ABDOMINAL INFECTIONS
A STUDY OF ETIOPATHOGENY AND MICROBIAL RESISTANCE TO ANTIBIOTIC THERAPY

SUMMARY OF PhD THESIS

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TABLE OF CONTENTS

FIRST PART

CURRENT STATUS OF THE PROBLEM

INTRODUCTION

CHAPTER 1. STRUCTURE AND FUNCTION OF PERITONEUM AND PERITONEAL CAVITY

CHAPTER 2. PATHOPHYSIOLOGY OF LOCAL AND SYSTEMIC RESPONSE TO ABDOMINAL INFECTION

CHAPTER 3. ABDOMINAL INFECTIONS

CHAPTER 4. DIAGNOSIS OF ABDOMINAL INFECTION

CHAPTER 5. PRINCIPLES OF THERAPY IN ABDOMINAL INFECTIONS

SECOND PART

PERSONAL RESEARCH
CHAPTER 6. PERSONAL RESEARCH

6.1. MOTIVATION AND OBJECTIVES

6.2. MATERIAL AND METHOD

CHAPTER 7. RESULTS - LOT A

CHAPTER 8. BACTERIOLOGICAL STUDY

CHAPTER 9. RESULTS - LOT B UPDATED STUDY OF GERMS RESISTANCE / SUSCEPTIBILITY IN ABDOMINAL INFECTIONS WITH GRAM NEGATIVE GERMS.

CHAPTER 10. DEDUCTIONS OF ANTIMICROBIAL THERAPY IN ABDOMINAL INFECTIONS

CHAPTER 11. DISCUSSIONS

CHAPTER 12. CONCLUSIONS

REFERENCES

ABSTRACT

Introduction

Abdominal infections (IIA) in general and acute peritonitis particularly, due to their clinical and evolutive potential, medical, social and economic impact are still a subject of debate among practitioners from different specialities: surgery, anesthesia and intensive care, internal medicine, and ending with laboratory medicine, particularly microbiology, immunology and pathological, epidemiology, and, not least, family medicine.

Despite progress in understanding the pathophysiological and therapeutic processes, the mortality from severe forms of acute peritonitis is still high, between 40-50%.

In the U.S., for example, morbidity due to septico-purulent diseases, abdominal infections in the last 40 years increased 40 times. In the past 20 years, the U.S. the incidence of sepsis increased from 82.7 to 240.4 per 100 000 inhabitants. Rates of septic shock deaths per 100 000 people followed an upward trend in 1970 was 1.7, 4.2 in 1980 and 7.9 in 1990. Angus and colaboratorii, in a study conducted in 847 federal hospitals in the U.S., in 1995, reported three cases of severe sepsis in each group of 1,000 inhabitants and an incidence of 68% in intensive care units. Overall mortality was about 28%, with variations according to age: 10% for children and 38% in adults and elderly. In the EU, there are about 100,000 annual deaths from severe sepsis and / or septic shock with an estimated cost of 4.8 - 6.4 billion euros, approximately 24-32% of the total costs of intensive care departments. This is determined by many factors including irrational and unfair antibiotherapy, increasing the number of major surgery, low body reactivity, immune imbalance, environmental pollution etc. A fearsome threat to public health at
the beginning of the XXI century is that the rate of development of antibiotic resistance by microorganisms has already exceed the capacity of the medical community to create new generation of antimicrobial preparations. Thus resistance to treatment is always one step ahead of available therapeutic possibilities. In this context surgical infections take on a new meaning and their treatment is a difficult task for professionals in the field.

Septico-purulent abdominal disorders are advanced forms, generalized or localized of the inflammatory processes that require a complex therapy. They are important not only through the development and persistence of diverse inflammatory outbreak location, but also through all significant changes and sometimes even fatal, of homeostasis, metabolism, microcirculation, which ultimately lead to hypoxia and cardiac cell and organic disorders, worsening the prognosis of the surgical patient. Establishing the relationship between infection and the body's response to aggression is a absolute necessary condition for the development and establishment of an effective therapy.

**PART II. PERSONAL RESEARCH**

**REASONS AND OBJECTIVES**

Abdominal infections are characterized by:

- mortality between 3 to 30%,
- origin: vermiform appendix, gastro-duodenal, intestinal, colo-rectal, hepato-biliary, pancreatic, uro-genital,
- involved germs: Gram-negative, Gram positive, in addition Aero / anaerobes
- recommended treatment:
  - surgical
  - antibiotics – essential, complementary
- usual antibiotic are prescribed empirically before the germs involved are detected.

Diversity ethyopathogenic forms of intra-abdominal infections, respectively diffuse peritonitis and / or localised infections and controversial therapeutic schemes mostly related to microbial germs and determinants of inflammation that permanently alter the natural or acquired resistance to one or more antibiotics.

These data led in the last decade to the prosecution of several surveys which have
brought a number of clarifications regarding the infectious status (infection, sepsis, septic syndrome, septic shock, etc.), helped shaping the diagnostic and therapeutic concepts that apply at current time and future therapeutic strategies premises.

Classification of intraabdominal infections knows a continue dynamics by adding new ethyopathogenic forms. Guided by these concerns, we intended to monitor ethyopathogenic and bacteriologic aspects, correlated with resistance to antibiotics and their implications in antimicrobial therapy.

The objectives are therefore:

- research of etiopathogeny of intraabdominal infections in their dynamics and variety, their place in a practical classification by extended summary of known data,
- extensive microbiological research related to ethyopathogenic mechanisms and the place of initial pathological processes and microbial resistance to antibiotics (Lot A),
- investigation of mediators of inflammation to assess and correlate the bacteriological results, the outcome seriousness to implement modern therapeutic strategies in medical practice,
- cercetarea rezistenței microbieni la antibiotice, o atență „actualizare” și cunoaștere ale acesteia pentru ca antibioticoterapia să aibă eficiență maximă (Lotul B), research of microbial resistance to antibiotics, a careful "update" and knowledge of it for maximum efficiency of antibiotic therapy (Lot B),
- deduction of antibiotherapy schemes in line with postoperative ethyopathogenic diagnosis and individual patient bacteriological research results.

MATERIAL AND METHOD

Were taken in study two groups of patients:

- **Lot A** - retrospective study on 2042 patients admitted in Emergency Hospital Craiova, diagnosed with diffused or localized (abscess) peritonitis from 1996 to 2005. Research is consistent regarding the group of patients and follows all the objectives set out above.
- **Lot B** - a multicenter prospective study conducted in 23 hospitals in Romania on a number of 665 patients in 2006:
  - 7 in Bucharest
  - 6 of Transylvania
  - 2 of Banat - Crisana
  - 4 of Moldova
  - 4 of Muntenia - Oltenia (Clinical Hospital no. 1 Craiova) - Dobrogea.

Research in the second batch (B) was a program to monitor bacterial resistance in intra-abdominal infections (Gram negative).

**RESULTS - Lot A**

BACTERIOLOGICAL DIAGNOSIS
The most frequent incidence of germs isolated from peritoneal fluid were:

- in community-acquired secondary peritonitis:
  - Bacilli G (-) aerobes (Enterobacteriaceae) - 61.8% of which:
    - E. coli - 44.9%
    - Pio 8%
    - Klebsiella 8%, Enterobacter 4%
    - gram positive aerobes cocci --
      - enterococcus 8%
      - bacteria G (+) anaerobic (Bacteroides fragilis) 18%.

- in nosocomial secondary peritonitis:
  - Bacillus G (-) aerobic 48.8% of which
    - Piocianic (Pseudomonas aeruginosa) 30%
    - Enterobacter 15.92%
  - Bacillus G (+) anaerobic - (Bacteroides fragilis) 15%

- tertiary peritonitis
  - Bacillus G (-) aerobic 27.75% of which E. coli 9.37%, Piocianic 18.75%, Klebsiella 6.89%,
  - Fungus 14%

- in primary peritonitis:
  - Bacillus G (-) aerobic 12%
  - Aerobic cocci 76% of which coagulazo-negative stafilococcus 48%, aureus 16%,
    Streptococcus 8%, enterococcus 4%
  - Aerobic cocci G (+) 4% and G (-) anaerobes 4%
  - Fungus 4%

- peritonitis with severe sepsis and septic shock, immunosuppressed
  - Aerobic Bacillus G (-) 76.20% of which: piocianic 40%, Enterobacter 25%, E. coli 8.15%
  - Aerobic cocci G (+) 10%, anaerobic G (-) 6.57%
  - Fungus 6.31%.

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**RESEARCH OF INFLAMMATORY MEDIATORS CORRELATED WITH SEVERITY OF PERITONITIS AND MICROBIAL VARIETY**

**Results of immunological investigations**

1. **C-reactive protein (CRP)** - useful to assess inflammatory reactions and the severity of the inflammatory response. Normal value is <10 ng% and increases 24 hours after the onset of systemic inflammation. CRP is a pro-inflammatory "trigger" by itself as it stimulates the monocyte production of IL 1, IL 6 and TNF-a, having role in modulating the inflammatory response.

2. **Procalcitonin** (PCT a \( \leq 0.1 \text{ ng / ml} \)).
   
PCT levels were increased especially in patients with sepsis, septic shock and severe systemic reactions. PCT qualifies to be placed in the daily tracking protocol of septic patients.
A single determination is sufficient for appropriate diagnosis and monitoring patients at risk of developing septic complications. Unlike other markers used, PCT facilitates also the dynamic tracing of patient’s clinical course.

3. Circulating immune complexes (CIC) and C3 complement component

Serum concentrations of circulating immune complexes showed higher values in patients with peritonitis from 8 to 18 pg/ml, control group showing values of 10 to 60 pg/ml. Serum concentrations of C3 complement component range from 42 to 136 pg/ml in patients with peritonitis, the values being inversely proportional to the severity of clinical manifestations. Control group included serum levels of C3 from 48 to 120 pg/ml. There is a low correlation between levels of circulating immune complexes and C3 component of complement in patients with acute peritonitis, the highest correlation between the C3 and CIC was found in patients with septic shock group.

A STUDY OF MICROBIAL RESISTANCE/SENSITIVITY TO ANTIBIOTICS

It is a phenomenon well documented and real, apparently increasing. This causes a restriction of therapeutic options that brings more failures and increased mortality. Bacteria has the intrinsic ability to produce enzymes to destroy beta-lactam antibiotics. Many types of germs acquire a plasmodic mediated resistance (pieces of plasma). The mechanisms by which bacteria becomes resistant confers varying levels of resistance to one or more classes of antibiotics. The values obtained correlate reasonably well with recent HELICS reports, that 50% of staphylococci found in Romanian hospitals are oxacillin-resistant.

GROUP B RESULTS

UPDATED STUDY OF MICROBIAL RESISTANCE / SENSITIVITY IN INTRAABDOMINAL INFECTIONS WITH GRAM-NEGATIVE BACTERIA

The research is a part of the monitoring program of bacterial resistance in abdominal infections (Gram-negative bacteria) that cause over 80% of these diseases and occurs between February and November 2006 and I personally participated by collecting biological samples from patients hospitalized and operated in emergency in 1st Surgery Clinic.

This is a prospective, multicenter study involving 23 hospitals from Romania: Bucharest 7, Transylvania 6, Banat - Crisana 2, 4 from Moldova and 4 from Muntenia - Oltenia - Dobrogea.

Results

I noticed that 25% of Escherichia coli are ESBL producing bacteria, so very resistant to antibiotics, followed by Klebsiella 12% and Enterobacter 9%. These results point out the seriousness of abdominal infections caused by these germs and thus inferences of appropriate anti-infective therapy. Regarding sensitivity to antibiotics based on microbial species (E.coli, Klebsiella, Enterobacter and ESBL producing bacteria), sensitivities decrease in order of mention from Ertapenem and Imipenem 100% to 44%, 13%.
Examining the results of the study of group B the following conclusions mark out:

In general for all the germs:
- the best: carbapenems - ertapenem - 100%, imipenem - 97%;
- the worst ampicillin - 31%;
- problem of resistance - fixed combinations:
  - cefoperazone / sulbactam - 86%
  - piperacillin / tazobactam - 83%
  - amoxicillin / sulbactam - 80%.

CONCLUSIONS

1. Intraabdominal infections are septico-purulent surgical diseases, separate nosologic entities and severe complications of pathological processes spontaneous or trauma with high lethality in severe forms, which decreased in the last 50 years by about 20%. Currently, lethality varies, depending on the clinical-evolutive form between 13 - 50%, reaching values up to 90% in immunocompromised patients, malignant diseases, premature births.

2. Etiopathogeny of community-acquired intraabdominal infections is in relation to direct contamination of peritoneal cavity. Source of infection was varied:
   - gastro-duodenal perforation 621 -31.33%
   - acute appendicitis 518 -26.13%
   - colon perforation 122 -6.15%
   - small intestine perforation 93 -4.69%
   - hepato-biliary pathology 71 -3.58%
   - urogenital pathology 77 -3.88%
   - nosocomial infections 214 -10.79%
   - peritoneal dialysis 15 -0.75%

3. The species isolated in our study regarding community-acquired intraabdominal infections were similar to those of commensal digestive flora depending the pathological process causing the disease and as in cases of nosocomial infections, peritoneal dialysis, etc.

4. About the germs’behavior against chemotherapy, we found the following: sensitivity testing is necessary and determination of ESBL producing bacteria.

5. In our study, the average susceptibility to antibiotics was 88.67%. Enterobacteriaceae remain predominantly isolated species in abdominal infections, they reach 86% in community-acquired infections Gram-negative.

a. General: Carbapenems are the most active antibiotics against Enterobacteriaceae worldwide, and in our study the best carbapenems were:
   - Ertapemen 100%
   - Imipemen 97%
Ampicillin the weakest 31%

Resistance to the fixed combination was:
- Cefoperazone / Sulbactam 86%
- Piperacillin / Tazobactam 83%
- Amoxicillin 80%

b. On the ESBL producing bacteria:

- the best carbapenems:
  - Ertapemen 100%
  - 100% Imipemen

- resistance to the fixed combination was:
  - Cefoperazone / Sulbactam 47%
  - Piperacillin / Tazobactam 50%
  - Amoxicillin / Calvulanat 21%

- ESBL sites:
  - 23% of total germs isolated
  - 26% of all Enterobacteriaceae

6. In surgery for optimal treatment of intraabdominal infections to complete surgical interventions, is necessary to establish antibiotherapy as early as possible. At first antibiotics should be chosen based on clinical-statistical criteria, probability of etiological diagnosis. Then initial therapy may be reconsidered depending on the clinical course of the patient, tolerance to antibiotics, clinical evolution, the result of bacteriological examination and antibiogram.

7. Of the 2042 patients with intraabdominal infections from group A 817 (40%) required changing of initial therapy:
  - change the initial antibiotic,
  - surgical reintervention.

8. In patients with abdominal infections a better selection of initial antibiotherapy may significantly influence the clinical outcome and costs of medical care.