveness of specific intensive care methods and more frequent use of antibiotics leading to selection of resistant bacterial strains. ICU patients already have a severe condition, which may further compromise their immune system. With the aging population, chronic diseases become more prevalent, adding to the overall worse outcome.

Moreover, these infections tend to be with more resistant pathogens, including multidrug-resistant (MDR) organisms. Consequently it is important to differentiate between nosocomial and community-acquired infections. This differentiation should be reflected in the choice of antibiotic therapy for each specific infection.

Therefore we believe that a tighter antibiotic control is mandatory. A first step to achieve this lays in the proper education of the medical staff. This review intends to fill a gap in the local medical literature in order to provide a basis for better medical education and more accurate treatment of ICU infections.

As a part of multi-series articles this review will cover the use of antibiotics in surgical infection prophylaxis, treatment of intra-abdominal infections and the use of antibiotics in necrotizing pancreatitis. Future articles will cover the treatment of severe community acquired infections and ICU nosocomial infections such as: severe community acquired pneumonia, hospital or ventilator pneumonia, urosepsis, severe CNS infections, fungal infections and idiopathic bacteremia.

2. SURGICAL ANTIBIOPROPHYLAXIS

During the last ten years several studies showed that antibiotics were used in an inadequate way from the point of view of their indications, timing and duration which lead to an increased resistance of the pathogens towards the antibiotics, followed by an increase of the mortality, morbidity and of the costs.\(^1,2\)

The prophylactic administration of the antibiotics for surgery is considered as a part of the antibiotic therapy. The goal of administering antibiotics in surgery is to reduce the surgical site infections rate (SSI).

Antibiotic prophylaxis consists in the administration of antibiotics before the potential bacterial contamination as the antibiotic must be present at the potentially contaminate site before the pathogens are there. The tissue drug levels must exceed the MIC of the chosen drug for the targeted pathogens during the entire surgical procedure.\(^3\)

For these reasons the chosen antibiotic must fulfill the following requirements:

- To be effective on the potentially contaminating pathogens;
- To build up an effective antibiotic concentration in the concerned tissue;
- To be administered before the hazardous maneuver: in 1976 Stone and coworkers demonstrated that the lowest rate of surgical site infection was noticed when the prophylactic antibiotic was given one hour before the surgery. The patients who received the antibiotic during the operation had similar SSI rates as those who did not receive any prophylaxis.\(^3\)
- To stop administration when the contamination risk is gone; there is no proof that continuing the antibiotic administration beyond 24 hours has a benefit.\(^4\)
- The antibiotic has to be administered in a sufficient dose: a normal therapeutic dose for that patient; if the procedure lasts for more than one half time of the drug (or two half lives depending on authors) then a new dose is required. The objective is to maintain the tissue concentration of the antibiotic at an active level.
- The antibiotic should have the least possible side effects.
- The antibiotics used for prophylaxis must not be used for therapeutic purposes.
Antibiotic prophylaxis has to be performed with cheaper drugs.

These requests involve a good knowledge of the surgery and of the potentially contaminating pathogens: identification and their susceptibility to antibiotics. For example in the orthopedic surgery (total hip replacement) there is a higher risk to acquire a staphylococcal infection as well as in vascular surgery and it makes sense to administer a drug which prevents the growth of these bacteria: usually first generation (cefazolin) or second generation cephalosporins are given. When allergy is present a glycopeptide is considered (vancomycin). In the colorectal surgery it is compulsory to cover the spectrum of the anaerobic pathogens and drugs such as metronidazole are useful.

It is also important to have good knowledge about the antibiotics to be used for prophylaxis.

Several studies showed also no benefit on the incidence of infections for postoperative administration of antibiotics.

The first dose is given before the induction of the anesthesia and is repeated if the surgery lasts more than a half life of the antibiotic.

The doses must never be smaller than a standard therapeutic dose and the administration should always be by the intravenous route.

The duration of the antibiotic prophylaxis is usually 24 hours and in special cases (diabetes mellitus, AIDS, neutropenia etc.) it can be prolonged to 48 hours. There is no study to prove the efficacy of the prophylaxis beyond this interval.

For a better management of the antibiotic prophylaxis surgical operations were classified into four classes by Altemeyer in 1955. These classes are:

**Altemeyer Class I**
- Clean surgery;
- No trauma;
- No inflammation;
- No perforation of a visceral cavity or of a contaminated viscus;
- No mistakes in asepsis;
- Level of infection: without antibiotic: 1 to 5%, with antibiotic: <1%.

**Altemeyer Class II**
- Clean but contaminated surgery;
- Opening of a hollow viscus with a minimal contamination (oropharynx, upper gastro-intestinal tract, respiratory tree, urinary tract or genital tract);
- Minimal rupture of the asepsis;
- Level of infections: without antibiotics: 5-15%, with antibiotics: < 7%.

**Altemeyer Class III**
- Contaminated surgery;
- Open trauma of less than 4 hours;
- Surgery on infected urine or gall;
- Important contamination by digestive tract content;
- Major mistakes in asepsis;
- Inflammation without pus;
- Level of infection: without antibiotic: >15%, with antibiotic: < 15%.

**Altemeyer Class IV**
- Open trauma lasting for more than 4 hours;
- Devitalized tissues;
- Bacterial infection with or without pus;
- Fecal contamination or foreign body;
- Ruptured visera;
- Level of infection: without antibiotic: >30%, with antibiotic: less.

The prescription of antibiotics for the surgery is part of the preoperative examination of the patient; the anesthesiologists and the surgeons will decide the antibiotic to be administered depending on the planned surgery, the patient’s case history (infectious and allergic episodes), microbial population in the hospital.

The best solution would be to establish an antibiotic prophylaxis guideline for each hospital. Antibiotic prophylaxis as already stated must be performed before the surgery, before the bacterial contamination and has to be short (24 h) to reduce the risk of increasing bacterial resistance. One single injection before the anesthetic induction proved its effectiveness for most of the surgical interventions.

If the surgery will last for more than 4 h the initial dose must be repeated. At identical effectiveness the least expensive drug will be used.

Most of the elective surgical interventions are done in patients with classes I or II of the Altemeyer classification. The patients which are in the classes III or IV need antibiotic therapy.

Two protocols of antibiotic prophylaxis are presented in the following tables as they were used as guidelines for anesthesiologists in the ICU Timisoara during the past years (almost ten years if the older versions of the protocols are considered). (Table 1)

Target pathogens are: *Enterobacteriaceae* (especially after craniotomy), *Staphylococcus aureus* and *S. epidermidis* (especially after CSF drainage) and anaerobes, mainly after cranio-cerebral wounds.

When the patient is allergic to betalactams vancomycin is recommended 15 mg/kg bodyweight in a single dose.
Table 1. Surgical prophylaxis in neurosurgery

<table>
<thead>
<tr>
<th>Surgical Intervention</th>
<th>SFR 1999/revied 2004</th>
<th>SANFORD 2005</th>
<th>Duration</th>
<th>Costs RON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniootomy</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 2g</td>
<td>Single dose</td>
<td>6</td>
</tr>
<tr>
<td>Shunt surgery</td>
<td>Oxacillin 2g</td>
<td>VA 10mg + GM 3mg, intraventricularly</td>
<td>Single dose</td>
<td>7.6</td>
</tr>
<tr>
<td>Cross sinuses</td>
<td>Cefazolin 2g</td>
<td>Augmentin 1.2g</td>
<td>Single dose</td>
<td>6</td>
</tr>
<tr>
<td>Spinal surgery</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 2g</td>
<td>Single dose</td>
<td>6/7.6</td>
</tr>
<tr>
<td>Craniocerebral wound</td>
<td>Amoxicillin/subactam 1.5g / 6h</td>
<td>No prophylaxis</td>
<td>48h</td>
<td>50.4</td>
</tr>
<tr>
<td>Skull base fracture</td>
<td>No prophylaxis</td>
<td>No prophylaxis</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

VA=vancomycin, GM=gentamicin

Table 2. Surgical prophylaxis in abdominal surgery (gastric, biliary and colonic)

<table>
<thead>
<tr>
<th>Surgical Intervention</th>
<th>SFR 1999/revied 2004</th>
<th>SANFORD 2005</th>
<th>Duration</th>
<th>Costs RON</th>
</tr>
</thead>
<tbody>
<tr>
<td>No opening of the digestive tract</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 2g</td>
<td>Single dose</td>
<td>6</td>
</tr>
<tr>
<td>Biliary surgery including laparoscopic colecystectomy</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 2g</td>
<td>Single dose / rep. at 12-24h</td>
<td>6</td>
</tr>
<tr>
<td>Pancreatic surgery</td>
<td>Cefazolin 2g</td>
<td>Cefazolin2g</td>
<td>Single dose</td>
<td>6</td>
</tr>
<tr>
<td>Hepatic surgery</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 2g</td>
<td>Single dose</td>
<td>6</td>
</tr>
<tr>
<td>Esophageal surgery</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 2g</td>
<td>Single dose</td>
<td>6</td>
</tr>
<tr>
<td>Uncomplicated hernia</td>
<td>No antibiotic prophylaxis</td>
<td>No antibiotic prophylaxis</td>
<td>6/6.2</td>
<td>0</td>
</tr>
<tr>
<td>Hernia or evagination with prosthetic material</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 2g</td>
<td>Single dose</td>
<td>6</td>
</tr>
<tr>
<td>Colorectal surgery including appendectomy</td>
<td>Ampicillin + Sulbactam 1.5 g</td>
<td>Cefazolin 2g + metronidazol 0.5g</td>
<td>Single dose</td>
<td>12.6</td>
</tr>
<tr>
<td>Proctological surgery</td>
<td>Metronidazol 0.5g</td>
<td>No antibiotic prophylaxis</td>
<td>Single dose</td>
<td>3.4</td>
</tr>
<tr>
<td>Abdominal wounds</td>
<td>Ampicillin + subactam 1.5g/6h</td>
<td>No antibiotic prophylaxis</td>
<td>48h</td>
<td>100.0</td>
</tr>
<tr>
<td>When allergy to Beta lactamines</td>
<td>Gentamicin 3mg/Age + metronidazol 1g</td>
<td>No antibiotic prophylaxis</td>
<td>Single dose</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Table 3. Prophylaxis for urologic surgery

<table>
<thead>
<tr>
<th>Surgical Intervention</th>
<th>SFR 1999/revied 2004</th>
<th>SANFORD 2005</th>
<th>Duration</th>
<th>Costs RON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic resection of the prostate and urinary bladder tumors</td>
<td>Cefuroxime 1.5 g</td>
<td>No antibiotic prophylaxis</td>
<td>Single dose</td>
<td>6.2</td>
</tr>
<tr>
<td>Nephrectomy or radical prostatectomy</td>
<td>No antibiotic prophylaxis</td>
<td>No antibiotic prophylaxis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transrectal prostatic biopsy</td>
<td>Ciprofloxacin 0.5g</td>
<td>Ciprofloxacin 0.5g</td>
<td>2 doses with 12h before and after the surgery</td>
<td>1</td>
</tr>
<tr>
<td>Nephrolithiasis and ureteral lithiasis: endoscopy</td>
<td>Cefuroxime 1.5 g</td>
<td>No antibiotic prophylaxis</td>
<td>Single dose</td>
<td>6.2</td>
</tr>
<tr>
<td>Lithotripsy - ESWL</td>
<td>No antibiotic prophylaxis</td>
<td>No antibiotic prophylaxis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgery of the scrotum and urinary incontinence</td>
<td>No antibiotic prophylaxis</td>
<td>No antibiotic prophylaxis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ureterotomy, cystoscopy</td>
<td>Prophylaxis for endocarditis</td>
<td>Prophylaxis for endocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cystectomy</td>
<td>Cefazolin 2g + metronidazol 0.5g</td>
<td>Cefazolin 2g + metronidazol 0.5g</td>
<td>Single dose; if &gt; 3 hours repeat dose</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Cefazolin has a central role in the antibiotic prophylaxis for the elective digestive surgery including biliary, hepatic and pancreatic surgery.\(^{16,17}\) The colorectal surgery has an about 40% risk of developing surgical site infection if antibiotic prophylaxis is not applied at all.\(^8\)
A review of Baum and coworkers compared the wound infection and mortality in patients who received antimicrobial prophylaxis for colorectal surgery and those who did not, using the results of 26 randomized controlled trials (RCTs) and it was found that the wound infection was higher in the non-antibiotic control group (36% versus 22%).18,19

The mortality was higher in the non-antibiotic group (11.2% versus 4.5%, p < 0.01) in the same study. In these patients it is necessary to cover always the anaerobic pathogens.

For the allergic patients the drug combination of gentamicin and metronidazole is useful.8,14,20 (Table 3)

The target pathogens are: enterobacteriaceae (E. Coli, Klebsiella, Proteus mirabilis), Enterococcus, Staphylococcus epidermidis.21,22

A study from 1999 suggests oral ciprofloxacin as a suitable drug for prophylaxis in transurethral resection of prostate.23,24 A lower rate of bacteriuria was noted after 500 mg ciprofloxacin compared to placebo although not reaching statistical significance.

In vascular surgery which corresponds to class Altemeyer I (except amputations for gangrene), prophylaxis is oriented mainly against staphylococci.21,22 Cephalosporins are useful in this case for the prophylaxis, but cefazolin and cefamandole may be also used.23,26

The thoracic but non cardiac surgery belongs either to Altemeier I or II classes, when the trachea or the bronchi are opened.7

The effectiveness of the cefuroxime prophylaxis did not decrease in a study comparing 403 patients (203 in 1987 and 200 in 1990) for vascular surgery. Although the use of this antibiotic increased six fold in the same hospital – the frequency of the infectious complications remained the same (3%). (Table 4)

A more interesting way of prevention may be the use of mupirocin soaked grafts which was evaluated in adult male rats against methicillin susceptible Staphylococcus epidermidis, methicillin resistant Staphylococcus aureus and VIRS and is recommended by some international guidelines.27 (Table 5)

Table 5. Prophylaxis for obstetrics and gynecological surgery

<table>
<thead>
<tr>
<th>Surgical Intervention</th>
<th>SPAR 1999/revised 200421,22</th>
<th>SANFORD 200527</th>
<th>Duration</th>
<th>Costs RON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 1g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>Cefazolin 2g</td>
<td>Cefazolin 1g</td>
<td>Single dose</td>
<td>6/3</td>
</tr>
</tbody>
</table>

The target pathogens are: anaerobes, streptococcus, E.Coli, S. aureus.22

The correct use of the antibiotics for the surgical prophylaxis reduces the incidence of surgical infections and has profound implications including the economic issues.2

Table 4. Prophylaxis for thoracic and vascular surgery

<table>
<thead>
<tr>
<th>Surgical Intervention</th>
<th>SPAR 1999/revised 200421,22</th>
<th>SANFORD 200527</th>
<th>Duration</th>
<th>Costs RON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic surgery</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Single dose</td>
<td>6/6,2</td>
</tr>
<tr>
<td>Procedures on the leg that involve groin incision</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Single dose</td>
<td>6/6,2</td>
</tr>
<tr>
<td>Any vascular procedure that inserts a foreign body</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Single dose</td>
<td>6/6,2</td>
</tr>
<tr>
<td>Carotidian surgery</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Cefazolin 2g or cefuroxim 1,5g</td>
<td>Single dose</td>
<td>6/6,2</td>
</tr>
<tr>
<td>Venous surgery</td>
<td>No antibiotic prophylaxis</td>
<td>No antibiotic prophylaxis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lower limb amputation for ischemia</td>
<td>As for aortic surgery</td>
<td>As for aortic surgery</td>
<td>48h /48h</td>
<td>100</td>
</tr>
<tr>
<td>Mediastinal surgery</td>
<td>As for aortic surgery</td>
<td>As for aortic surgery</td>
<td>Single dose</td>
<td>6/6,2</td>
</tr>
<tr>
<td>Thoracic wound</td>
<td>Cefazolin 2g or cefuroxim 1,5g/12h</td>
<td>Cefazolin 2g or cefuroxim 1,5g/12h</td>
<td>48h</td>
<td>24/24,8</td>
</tr>
<tr>
<td>Thoracic Drainage</td>
<td>No Antibiotic prophylaxis</td>
<td>No Antibiotic prophylaxis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
3. INTRA-ABDOMINAL AND RETROPERITONEAL INFECTIONS

Complicated intra-abdominal infections
There are a number of different classifications of intra-abdominal infections; however we will follow only those which are crucial for a better understanding of the different treatment strategies.

From a practical point of view, intra-abdominal infections can be classified according to the site of infection into:
- infections that extend beyond the hollow viscus of origin into the peritoneal space (complicated intra-abdominal infections), and
- infections of various intra-abdominal structures without affecting the peritoneal space.

This classification is important, as most complicated intra-abdominal infections do require some sort of surgery or percutaneous intervention for the definite treatment.

Infections not involving the peritoneal space can usually be controlled by systemic antibiotic treatment or sometimes by local measures (e.g. percutaneous abscess drainage), without the need for a more invasive procedure (e.g. laparotomy/ laparoscopy).

The intra-peritoneal infections can become localized and walled off, if the immune system had time and was able to mount an effective immune response and confine the infectious process.

On the other hand, if no such effective response could be mounted, the infection spreads through the peritoneal space becoming a generalized infection, shortly diffuse peritonitis, implying a worse outcome if appropriate therapy is not instituted.

It follows a detailed account only on those infections affecting the peritoneal space. Other intra-abdominal infectious processes will be mentioned briefly only when indicated.

Classification
An etiopathogenic classification which has gained wide support distinguishes between primary, secondary and tertiary peritonitis. As there are significant differences in treatment options and outcome between these entities, we will briefly describe them, after which a more thorough discussion of the treatment options will follow with special emphasis on the antibiotic treatment.

Primary peritonitis implies no obvious underlying infectious source for the peritonitis, as it happens in secondary peritonitis.

In secondary peritonitis there is a direct seeding of micro-organisms (mainly enteric bacteria) into the peritoneal cavity from a septic intra-abdominal or extra-abdominal site. The seeding may follow a mucosal mechanical breach or a functional breach as in the bacterial translocation after non-specific gut injury.

Tertiary peritonitis is a clinical syndrome characterized by an intra-abdominal infection that persists or recurs beyond 48 hours after apparently adequate treatment of primary or secondary peritonitis in the context of a critical illness.

This classification is important not only because it differentiates between patients with different epidemiological backgrounds and underlying etiologies, but also because of different comorbidities, risk factors, management strategies and outcome.

Primary peritonitis
Primary peritonitis most commonly occurs in children and is due to \textit{S. pneumoniae} or \textit{\beta}-haemolytic streptococci. In adults it is frequently associated with ascites in cirrhotic patients and less often with the nephrotic syndrome. In this population the infection is predominantly due to enterobacteriaceae like \textit{E. coli} and \textit{Klebsiella}.

The microbiologic flora recovered from children with primary peritonitis has a similar resistance profile to that in the community, being comprised mostly of susceptible organisms. On the other hand, primary peritonitis in the adult population can be caused by more resistant organisms and can progress more easily to tertiary peritonitis (see tertiary peritonitis).

Another form of primary peritonitis frequently encountered in the past, but exceedingly rare nowadays in the western world, where it is mainly seen in immigrants from Africa and Asia, is tuberculous peritonitis. We won't detail this entity any further, however it must be mentioned, just as a note of caution, that suprainfections with other enteric bacteria or fungi as well as the development of intra-abdominal abscesses frequently complicates this disease, highlighting the severe prognosis and substantial morbidity associated with this serious entity.

Secondary peritonitis
Secondary peritonitis is usually due to a local injury (mechanical or functional) of the gut wall allowing infected content to spill into the peritoneal space. Frequent causes include perforations (e.g. perforated gastric or duodenal ulcers; other perforated abdominal hollow viscus), and gangrene of an intra-abdominal organ, most often of the gastrointestinal tract (appendicitis, cholecystitis, gut necrosis due to volvulus, hernia or ischemia), but in women the genitourinary tract can be involved, too.
Of paramount importance is the level of the lesion. An injury up to the proximal ileum will frequently yield an infection with facultative and aerobic gram-negative organisms (mostly enterobacteriaceae) but rarely with anaerobic bacteria. On the other hand, a lesion beyond the proximal ileum will result in a mixed infection, including both aerobic and facultative bacteria and also anaerobic microorganisms. Any antibiotic treatment must include an anaerobic component if a distal infection is suspected. It must be noted, that the cephalosporins, fluoroquinolones and aminoglycosides have no activity against anaerobes.

An exception to the previous rule occurs in acute pancreatitis, which if it becomes infected, follows usually the pattern of a distal lesion with a mixed aerobic-anaerobic flora. The antibiotic treatment/prophylaxis in acute pancreatitis will be discussed later in greater detail.

Another peculiarity is the isolation of Gram positive bacteria (streptococci, enterococci, rarely staphylococci) in infections originating from the proximal alimentary tract (esophageal, gastric, duodenal or biliary system origin). The usual antibiotic drugs can be deployed safely as for other proximal digestive tract infections; however the physician must bear in mind, especially in nosocomial infections, that resistant Gram positive organisms may occur (see later).

Current studies do not demonstrate any benefit in community-acquired infections for regimens that routinely cover enterococci. Consequently, the deployed antibiotic regimen should be as for any other digestive tract infection. Whenever there is clinical worsening, the physician must also take into consideration those bacteria (see tertiary peritonitis).

Another useful division of secondary peritonitis is into community-acquired and healthcare–associated intra-abdominal infections. This has practical consequences for the treatment, as the former will respond much more reliable to current antibiotic strategies, while in the latter a knowledge of local resistance rates is needed for an optimal empirical treatment and even with such an optimised treatment, treatment failure is much more common. This distinction is the single most important factor in selecting the correct treatment strategy.

Because of different etiologies seen in older populations, a more detailed characterization of secondary peritonitis should also take into account the age of the patient.

In younger patients (≤65 years), appendicitis causes most of the intra-abdominal infections (61%) followed by intra-abdominal abscesses (14%), while any of cholecystitis and cholangitis, diverticulitis, and other colonic pathology constitute less than 10% of cases.

The spectrum of diseases is different in older patients (>65 years) and includes appendicitis (28%), diverticulitis (28%), cholecystitis (12%), cholangitis (12%), abscesses (9%) and other causes (11%, mostly colonic pathology).

As distal pathology is rare in younger patients (excluding appendicitis), a narrow spectrum antibiotic regimen can usually be employed. Most cases of appendicitis are not perforated and a prophylactic regimen for less than 24 hours is usually indicated.

In older patients, however, a more aggressive management is indicated, considering the overall worse prognosis and greater morbidity in this age group. The comorbidities in this latter group favor various complications (COPD → VAP, aged skin and atherosclerosis → impaired wound healing; relative immune incompetence → greater propensity for infections).

Old people also tend to present late in the course of their illness, e.g. appendicitis is often perforated in this age group due to delays in the diagnosis, necessitating treatment as for generalized peritonitis. The morbidity for appendicitis rises to 40% with increasing age and the mortality is up to 14%, much higher than that in younger people.

**Tertiary peritonitis**

Like previously stated, tertiary peritonitis is characterized by a recurrence or a persistence of the intra-abdominal infection beyond 48 h despite apparently adequate treatment. Clinically it is characterised by poorly defined fluid collections and because of the poor peritoneal response, there is only a reduced tendency for abscess formation.

Tertiary peritonitis occurs most commonly after post-operative peritonitis, pancreatitis and necrotic bowel. A proximal source of infection (up to and including the small bowel) is found in almost two third of cases, while appendicitis is only an exceptional cause. The underlying diseases portend already an unfavorable prognosis, partly explaining the high mortality seen with tertiary peritonitis (up to 64% in ICU patients and twofold higher compared with secondary peritonitis)

The bacterial flora consists mainly of organisms with low intrinsic virulence. Enterococci predominate, followed by Candida and less often by coagulase-negative staphylococci (CoNS), Enterobacter or Pseudomonas species. This has important repercussions on the selection of the optimal empiric antibiotic treatment,
as none of the cephalosporins shows any significant activity against the enterococci, while nosocomial isolates of CoNS, Enterobacter and Pseudomonas often show or develop multiple drug resistances (MDR) under a given antibiotic therapy. Such MDR-organisms will be briefly discussed later.

Of course, any of the antibiotics is ineffective against Candida or other fungi, which strengthens the need for intra-operative cultures and should sensitize the treating physician to the possibility of a fungal co-infection if symptoms persist despite broad antibiotic coverage.

If fungal infection is suspected, the antifungal treatment can be deferred in most instances until fungal isolation and identification. In severe cases, the empirical addition of fluconazole may be warranted, however there is currently no data to support the routine use of a preemptive therapy or of an antifungal prophylaxis.

If Candida albicans is detected, fluconazole is a viable treatment option. Fluconazole-resistant C. albicans is rare in patients not previously treated with fluconazole. In rare instances, other treatment strategies may be needed (e.g. amphotericin B – not available in Romania, caspofungin or voriconazol). In such cases, the expertise of an experienced infectious disease specialist should be sought.

**When to treat?**

In critically-ill patients, rapid resuscitation is essential and should precede any other therapeutic interventions. After successful resuscitation, the need for antibiotic therapy and for emergency surgery should be assessed.

It cannot be overemphasized the importance of surgery in complicated intra-abdominal infections. A surgical intervention is required almost always for effective cure of the infection. If an adequate surgical control of the infectious source can not be achieved, the mortality rate doubles even with a correct surgical intervention. Without an appropriate surgical intervention, the mortality rate rises still further approaching 90% in patients with postoperative peritonitis.

An antimicrobial therapy should begin as soon as an intra-abdominal infection is suspected. Cultures, if taken, are usually positive only after one or two days and the susceptibility testing and species determination will take another 24 to 48 h. When the results of the culture are available, the empiric therapy should be adapted based on the results of the culture.

An effective antibiotic therapy should begin prior to any surgical intervention (see also section on prophylaxis).

An intra-abdominal infection is suspected on clinical grounds, on the history of the disease and on the findings at the time of operative or percutaneous intervention. For any other intervention in the absence of signs of infection, the antibacterial regimen should be as that recommended for prophylaxis.

Secondary peritonitis is the leading cause of complicated intra-abdominal infections. At the same time, most tertiary peritonitis follow an episode of secondary peritonitis. To better understand the need for an antibiotic treatment, the various diseases that cause secondary peritonitis will be shortly described with particular emphasis on the risk for generalized infection. The antibacterial therapy is instituted depending on this risk for the various disease entities.

Appendicitis, in the absence of perforation or peritonitis, requires only prophylactic antibiotics covering facultative and obligate anaerobes (see prophylaxis). As previously stated, appendicitis in the elderly is often perforated and thus needs a full antibiotic treatment.

Trauma to the bowel (penetrating, blunt or iatrogenic) – if it is repaired within 12 h – should be treated as for prophylaxis with antibiotics for less than 24 h. The same applies to acute perforations of the stomach, duodenum and proximal jejunum. In the absence of antacid therapy or malignancy or signs of infectious peritonitis (chemical peritonitis may occur) a prophylactic regimen is sufficient.

Bowel perforations beyond 12 h and gastroduodenal perforations greater than 24 h old should be treated with therapeutic antimicrobials. Bowel necrosis without signs of perforation can be managed with a prophylactic regimen. If perforation or infected peritoneal fluid is present, an aggressive strategy must be pursued.

Acute cholecystitis is mostly of non-infectious origin. However, if an infection is suspected, a simple prophylactic regimen can be employed in the absence of a perforation. In more severe disease (e.g. in elderly patients) and with perforation, a full antibiotic therapy should be instituted.

Intraoperative contamination of the operative field with enteric content should be treated for less than 24 h as for prophylaxis.

Any established intra-abdominal infection needs full antibiotic therapy.

**Duration of the antibiotic treatment**

The antibiotic therapy can be discontinued as soon as 5-7 days after institution if the patient shows no signs of infection in the previous 48 hours, i.e. there is
a normalization of temperature and WBC count and return of the gastrointestinal function.37

Persistence of signs of infection beyond 5-7 days should prompt the physician to undertake further investigations.

Risk stratification
Simple risk factors for a worse outcome, applicable at the bedside, are advanced age and the presence of a healthcare associated infection (see discussion on secondary peritonitis).

While there have been various descriptions of risk indexes, most are of limited scope and won’t be discussed any further. One useful predictor of outcome in ICU-patients is the APACHE II score. A score greater than 15-20 is usually associated with a much worse prognosis and warrants a more aggressive approach.34

Community-acquired secondary peritonitis usually presents with an APACHE II score of 8 or less, while in severe cases, especially in ICU patients and tertiary care centers, the score rises to 11-12. Patients who progress to tertiary peritonitis have an even higher score, with a mean of around 14-15.34 Age, the APACHE II score, various chronic diseases (such as cerebrovascular disease, malignancy and liver disease) were also independent risk factors for death.34,39

Another classification employed in recent guidelines (see below) distinguishes between low-to-moderate severity infections and high severity infections. The latter group extends beyond the group of patients described in the previous paragraph to those with immunosuppression, other chronic diseases and poor nutritional status. The inability to obtain adequate control of the source of infection portends a poor prognosis, too.36

Other risk indexes are useful to predict the surgical site infection (SSI) rate. A simple prediction can be achieved using the National Research Council’s wound classification scheme which defines clean, clean-contaminated, contaminated and dirty wounds. The SSI rate increases 3.5 times in the last category. A better risk stratification can be obtained using the National Nosocomial Infections Surveillance (NNIS) risk index. In addition to the risk of endogenous wound contamination, this takes into account the operation time (as a measure of operation complexity) and the ASA score (American Association of Anaesthesiology score as a measure of the patients general health).

There are 4 risk levels, with patients on the highest risk level having a 9-times higher risk to develop an SSI.39 The NNIS risk is different for the various operative procedures and also for the use of laparoscopy vs laparotomy.40 Surgical site infections will be covered in full detail in a separate article.

Antibiotic regimens
For a comprehensive review of treatment options the interested reader is referred to the joint Infectious Diseases Society of America (IDSA), American Society of Microbiology (ASM) and Surgical Infection Society (SIS) guidelines for the selection of anti-infective agents for complicated intra-abdominal infections freely available on the net.37

Our review will focus on recent developments as well as on therapeutic challenges following the dramatic increase in resistance rates in some areas of the world (e.g., Eastern Europe).

The primary scope of the ensuing discussion is to improve the management of intra-abdominal infections in ICU-patients, which obviously are more severely ill and do have more often health-care associated infections (post-operative and tertiary peritonitis), but some of the described resistance mechanisms may well be present in the community so that the scope of this review is much wider. In all these circumstances, wise clinical decisions are needed, too.

The latest IDSA guideline from 2003 suggests the use of narrower spectrum antibiotic treatment for community-acquired peritonitis of mild-to-moderate severity. Recommended regimens include ampicillin/subbactam, cefazolin or cefuroxime plus metronidazole, ticarcillin/clavulanate, ertapenem, and quinolones plus metronidazole.

High risk patients, including patients with severe disease might benefit from regimens with a broader spectrum like imipenem/cilastatin, meropenem, third- or fourth-generation cephalosporins (cefotaxime, ceftriaxone, cefixime, ceftazidime, and cefepime) plus metronidazole, ciprofloxacin plus metronidazole, and piperacillin/tazobactam.

Local Resistance Patterns
While there are no studies to favor one treatment over the other, there are still some important microbiologic factors that deserve emphasis. International studies show a rise in the resistance rates across the globe, and particularly pronounced in certain regions like Eastern Europe. The latest SMART study covering the year 2003 shows a rate of ESBL production ranging between 10%-13% in E. coli and between 14%-20% in Klebsiella in high prevalence regions (Latin America, the Middle East; no data for Eastern Europe).41 Similar high rates were seen in the SENTRY study over the last few years (22.6% of K. pneumoniae in Europe and 45% in Latin America expressed an ESBL-phenotype; 84% of isolates were confirmed as ESBL-producers.
Resistance rates are still low in international studies and in the MYSTIC study (58% of *K. pneumoniae* had an ESBL-phenotype in Eastern Europe).42,43

Whereas ample evidence points to a crucial role of early adequate antibiotic treatment for a favorable outcome in a number of infections (e.g. bacteremia, VAP), the situation is less clear in intra-abdominal infections. There is conflicting evidence with regard to the influence of a correct empiric therapy and the delay of such a therapy on outcome. Until firm data is available, it is nevertheless prudent to optimize the treatment to the local resistance patterns.

Given the high local resistance rate of enterobacteriaceae to ampicillin/sublactam, ticarcollin/clavulanate (TCC >74%) and fluoroquinolones (FQ >60%) such regimens can not be recommended for routine use in our hospital (T. Singh, personal communication). There is also a great concern about high rates of ESBL in the local community (although no screening data are available, international trends underscore this), making any cephalosporin-based treatment unreliable. Taking all these considerations into account, the only active treatment is expected to be with a carbapenem (e.g., ertapenem for low risk infections, respectively imipenem or meropenem for high risk patients).

**International studies - specific problems**

Most of the clinical studies performed included only patients with less severe disease (e.g. high proportion of appendicitis) or less severe APACHE II score (or often did not include a disease severity stratification).44 Such studies are poorly applicable to ICU patients or patients with healthcare-associated peritonitis.

Further, most of these studies were done in regions of low bacterial resistance. Indeed, some of the studies were done in regions of extreme low resistance rate, like some of the cost-effectiveness studies performed in Switzerland (where 82% of Enterobacteriaceae are still susceptible to ampicillin/sublactam and resistance rates to ciprofloxacin are below 2%).45

Many of the studies comparing carbapenems to alternative regimens were done in the 90's, when ESBL-expressing bacteria were rare overall. Some studies demonstrated a cost-benefit ratio favorable for imipenem even in those circumstances, despite higher costs of the drug (but favorable total hospital-days charges46 and exclusion of severe disease.47

**Carbapenems**

Imipenem and meropenem are well-established treatment options in intra-abdominal infections.46,47 Resistance rates are still low in international studies (with the notable exception of non-fermenters, but see also below). The fact that the carbapenems show excellent activity on ESBL-producing strains greatly favors their empirical use in intra-abdominal infections.

The usual dosage is 2 g of imipenem per day divided into 4 doses, respectively 3 g of meropenem daily divided into 3 doses. However, good results were reported with lower dosages, e.g. 1.5 g of imipenem daily divided into 3 doses.48 One advantage of imipenem over meropenem is its greater activity on Gram-positive cocci, especially on Enterococci, favoring its use in tertiary peritonitis.

Despite the clinical equivalence of imipenem and meropenem-based treatments, a cost-efficiency analysis in Romania clearly favors an imipenem-based regimen. The daily treatment costs using the maximally allowed prices for antibiotics in Romania (valid from 16th of September 2005) are as follows: imipenem 2 g, 68.7 €/day; 1.5 g, 51.5 €/day; meropenem 3 g, 100 €/day, 2 g, 66.9 €/day; PIP/TAZ 3x4.5 g, 67.7 €/day, TCC 4x3.2 g, 56.2 €/day and ertapenem 1g, 42.4 €/day.49 Actual prices are lower for imipenem and ertapenem in our county hospital, while the upper price limit for the other drugs was higher prior to September 15, 2005. Currency conversion was calculated using 3.44 RON = 1 Euro.

**Ertapenem**

Ertapenem, a carbapenem with a longer half-life, has excellent activity against the Enterobacteriaceae (including ESBL and AmpC-producers) and various other organisms, including anaerobes and many Gram-positive cocci.50 It is however less active against non-fermenters with 33% of *P. aeruginosa* and 30% of *Acinetobacter* isolates being resistant.51 Most enterococci are also resistant.

This resistance pattern precludes its use in infections where Pseudomonas or enterococci are suspected (e.g., nosocomial infections, tertiary peritonitis, especially if life-threatening). Its primary use should include community-acquired infections and other mild-to-moderate infections.

Ertapenem compared favorable against a number of cephalosporins (cefepim and ceftriaxone) and piperacillin/tazobactam when tested on Enterobacteriaceae expressing various ß-lactamases (ESBLs and AmpC-types), being rapidly bactericidal.52 It showed also excellent activity on various anaerobes (97.2% susceptible).53,54

Clinical studies also showed the equivalency of ertapenem and piperacillin/tazobactam, cure-rates ranging from 77.3% in colonic pathology to 90% in
small intestine pathology. Particularly promising is the low propensity of ertapenem to induce resistance development. Considering its excellent clinical profile in view of local resistance concerns, its ease of administration and the price-advantage over comparable drugs, ertapenem should be the first choice in mild-to-moderate disease.

**Resistance due to Extended Spectrum β-Lactamase (ESBL)-production**

Despite favorable comparisons of cephalosporin-based therapies against imipenem-based treatment strategies in a number of studies (for a recent study with cefepim see Ref. 57), one should be aware that a dramatic inoculum effect occurs with all cephalosporins in ESBL-producers. Even if a substantial number of ESBL-producers show an acceptable in vitro susceptibility to various cephalosporins at a standard inoculum size of $10^5$ bacteria, e.g. 79%-89% of isolates tested susceptible to cefepim, a dramatic inoculum effect occurs.

At an inoculum size of $10^7$ bacteria, the susceptibility to cefepim drops to 0% for ESBL-producing *Klebsiella* and to 5% for ESBL-producing *E. coli* strains. Similar results were seen for any of a battery of other extended-spectrum cephalosporins (excluding the cephemycin cefotetan, which retained 90%-100% activity). Of any of the penicillins and cephalosporins tested, piperacillin/tazobactam retained the highest activity, but even this compound showed a marked decrease in susceptibility rates which were down to 58% for *E. coli* and 22% for *K. pneumoniae*. As expected, the carbapenems retained their full activity against those ESBL-producing strains.

Dramatic inoculum effects were seen in other Enterobacteriaceae as well (e.g., in *Enterobacter* and *Citrobacter*). One must note that the bacterial burden is usually high in peritonitis or within an abscess, so that one can expect a marked in vivo loss of activity with any agent that shows a significant in vitro inoculum effect.

Clinical data also support this concept, indicating a high failure rate and increased mortality (80% vs. 30%) in various infections with ESBL-producing strains. The highest activity in the aforementioned study was observed with the carbapenems. Other studies show an increased morbidity and mortality in infections with resistant Gram-negative bacilli, too. The mortality doubles with inappropriate therapy or resistant *E. coli* and *Klebsiella spp.*, albeit it was not different from a matched population.

As a consequence, penicillins and cephalosporins must not be considered as a viable alternative in areas of high local ESBL prevalence and should be best avoided altogether. Cephamycins, while still active against many ESBL-strains, show no activity against Pseudomonas or against anaerobes, leaving the carbapenems as the first choice in the antibiotic treatment of intra-abdominal infections (especially when Pseudomonas is a concern like in tertiary peritonitis).

A multicenter observational study showed the superiority of early carbapenem treatment in ESBL-producing *Klebsiella* bacteremia. Instituting effective treatment within 5 days reduced the mortality from 63% to 14% in the carbapenem group. In comparison with other active regimens based on different antibiotics (e.g., fluoroquinolones), the greatest reduction was seen with carbapenems. Similar principles should apply to intra-abdominal infections with ESBL-producing strains, although this concept has been challenged in a recent study. While infection with resistant Gram-negative rods independently predicted mortality, this was more likely due to the selection of certain bacteria than to the resistance per se.

**Fluoroquinolones**

Another area of concern is the high prevalence of additional resistance in ESBL-producers (e.g. ciprofloxacin susceptibility less than 54% and down to 31% in *E. coli*). This rate of resistance is definitely higher than previously reported rates for the 1996-1997 period. Even more disturbing is the possibility of treatment failures in infections with ciprofloxacin-susceptible isolates. An adverse outcome is well documented in invasive infections with Salmonella, another member of the family Enterobacteriaceae. Nalidixic acid-resistant Salmonellae, although in vitro still ciprofloxacin-susceptible, pose particular problems due to the high clinical treatment failure rate observed with current treatment regimens.

As nalidixic acid-resistant Salmonellae have reduced susceptibility to other fluoroquinolones as well (MICs usually in the range 0,12-0,5 µg/dl), the 24h-AUC/MIC for these strains decreases to 40-50, explaining the observed treatment failure. The successful clearance of Gram negative bacteria requires usually a value greater than 125. Because of the unfavorable outcome, new resistance breakpoints might be reasonable in this setting. As with the Salmonellae, this may well apply to infections with other Enterobacteriaceae. A recent survey identified 40% of fluoroquinolone-susceptible *E. coli* as harboring a first-stage mutation for fluoroquinolone-resistance. Such mutations may create a population of organisms that will rapidly develop high-level resistance once a second mutation is
acquired. Robust studies to analyze the impact of this resistance mechanism in intra-abdominal infections are nevertheless lacking.

Various risk factors for bacteremia with ciprofloxacin-resistant K. pneumoniae were identified in a recent study, including an indwelling urinary catheter, receipt of a quinolone in the 2 weeks before the onset of K. pneumoniae bacteremia, and receipt of a third-generation cephalosporin in those 2 weeks. Some 60% of ciprofloxacin-resistant K. pneumoniae expressed also extended spectrum β-lactamases. While the above study refers only to bacteremias (and most intra-abdominal infections show no bacteremia), there is nevertheless no reason for dissimilar resistance profiles in intra-abdominal infections. The physicians should be aware of the above risk factors and should make careful clinical judgements when treating patients with any of the above risk factors.

Another area that deserves special attention is the propensity of third-generation cephalosporins and fluoroquinolones to favor the spread of MDR-bacteria. Considering all of the above evidence, including the resistance data, one must clearly discourage the empirical use of cephalosporins and fluoroquinolones in intra-abdominal infections.

**Aminoglycosides**

Early work in intra-abdominal infections has shown that in mixed aerobic-anaerobic infections, monotherapy with an aminoglycoside had a dramatic effect on mortality, yet it had little impact on abscess formation and resolution. Following these observations, an antianaerobic agent was added to the regimen. Studies with gentamicin and clindamycin showed a clinical success rate of 80% (somewhat lower than for newer regimens but statistically not significant).

As newer drugs with better safety profiles appeared and the resistance rate to aminoglycosides rose (30% for amikacin), aminoglycoside-based therapies were supplanted by other regimens. Furthermore, studies comparing β-lactam based therapies against monotherapy with an aminoglycoside in Gram-negative bacteremias showed a higher mortality rate with the latter regimen. Theoretical considerations such as the poor activity of aminoglycosides under acidic conditions discourage the empirical use of this class in intra-abdominal infections.

Another area of active research is the addition of aminoglycosides to other agents with broad spectrum Gram-negative coverage. Current evidence, including a recent metaanalysis, points against the routine use of aminoglycoside combinations. Nevertheless, such studies were done in regions with reduced resistance rates. It is unknown if aminoglycoside-addition would have some impact on outcome in infections with β-lactam resistant organisms. Until such data is available, aminoglycosides should be best reserved for infections with MDR-organisms.

**MDR-Organisms**

Although CoNS are rarely encountered in intra-abdominal infections, they constitute the second most frequent cause of bloodstream infection in nosocomial settings and are frequently encountered in tertiary peritonitis, too. The propensity of nosocomial CoNS to develop MDR poses a therapeutic challenge. Nosocomial CoNS are often methicillin-resistant (>70%) as is frequently the case with clindamycin, macrolides, ciprofloxacin and aminoglycosides (resistance rates between 47-72% for the different drugs in Europe and Latin America) reducing the available armamentarium to glycopeptides and some newer drugs (linezolid, quinupristin/ dalfopristin and daptomycin – currently not licensed), both of which are substantially more expensive and usually unavailable in resource-poor settings. The recent increase in glycopeptide intermediate-susceptibility in both S. aureus and CoNS poses additional problems and calls for widespread monitoring of this problem. The susceptibility to any of the drugs employed should be tested prior to use.

The highest resistance rate is found however in non-fermentative bacteria, but luckily, except for Pseudomonas, which accounts for 11% of the Gram negative bacteria, their prevalence in intra-abdominal infections is very limited (e.g. A. baumannii 1.5% in the latest SMART study). The non-fermenters deserve some special attention and will be briefly discussed below.

If such MDR-bacteria are isolated, the expertise of an infectious disease specialist familiar with the treatment of MDR-bacteria should be sought.

**Pseudomonas and other non-fermenters**

Non-fermenters constitute an important class of pathogens primarily encountered in nosocomial settings. Pseudomonas spp. is the most frequent non-fermenter isolated in intra-abdominal infections constituting 11% of Gram-negative bacilli in the latest SMART study. Other organisms are rarely encountered, albeit they might play a very important role in special circumstances (e.g. Acinetobacter: 1.5% in intra-abdominal infections, but an important pathogen in VAP). This class is covered separately because of the therapeutic challenges they pose.

Firstly, it should be noted that Pseudomonas is intrinsically resistant to many antibiotic classes. Not surprisingly, the number of β-lactam antibiotics with
consistent activity is very limited. Active penicillins comprise only carboxy- and ureidopenicillins (e.g. ticarcillin, piperacillin), while the cephalosporin group includes only ceftazidime and cefepim.

There are still further notable differences in the activity between these drugs. β-Lactam antibiotics show a time-dependent killing and for optimal activity, the free drug concentration must exceed the MIC for various proportions of time (%T>MIC). Cephalosporins need a %T>MIC of 60-70%. This may be nevertheless higher in infections with Pseudomonas, values as high as 83-95% being reported for cefepim.77

Penicillins show usually an intermediate value for %T>MIC (40-50%), but again, this may be higher for Pseudomonas, reaching 100% for ticarcillin.76 The lowest value is seen with carbapenems (40%). The physician must be aware of these differences. As ticarcillin is less active than piperacillin, its use should be severely restricted, if it is used at all.

In addition, ticarcillin is less active on Gram-positive cocci and it is inactive against enterococci, making it an inadequate treatment in cases where these organisms may play an important role (e.g. in tertiary peritonitis).79 Considering the propensity of clavulanate to induce AmpC-type enzymes, it is desirable to avoid the use of ticarcillin/ clavulanate combinations in infections with Enterobacteriaceae, too, whenever this resistance mechanism may play a significant problem.80,81 Few microbiology laboratories report AmpC expression, this fact undoubtedly hampering our understanding of resistance trends. Indirect evidence may come from resistance to amoxicillin/ clavulanate: some 40% of E. coli isolates from Turkey were resistant to this combination.82

More direct evidence comes from resistance rates to cefoxitin, globally 90% of E. coli and 85% of K. pneumoniae strains being susceptible in the latest SMART study, but susceptibility drops sharp in other regions of the world, being as low as 40% in the group of ESBL-producers.41,42 Enterobacter was uniformly resistant. Under these circumstances it is surely no effect for the latter combination.83

Like other Gram-negative bacilli, Pseudomonas may express different ESBLs, both TEM and SHV-types, but some other types have been isolated as well (e.g. PER-1 in Turkey).83 With the widespread dissemination of metallo-β-lactamas (VIM and IMP-type, but other are emerging, too, e.g. GIM and SPM), the resistance situation is even more daunting.

Of particular concern is the rising carbapenem resistance seen in Pseudomonas and even more so the appearance of metallo-β-lactamas in Klebsiella and other Gram negative bacilli, as evidenced by a recent outbreak in Greek hospitals.84,85 These metallo-β-lactamas, of VIM-type in Southern Europe, can degrade every β-lactam, conferring widespread resistance to this whole class of antibiotics. A further rise of this particular resistance would severely compromise treatment options in infections with Gram negative bacilli.

Another peculiarity of these metallo-β-lactamas is the in vitro susceptibility phenotype conferred to the bacteria. While the isolates exhibit reduced susceptibilities to carbapenems, the MICs usually still fall within the susceptible range (2-4 μg/ml for Klebsiella), posing severe interpretation and diagnostic problems, especially in resource-poor settings.85

Around 40-50% of imipenem-resistance in Pseudomonas is due to metallo-β-lactamas. Other resistance mechanisms include porin-mutations (e.g. OprD-mutations) and efflux pumps. There is no easy treatment for infections with carbapenem-resistant organisms and the treating physician is strongly encouraged to consult an infectious disease specialist.

Global resistance trends point to an increase in resistance rates for all classes of antibiotics. Ceftazidime and cefepim resistance rates are around 20%, while carbapenem resistance lays between 14-18%.81 There is also an increase in MDR-isolates, further compromising treatment options (9.9% in the TRUST study for 2003 and 14% in the Intensive Care Unit Surveillance Study for 2002).86,87

If an infection with P. aeruginosa is documented, an antibiotic combination therapy should be seriously considered. Theoretical models favor both carbapenem-fluoroquinolone, carbapenem-colistin and carbapenem-aminoglycoside combinations, but the efficacy of any of these combinations could not be verified in clinical studies.87-89 There is a small number of studies pointing to an advantage (albeit statistically non-significant), but most published clinical data shows actually no effect for the latter combination.72-74

Given the current recommendations to extensively use carbapenems in nosocomial settings and in most community-acquired infections, a screening program to track metallo-β-lactamas is urgently needed.

**Conclusions**

- Resistance trends are challenging.
- The carbapenems show the greatest activity.
- Activity and cost issues greatly favor imipenem over meropenem (cost) and piperacillin/ tazobactam (activity and cost).
- Penicillins and cephalosporins should be best
avoided when ESBL-producers cannot be ruled out.

- Fluoroquinolones and aminoglycosides should not be used empirically.
- Metallo-ß-lactamases could pose a serious threat in the future as treatment shifts to carbapenems. There is an urgent need for active screening for metallo-ß-lactamases production.
- One important focus should be on prevention of infection and spread of MDR-organisms. The best way to avoid resistance development is through antibiotic restriction. Whenever feasible, antibiotics should be withheld.
- Other precautions and antiseptic measures should be strictly employed.
- In infections with MDR-strains, the expertise of an infectious disease specialist should be sought.

4. ACUTE NECROTIZING PANCREATITIS

Pancreatic necrosis occurs in 20 to 30% of all pancreatitis cases essentially determining the severity of the disease as defined by the 1992 Atlanta International Symposium on acute Pancreatitis (Table 6). Overall incidence of acute pancreatitis in Europe is between 20 to 70 cases per 100,000, in the United States a total number of 185,000 new cases emerge per year. Determinants of the natural course of acute pancreatitis are pancreatic parenchymal necrosis, extrapancreatic retroperitoneal fatty tissue necrosis, biologically active compounds in pancreatic ascites and infection of necrosis. The presence of necrosis determines a rise in mortality from almost 0 in the case of mild acute pancreatitis to 50% in the severe form. Recent national quality management standards for auditing hospital units in England set an acceptable upper limit for overall mortality of less than 10% and of no more than 30% in complicated cases. This is in sharp contrast to the situation in Romania where a recent study revealed a mortality of 70% in complicated cases (Dr. T Singh, personal communication). By definition pancreatic necrosis represents a severe form of disease. The main causes for mortality in the severe form of pancreatitis are early MOF and infectious complications of the necrotic areas.

Identifying patients with necrosis

Necrosis can be identified pathologically during surgery or at the time of autopsy. Since surgery is not necessary in the absence of necrosis and death should be avoided, it is desirable to identify patients with pancreatic necrosis (PN) before any of these two events occur. There are two other ways to determine if necrosis is present or not: by using clinical scoring systems to probabilistically predict necrosis or by visualizing it by imaging techniques.

Several scoring systems have been developed in order to stratify risk in acute pancreatitis each with its own advantages and disadvantages. Systems such as the Ranson criteria Imrie-Glasgow scoring system, Apache II score have been described elsewhere and will not be further detailed here. It is important to say however that these scoring systems, together with a high C-reactive protein level, are only probabilistic indicators of necrosis thus prompting the physician to perform an imaging study in order to assess for necrosis.

Contrast-enhanced abdominal CT (CECT) is the gold standard for the noninvasive diagnosis of pancreatic necrosis. Other techniques, such as ultrasonography, ERCP, and angiography are useful for problem solving and for specific evaluation of the pancreatic and biliary ducts and vascular system when involvement is known to be present and more precise anatomical information is required. The major role of CECT is the detection and quantification of parenchymal and peripancreatic necrosis, detecting it with a sensitivity of more than 90% for a degree of necrosis affecting at least 30% of the gland.

The consequences of present necrosis are shown in Figure 1. Staging may also be done using CECT and this method is relevant not only for prognosis but also for problem solving and for specific evaluation of the pancreatic and biliary ducts and vascular system when involvement is known to be present and more precise anatomical information is required. The major role of CECT is the detection and quantification of parenchymal and peripancreatic necrosis, detecting it with a sensitivity of more than 90% for a degree of necrosis affecting at least 30% of the gland.

The consequences of present necrosis are shown in Figure 1. Staging may also be done using CECT and this method is relevant not only for prognosis but also for problem solving and for specific evaluation of the pancreatic and biliary ducts and vascular system when involvement is known to be present and more precise anatomical information is required. The major role of CECT is the detection and quantification of parenchymal and peripancreatic necrosis, detecting it with a sensitivity of more than 90% for a degree of necrosis affecting at least 30% of the gland.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>Acute inflammation of the pancreas</td>
</tr>
<tr>
<td>Mild acute pancreatitis</td>
<td>Minimal organ dysfunction responsive to fluid administration</td>
</tr>
<tr>
<td>Severe acute pancreatitis</td>
<td>One of the following: Local complications (pancreatic necrosis, pancreatic pseudocyst, pancreatic abscess)</td>
</tr>
<tr>
<td>Acute fluid collections</td>
<td>Fluid collection in or near the pancreas</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
<td>Occurs early in the course Lack of a defined wall</td>
</tr>
<tr>
<td>Acute pseudocyst</td>
<td>Non viable pancreatic tissue Diagnosis by i.v. contrast enhanced CT scan</td>
</tr>
<tr>
<td>Acute pseudocyst</td>
<td>Fluid collections containing pancreatic secretions Defined wall</td>
</tr>
<tr>
<td>Pancreatic abscess</td>
<td>Collection of pus Usually in or near the pancreas</td>
</tr>
<tr>
<td>Infected necrosis</td>
<td>Pancreatic non viable tissue colonized by live bacteria</td>
</tr>
<tr>
<td>Infected pseudocyst</td>
<td>Fluid collection with bacterial growth</td>
</tr>
</tbody>
</table>
for treatment. The morphological severity of acute pancreatitis can be determined using the CT severity index (CTSI) developed by Balthasar and coworkers. Morbidity and mortality increase along with the rise of the score.

Timing and use of the CT scan is somewhat controversial. Some authors and guidelines recommend the broad use of CECT in order to detect pancreatic necrosis, while others view it as having only limited use in identifying already infected necrosis. Some of the restricted use is due to anxieties about the potential extension of necrosis and exacerbation of renal impairment following injection of contrast media. However, we believe that the far more accurate prognosis after a CECT scan and the potential therapeutic implications warrant its use in selected cases. Patient selection should be based on the clinical status and the use of scoring systems to determine those patients with a high probability of necrosis (clinically severe acute pancreatitis). Timing of the initial scan should be late enough to allow for the lesions to be fully constituted but not so late that potential therapeutic measures can no longer be used, therefore at 72 h from the onset of abdominal pain seems appropriate timing.

Follow up CT scans should be performed as necessary probably excluding patients with a low CTSI (0-2) and performing a new scan for patients with a higher score between days 7 and 10. Also it should be noted that in a patient with an initially mild form of the disease but with later rapidly deteriorated clinical situation a CECT is indicated.

Detection of pancreatic necroses using contrast enhanced MRI techniques are tested with considerable success but they are still considered an adjunct to CECT scans.

**Infection of pancreatic necroses**

Infection occurs in 40-70% of pancreatic necrosis and is the main life-threatening complication in necrotizing pancreatitis accounting for 80% of deaths. The extent of necrosis is related to the incidence of infection as shown in Table 7. Treating and preventing infected pancreatic necrosis are probably the main therapeutic ways to reduce mortality in NP.

**Table 7. Correlation of the extent of necrosis with rate of infection in patients with severe acute pancreatitis (adapted from 115)**

<table>
<thead>
<tr>
<th>Extent of necrosis</th>
<th>Sterile (n=155)</th>
<th>Infected (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30%</td>
<td>78 %</td>
<td>22 %</td>
</tr>
<tr>
<td>30% to 50%</td>
<td>61 %</td>
<td>39 %</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>32 %</td>
<td>68 %</td>
</tr>
</tbody>
</table>

The high rate of infection is partly motivated by the fact that the area of necrosis is a perfect growth media for bacteria. The pancreatic fluid collections containing necrotic material, enzymes and edematous edematous exudate is practically isolated from the circulation and thus from immunological mechanisms due to microthrombosis in the perinecrotic tissue.

The mechanisms of bacterial invasion have been described elsewhere it is sufficient to say that the main way bacteria are thought to penetrate into the pancreatic and peripancreatic fluid collections is through translocation from the gut. Gram positive and negative bacteria as well as anaerobes are usually recovered from the infected necrotic material. Fungi have also been isolated. Gram negative aerobic bacteria is usually present but also Gram positive and fungi have been found as shown in Table 8.

**Table 8. Bacteria in pancreatic necrosis: 87 patients (Schmid et al.)**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>25 %</td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>17 %</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>15 %</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>9 %</td>
</tr>
<tr>
<td>Proteus spp</td>
<td>9 %</td>
</tr>
<tr>
<td>Candida</td>
<td>4 %</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>3 %</td>
</tr>
<tr>
<td>Enterocacter spp</td>
<td>3 %</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>16 %</td>
</tr>
<tr>
<td>Monomicrobial</td>
<td>76 %</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>24 %</td>
</tr>
</tbody>
</table>

Pancreatic infection is manifested morphologically as infected necrosis which generally occurs in the second week of progression of the disease, or as pancreatic abscess occurring later in the disease, after the fourth week. A third variant is an infected pancreatic pseudocyst. For the definitions of these
entities the reader can check Table 6 or Ref.112.

To determine whether necrosis is infected or not CECT alone is not sufficient. Patients with CECT proven necrosis and clinical signs of sepsis should undergo fine needle aspiration (FNA) of the necrotic areas under ultrasound (US) or CT guidance.93 The sample collected through FNA is then generally gram stained and cultured. The proven infection is an absolute indication for surgery or more recently for percutaneous intervention.113

Antibiotic efficacy in necrotic pancreatic lesions

It is widely accepted that an antibiotic regimen should ensure an appropriate drug concentration at the site of infection.109 An altered pharmacokinetic behavior of antibiotics has been described and reviewed before and it is now recognized that this altered behavior is due to the presence of a barrier similar to the blood-brain barrier.92 This blood-pancreas barrier is responsible for selective uptake of antibiotics into the pancreas. A discussion of local antibiotic concentrations is therefore important. The penetration of antibiotics in the pancreatic necroses was the aim of several studies.108,109,111 Efficacy was also studied. Essentially antibiotics can be divided into three classes according to penetration into the pancreas.109

I. The quinolones ciprofloxacin and ofloxacin and tazobactam have excellent penetration into the pancreatic tissue achieving concentrations of 80-100% of that found in blood serum.

II. Imipenem and cephalosporins have good penetration levels reaching 50% of that found in blood serum.

III. The aminoglycosides have low tissue penetration in the pancreas.

In order to interpret this data concerning tissue penetration one must also take into account the MIC of the bacteria involved in infection of pancreatic necrosis. This has been done by calculating an efficacy factor for antibiotics.109 The efficacy factor represents the percentage of bacteria whose growth would be inhibited by an antibiotic at the concentration it achieves in the pancreas. Such factors were calculated for several antibiotics and are given in Table 9. Imipenem was proven to have the highest efficacy factor reaching 0.98 thus inhibiting 98% of all bacterial strains that were recovered from necrotic samples. This study concluded that imipenem, quinolones, and third generation cephalosporins are useful in preventing infection in the necrotized pancreas.

The data was confirmed in a study by Bassi and coworkers that concluded that pefloxacin, metronidazole, imipenem and mezlocilin are potentially useful for antibiotic prophylaxis in PN.108

In a newer study cefepime proved its capacity to penetrate the pancreatic necrotic lesions and possibly inhibit bacterial growth.111

Preventing infection in NP

Given the high rate of infection of pancreatic necrosis (40-70%) and the high rate of mortality attributable to this infection (80% of the mortality in pancreatitis) it makes good sense to try to prevent it.136 However until now no way of preventing infection of the necrotized pancreas has been definitively proven. Several ways of reducing the infection rate have been tried including: systemic antibiotic prophylaxis, selective gut decontamination or intra arterial antibiotic prophylaxis.114 None of these methods has been proven to significantly improve mortality in a large double blind randomized controlled trial (RCT) and therefore so far no international guideline has recommended without any doubt the use of a method for preventing infection in NP. The most tested and most promising method is the use of systemic antibiotic prophylaxis.

The idea to use antibiotics to prevent pancreatic infection in acute pancreatitis is not new three RCT were published in the mid 1970's using ampicillin as a prophylactic agent.115-117 The results of those studies are not interpretable because of two major drawbacks: one is the lack of CECT diagnosis of necrosis and the other is the fact that ampicillin does not penetrate well into the pancreas.109,114

More recently after the introduction of the CT and the publication by Balthasar and coworkers of the CTSI for acute pancreatitis, nine RCTs have been published including a study by Luiten and coworkers using SDD associated together with systemic antibiotic prophylaxis (see Table 10).118 Seven of these studies are discussed here in more detail the other two only being mentioned because of the very low number of patients.

The first RCT using antibiotic prophylaxis in

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Efficacy factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>0.98</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.87</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.86</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.79</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.78</td>
</tr>
<tr>
<td>Piperacilin</td>
<td>0.72</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0.14</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>0.12</td>
</tr>
</tbody>
</table>

An efficacy factor of 1.0 would be optimal with complete inhibition of bacterial growth at the concentration achieved by the drug in the pancreas.
pancreatitis was the one published by Pederzoli and coworkers in 1993 using imipenem.106 The study included 74 patients selected after the CECT scan had demonstrated necrosis of the pancreas. The patients were randomized to receive either imipenem 0.5 gram every eight hours or placebo. Duration of treatment was 14 days. The study concluded that the rate of pancreatic infection could be significantly reduced (12.2 % versus 30.3 %, p<0.01) together with the rate of extrapancreatic infection; however neither mortality (overall 9.4 %) nor the necessity for surgery (31 %) were significantly different. There was however a trend towards reducing mortality. This was explained by the authors as a consequence of the low number of patients studied.

Some flaws of this study are the fact that only two of the 16 patients with > 50% necrosis were randomized to the control group thus creating a bias. Furthermore the main indication for surgery is the infection of the necrosis and in fact 90% of noninfected necroses do not require surgery, prompting the question why there were no differences in rate of operation when there were differences in infection rate.113

Sainio and coworkers published a study performed in Finland on 60 patients with severe acute pancreatitis using cefuroxime as a prophylactic agent.119 This is the only study to demonstrate significant differences in mortality between placebo and case groups. However it failed to demonstrate significant differences in infection rate. Moreover the randomization seems to have been less than homogenous since two of the patients randomized to the placebo/control group died in the acute phase due to MOF. If these patients are excluded than the differences in mortality are no longer significant, also explaining the lack of significance in infection rate. Additionally it must be noted that, although the pancreatic pharmacokinetics of cefuroxime are unknown, in general second generation cephalosporins have poor penetration into the pancreas, making them unlikely agents for good prophylaxis in NP. This is in contrast to third generation cephalosporins that penetrate much better achieving adequate concentrations.109,111

Selective digestive decontamination (SDD) was used in a study by Luiten and coworkers in combination with i.v. cefotaxime including 102 patients with a Balthasar score of at least D or E which implies necrosis of the pancreas.80,118 The study demonstrated a significant difference in the infection rate of the necrotic pancreas (38% versus 18%, p=0.03) but with no significant difference in mortality. The main drawbacks of this study are: its method of prophylaxis which is cumbersome when it comes to putting it into practice since it involves rectal and oral decontamination and the fact that they also used cefotaxime making it impossible to tell if the systemic antibiotic reduced the infection rate or the SDD.

A more ambitious study was the one published by Isenmann and coworkers using ciprofloxacin and metronidazole versus placebo in a double blind randomized multicenter study.120 The study had a target of 200 patients that was calculated as necessary in order to reduce infection from 40 % to 20 % with a power of 90%. Patients were included on CECT.

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**Table 10. Prospective randomised trials of prophylactic antibiotic treatment in severe acute pancreatitis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>Patients</th>
<th>Control</th>
<th>Case</th>
<th>p</th>
<th>Control</th>
<th>Case</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli et al.</td>
<td>1993</td>
<td>Imipenem</td>
<td>74</td>
<td>30</td>
<td>12</td>
<td>p&lt;0.01</td>
<td>12</td>
<td>7</td>
<td>ns</td>
</tr>
<tr>
<td>Luiten et al.</td>
<td>1995</td>
<td>SDD/cefotaxim</td>
<td>102</td>
<td>38</td>
<td>18</td>
<td>p=0.03</td>
<td>35</td>
<td>22</td>
<td>ns</td>
</tr>
<tr>
<td>Sainio et al.</td>
<td>1995</td>
<td>Cefuroxim</td>
<td>60</td>
<td>40</td>
<td>30</td>
<td>ns</td>
<td>23</td>
<td>3</td>
<td>p=0.028</td>
</tr>
<tr>
<td>Delcenserie et al.</td>
<td>1996</td>
<td>Ceftazidim/amikacine/metronidazole</td>
<td>23</td>
<td>58</td>
<td>0</td>
<td>p=0.03</td>
<td>25</td>
<td>9</td>
<td>ns</td>
</tr>
<tr>
<td>Schwartz et al.</td>
<td>1997</td>
<td>Ofloxacin/metronidazole</td>
<td>26</td>
<td>53</td>
<td>61</td>
<td>ns</td>
<td>15</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Isenmann et al.</td>
<td>2003</td>
<td>Ciprofloxacin/metronidazole</td>
<td>114</td>
<td>9</td>
<td>12</td>
<td>ns</td>
<td>7</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>Bassi et al.</td>
<td>1996</td>
<td>Pefloxacin vs Imipenem</td>
<td>60</td>
<td>Pefloxacin</td>
<td>34</td>
<td>10</td>
<td>Pefloxacin</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Manes et al.</td>
<td>2003</td>
<td>Meropenem vs Imipenem</td>
<td>176</td>
<td>Meropenem</td>
<td>12</td>
<td>14</td>
<td>Meropenem</td>
<td>14</td>
<td>ns</td>
</tr>
<tr>
<td>Maravi-Porra et al.</td>
<td>2003</td>
<td>Imipenem 14 vs. Imipenem free</td>
<td>92</td>
<td>IMI 14</td>
<td>28</td>
<td>30</td>
<td>IMI free</td>
<td>19</td>
<td>17</td>
</tr>
</tbody>
</table>

* control groups imply the use of a placebo.
diagnosed necrosis or a serum C-reactive protein >150mg/L. The medication given (ciprofloxacin 2x400mg/day and metronidazole 2x500mg/day) was prescribed for at least 14 days since the beginning of pain. In the presence of clinical signs of infection drug administration was continued until the 21st day. The study was interrupted after enrolled 119 patients since an interim analysis proved no difference between the two groups in the pancreatic infection rate (12% in the case group versus 9% in the control group p=0.585). Only 76 patients had CECT proven pancreatic necrosis at the end of the study.

This particular study while still one of the most ambitious had some important flaws making its conclusions hard to interpret. Firstly the selection of patients wasn't based only on CECT proof of necrosis but also on the elevated serum C-reactive protein which lead to the inclusion of patients without necrosis (n=43). Although ciprofloxacin has good penetration into the pancreas it is not very active against the usual flora of the necrotized pancreas (see above). This is in general true of quinolones that had been previously used in trials for prophylaxis in necrotizing pancreatitis so it was a known fact at the initiation of the study. To add to this is the fact that the FNAB isolated Staphylococcus epidermidis in 5 cases. This is more likely to be a contamination germ than an infective agent as pointed out by Bassi and Falconi. In conclusion this study although performed under flawless statistical conditions had errors in the choice of patients and antibiotics and in the bacteriological testing making it difficult to draw a firm conclusion.

The two studies of Delcenserie et al. and Schwartz et al. failed to recruit enough patients in order to demonstrate statistical significance and therefore are only mentioned here. A study by Bassi et al. compared imipenem to pefloxacin in preventing infectious complications in NP. This study included 60 patient with at least 50% necrosis of the pancreas that were treated for 14 days with either imipenem 0,5 g three times daily or pefloxacin 400mg twice daily. This resulted in a significant reduction of pancreatic infection (34% versus 10%, p<0.05) in the imipenem group however mortality again was not significantly different. Comments about this study except for the small number of patients are the use of a quinolone alone (i.e. no protection against anaerobes) and the introduction of therapy late in the disease (as late as 120 hours). On the other hand they selected only patients with over 50% necrosis group in which the infection rate is expected to be highest. Another study comparing two antibiotic regimens for the prophylaxis of septic complications in acute pancreatitis is the one by Manes et al. They randomised 176 patients to receive either 0,5 g meropenem tid or 0,5g imipenem qid. The results show no significant difference in the pancreatic infection rate between the two groups (11.4% versus 13.6%) and also no significant difference in mortality. FNAB proven infection was managed surgically. The low incidence of infection in both groups should be pointed at. One would expect a much higher rate of infection in the presence of pancreatic necrosis.

Three meta-analyses have been published so far with reference to these trials. Each included a different number of trials, the one by Golub et al. having included the most. All concluded that significant differences could be identified in the rate of pancreatic infection, extrapanceric infection and in the mortality rates between the control and case groups in these RCTs. However the heterogeneity of the various trials makes the conclusions of these meta-analyses less valuable.

The recommendations of the guidelines are for the most part ambiguous enough to leave the decision making to the bedside physician. Only the guideline by the working party at the Bangkok World Congress of Gastroenterology in 2002 makes a strong recommendation to use imipenem as a prophylactic agent. A few reviews have also tried to clear this issue but they too had limited success in spite of the optimism they have regarding RCT in acute pancreatitis.

We have demonstrated so far, that the question of using prophylaxis for pancreatic infection is difficult to answer. None of the RCT gave a clear result and the data obtained from the meta-analyses is not convincing enough. However the question still remains: is antibiotic prophylaxis beneficial to the patient with NP? It is the opinion of these reviewers that use of an antibiotic is probably more beneficial than harmful in NP. This is because in the case of infected necrosis the only therapeutic solution is necrsectomy, usually by open surgery, leading to a rise in mortality 3 to 4 fold. Such a high mortality rate makes the apparition of resistant germs less than relevant especially since conservative treatment (i.e., antibiotics) of infected necroses leads to a mortality of 100%. Concerns about the spread of resistance throughout the hospital should be appeased by the relatively low numbers of patients. Therefore we do recommend the use of a prophylactic agent in those cases where the CECT shows necrosis of the pancreas.

Which agent to choose is a question somewhat easier to answer given that some antibiotics do not
penetrate sufficiently in the necrotic areas of the pancreas (i.e., aminoglycosides) others that penetrate do not cover the full spectrum of bacteria that might infect the pancreas (i.e., cephalosporins) and finally, some were tested and did not achieve good results (quinolones, and some cephalosporins, see above). We are left mainly with carbapenems to choose from and since imipenem has been the most widely tested antibiotic for prophylactic use in NP it is probably the best choice for now.

The length of time an agent should be administered is another important issue to be addressed. One of the basic principles of antibiotic prophylaxis is that an agent is effective if administered prior to the contaminating event and throughout the duration of contamination. However in NP the timing of the contamination is yet to be determined. Most studies in NP tested the administration of antibiotics for at least 14 days. One study by Maravi-Poma and coworkers addresses this question directly. The study randomized patients to receive imipenem either for 14 days only or for at least 14 days and as long as systemic complications persisted. The study analyzed results from 92 patients and concluded no significant difference in infection rate or mortality existed between the two groups. However they found that a subgroup of patients, those with persisting systemic complications, mortality tended to be lower in the case than in the control group (8.8% versus 25%). The problem raised in this case is what was the role of the antibiotic administered after the 14th day in patients with persisting symptoms, was it still a prophylactic agent or its true role was therapeutic in spite of the intention of the researchers. Another important conclusion of this study was that imipenem use did not yield a high incidence of resistant pathogens but they did observe an increased rate of Candida infection as compared to that in other studies, a conclusion similar to that of the meta-analysis by Vitallatopo and coworkers.

This increased rate of Candida infection prompts the question of antifungal prophylaxis. One Belgian study has retrospectively analyzed the risk factors for fungal infection in 46 patients with severe acute pancreatitis. No risk factors were found. Furthermore they concluded that early antifungal therapy, administered in 18 of 46 patients, did not reduce the risk of fungal infection. Even though this is a cohort study its conclusions are backed up by the mainstream opinion stating that antifungals should be withheld until proof of infection is brought, in spite of the high mortality attributable to nosocomial candidemia.

Management of infected necroses

Infection of the necroses usually occurs during weeks 2-4 of evolution in ANP patients. This is generally signaled by the deterioration of clinical status with the presence of signs of sepsis. FNAB is thought to be necessary in order to confirm the contamination of necroses by bacteria. Conservative treatment of patients with infected necrotizing pancreatitis yields a mortality rate of 100%. It is accepted nowadays that the presence of infected necroses in an ANP patient is an absolute indication for surgery. However there are some questions to be answered. What is the optimal time for the operation, what type of operation should be performed, should sterile necroses be operated upon. To answer these questions more clinical, randomized, controlled studies are needed.

An answer to the question of surgery in sterile necroses is suggested by a recent Dutch study that found operating upon a sterile necrosis to be a risk factor for mortality. However, they also concluded, probably only 90-95% of sterile necroses can be managed without surgery.

The role of antibiotics in infected necroses is limited. One can only imagine using them for postponing the moment of surgery. However the presence of infected necrotic material in the retroperitoneum leads to a rapidly deteriorating clinical status so a delay of the necrectomy might not be possible. The choice of the antibiotic agents used should take into account pancreatic penetration and the results of FNAB and blood cultures. An empiric treatment cannot be recommended after prolonged prophylaxis. In the case of delayed surgery one must bear in mind the mortality rate of symptomatic infected pancreatic necroses. Less invasive techniques for necrectomy are being evaluated.

CONCLUSION

Therefore we suggest that the use of imipenem/cilastatin 0.5g qid as a prophylactic agent, from the moment of the CECT diagnosis of necrosis of the pancreas, is the wise choice even in the absence of clear cut evidence concerning a benefit on mortality. Duration of prophylaxis should be at least 14 days and can be continued if signs of systemic inflammation persist. Combining prophylaxis with early enteral feeding should further reduce the incidence of infected necrosis and thus possibly the need for surgery and thus the mortality. In the presence of newly installed or persisting signs of systemic inflammation and/or
MOF, FNAB should be performed under US or CT guidance. Proof of infection implies the need for surgery, but the timing of the necrectomy is a bedside decision. Antibiotics can be useful in infected necrosis only for delaying the moment of surgery. Antifungal prophylaxis is not recommended at this point. A large double blind randomized multicenter controlled trial concerning antibiotic prophylaxis in ANP is a must in the near future.

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