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**GENERAL MEDICINE**



**PREDICTIVE FACTORS IN SECONDARY ACUTE PERITONITIS**

**ABSTRACT OF PHD THESIS**

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## **Published scientific articles:**

**Meropenem antibiotic therapy in acute secondary peritonitis, therapeutic effects superior to other therapies – experimental clinical and histopathological study in the laboratory animal;** Costin George Florea, Daniel Alin Cristian, Ionuț Simion Coman, Cristin Coman, Teodoru Soare, Anwar Erchid, Iancu Emil Pleșea, Mircea Lițescu, Valentin Titus Grigorean, Romanian Journal of Morphology and Embryology, 2022, Volume 63, Number 4, pages 615 - 623 (indexed in Clarivate Analytics, National Library of Medicine, Medline, PubMed, SciVerse Scopus, Embase, SJR, Index Copernicus, National Research Council; ISSN (print) 1220–0522, ISSN (online) 2066–8279 doi: 10.47162/RJME.63.4.03, 2021 JCR Science Edition Impact Factor 0,833, 5-Year Impact Factor 1.24, Article Influence Score 0.219); <https://rjme.ro/archive/63/4/3/>

**First-line Meropenem antibiotic therapy in acute peritonitis secondary to colic perforation. Clinica and Histopathological study on the laboratory animal.** C. G. Florea, T. Soare, I. S. Coman, C. Coman, M. Lițescu, C. Burleanu, Violeta Elena Coman, Raluca Maria Florea, A. Erchid, V. T. Grigorean; The Medical-Surgical Journal, volumul 127, numărul 1, 2023, indexată Web of Science Core Collection - Emerging Science Citation Index, ISSN-L: 2286-2560, online ISSN: 2286-2560, print ISSN: 0048-7848; <https://www.revmedchir.ro/index.php/revmedchir/article/view/2712>

**Is the Mannheim index still useful in the prognosis of patients with secondary acute peritonitis?** C. G. Florea, I. S. Coman, M. Lițescu, C. Burleanu, Violeta Elena Coman, Raluca Maria Florea, A. Erchid, V. T. Grigorean; The Medical-Surgical Journal, volumul 127, numărul 1, 2023, indexată Web of Science Core Collection - Emerging Science Citation Index, ISSN-L: 2286-2560, online ISSN: 2286-2560, print ISSN: 0048-7848; <https://www.revmedchir.ro/index.php/revmedchir/article/view/2762>

## **REZUMATULUI NOTES REGARDING THE EDITING OF THE SUMMARY**

This paper represents the summary of the doctoral thesis entitled "Predictive factors in secondary acute peritonitis", proposing to highlight the main elements of the thesis, both from the general part, regarding the data from the literature, and from the special part, regarding the two studies carried out within the doctoral thesis.

### **Introduction**

Acute peritonitis is an inflammation of the parietal peritoneum, which can have multiple etiologies and whose consequences are reflected both on the digestive tube and on a systemic level, through a multiorgan involvement.

This pathology represents one of the most common ailments encountered in general surgery departments, often representing a challenge both from the point of view of establishing the obstructive mechanism and from the point of view of the instituted therapeutic plan.

We chose for the topic of acute peritonitis considering the large number of such cases that we face in daily surgical activity. On the other hand, by consulting the specialized literature,

I noticed that this pathology is not covered as much as one would think, despite the very promising possibilities to approach it scientifically.

Thus, in the first section of the present work, named "The current state of knowledge", we tried to briefly present the anatomical data of the peritoneal cavity and peritoneum, notions of the physiology of the digestive tract, as well as physiopathological mechanisms involved in acute peritonitis. We also presented the main classifications of acute peritonitis, its diagnosis with all the steps it entails, as well as the principles of medical-surgical treatment that must be instituted.

The second section, of personal contributions, is opened with a study that includes patients diagnosed and operated on for acute peritonitis in the General Surgery Clinic of the Emergency Clinical Hospital "Bagdasar-Arseni" in Bucharest between 2016 and 2019. The study monitored multiple clinical and biological parameters of the group of patients studied, the cause of peritonitis, the procedures performed, as well as their postoperative evolution. A statistical analysis of the group of patients was also carried out.

The second study presented in this paper was carried out within the "Cantacuzino" National Research Institute, under the guidance of Dr. Cristin Coman and was an experimental one, carried out on rats. They had a digestive perforation, either at the level of the jejunum or at the level of the sigmoid colon, with the dynamic monitoring of multiple clinical, imaging, biological parameters, as well as the histopathological analysis of the perforated segments of the digestive tract and the peritoneum.

Last but not least, we mention that all the ethical and deontological principles of the present work were respected in terms of the confidentiality of the patients' personal data and the bibliographic references used.

## **I. The current state of knowledge**

### **1. Anatomy of peritoneum**

The peritoneum is a serous membrane consisting of two sheets, the parietal lining the abdominal and pelvic cavity, and the visceral covering the organs, with the peritoneal cavity between the two sheets.

The parietal peritoneum is thicker and more resistant compared to the visceral peritoneum, but the latter is more adherent to the covered organs.

The visceral peritoneum is very adherent to the surface of the organs, where it is part of their structure, forming their serous tunic (stomach, liver). The connection between the organs and the visceral peritoneum is made with the help of a subserous layer.

The peritoneal cavity is a normally virtual cavity that becomes real with large fluid collections. It consists of a thin sheet of serous fluid that lies between the two layers of the peritoneum.

The peritoneal cavity is closed in men, while in women it communicates with the ureteric tubes, and with their help with the uterus, the vagina and the outside through an opening.

### **2. Histology and physiology**

From a histological point of view, the peritoneum consists of the mesothelium, located on the outside, made up of mesothelial cells arranged in a continuous layer, covering the underlying connective tissue, and of connective cells, which are in small numbers. (1) If the number of mesothelial cells decreases, adhesions occur between the two sheets. (2) At the level of the apical pole of the mesothelial cells there are microvilli, which help to increase the functional surface of the peritoneum, having a role in the absorption function. (1)

The peritoneal cavity contains approximately 50 ml of isotonic fluid and less than 300 mononuclear cells. The peritoneal fluid consists of water, proteins, electrolytes and different types of cells, facilitating the movements of the viscera.(2)

Functions of the peritoneum: Secretory function; Absorption function; Defense function; Warehouse function.

### **3. Abdominal sepsis**

Intra-abdominal sepsis is the second most common cause of sepsis, with an increased mortality rate. Despite the progress made in the diagnosis and both surgical and antibiotic treatment of peritonitis, its mortality remains high, mostly associated with intra-abdominal complications. (3)

The World Society of Emergency Surgery recommends that in the case of patients with sepsis or septic shock with an abdominal starting point, hemodynamic rebalancing treatment, antibiotics and control of the source of the peritonitis should be administered as soon as possible. (4)

Peritonitis is defined as acute or chronic inflammation of the serous peritoneum, due to physicochemical, infectious, or iatrogenic agents.

#### **Classification of peritonitis::**

**Depending on the nature of the inflammation:** Chemical - aseptic, it occurs through chemical irritation of the serosa, as happens in the case of a perforated ulcer; Microbial – septic, occurs through microbial proliferation

**Depending on the method of inoculation:** Primary – this is the result of bacterial translocation; Secondary – this is caused by direct contamination from a nearby organ due to perforation, injury or necrosis. (5,6); Tertiary – this occurs when primary or secondary peritonitis recurs or persists despite appropriate treatment.

**Depending on the extent of the inflammation:** Diffuse (generalized); locate

**Depending on the evolution:** Acute; Chronic;

**Depending on the appearance of the exudate:** Serous; Fibrinous; Purulent

### **Pathophysiology of peritonitis**

**Local changes:** Fenestration of the peritoneal serosa; the release of immune mediators and the appearance of the inflammatory response; migration into the peritoneal cavity of polymorphonuclear cells and macrophages; hyperemia and increased capillary permeability; the formation of adhesions by the appearance of fibrous exudate; partial resorption of peritoneal fluid.

**Visceral and systemic manifestations:** Intestinal hypermotility initially then hypomotility, reaching adynamia; disruption of respiratory dynamics followed by increased oxygen demand and metabolic acidosis, hypovolemia; metabolic changes such as hypoxemia, acidosis, hypercatabolism and anaerobiosis; coagulation disorder; cardio-circulatory changes; alteration of renal function; systemic cytotoxicity. (1)

### **Pathology**

Secondary peritonitis can be classified according to the appearance of the peritoneal effusion discovered intraoperatively, macroscopically in: Sero-fibrinous peritonitis; Purulent peritonitis; Fecaloid peritonitis; Biliary peritonitis.

Peritonitis has different evolutionary stages: Early peritonitis; Staged peritonitis; Neglected peritonitis. (7,8)

### **Microbiology**

Secondary peritonitis are polymicrobial infections, from the gastrointestinal flora. The most frequent pathogens encountered are: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, streptococci, enterococci, anaerobic agents (*Bacteroides fragilis*), peptococci and peptostreptococci. Between 20%-30% of sepsis cases are caused by *Escherichia coli*, *Bacteroides fragilis*, and both. (9) Multiresistant bacteria (*Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci) appear in patients with recent hospitalizations or antibiotic treatment. (10)

### **Etiology of secondary peritonitis**

At the level of all organs, secondary peritonitis can occur following trauma, most often through penetration, but also iatrogenically (endoscopic procedures, anastomosis dehiscence, etc.)

### **Clinical diagnosis**

**Symptoms:** Pain, Vomiting, Intestinal transit, Fever and chills, Other symptoms: hiccups and abdominal distension as a result of paralytic ileus.(7)

**The positive diagnosis** is usually easy to make considering that the patient most often presents with abdominal pain, with muscle contracture or defense, fever and leukocytosis, and imaging investigations (abdominal ultrasound, empty abdominal radiography and computed tomography) complete the diagnosis.

### **Differential diagnosis**

**Acute surgical abdomen:** intestinal occlusion, acute pancreatitis, entero-mesenteric infarction, hemoperitoneum;

**Acute non-surgical abdomen:** reno-ureteral colic, cystitis, pyelonephritis, gastritis, duodenitis, colitis, recto-colitis, Crohn's disease, diverticulitis, gastric or duodenal ulcer, mesenteric ischemia, aortic aneurysm, renal or splenic infarction;

**Extra-abdominal pathologies:** diabetic ketoacidosis, uremia, herpes zoster, acute myocardial infarction, pericarditis, pleurisy, pneumonia, pulmonary embolism. (11)

### **Treatment of secondary acute peritonitis**

It has the following objectives: stopping germs from entering the peritoneal cavity and removing germs near the source of contamination. This objective is achieved surgically; administration of antibiotic therapy; medical therapy for the prophylaxis of multiple organ failure.(1)

1. **Treatment of hydroelectrolytic imbalances and correction of organ dysfunctions** – this is important to decrease the imbalances produced by acute peritonitis and must be preoperative, transoperative and postoperative.
2. **Antibiotic treatment**

Peritonita acută secundară este o patologie pluribacteriană, motiv pentru care tratamentul antibiotic trebuie să vizeze enterobacteriile, germenii anaerobi și mai rar *Pseudomonas aeruginosa*, *Staphylococcus aureus* și fungi.



Tratamentul antibiotic trebuie început cât mai repede, dar înainte de inițierea lui este recomandat să se recolteze probe pentru investigații bacteriologice. Selectarea necorespunzătoare a tratamentului antibiotic inițial sau administrarea de doze inadecvate poate să ducă la prognosticul nefavorabil al pacienților și la selectarea tulpinilor rezistente.(12)

Tratamentul antibiotic trebuie să înceapă preoperator cu două antibiotice cu spectru larg, după obținerea antibiogramei se trece la un antibiotic electiv sau o anumită combinație. Durata tratamentului variază de la o zi până la 2-3 săptămâni.

3. other studies are ongoing for granulocyte and macrophage colony stimulating factors (G-CSF and GM-CSF), for the PD-1 molecule and interleukin 7.

#### **4. Surgical treatment**

Surgical treatment is the most important step for solving acute secondary peritonitis, with the following goals: control of the source of contamination, abdominal lavage, removal of the contents of the peritoneum and drainage of the peritoneal cavity.(7)

In order to reduce mortality and morbidity, it is necessary to control the source of contamination as quickly as possible. (13) This control is done through different techniques, depending on the etiology of peritonitis: suture, extirpation of the affected organ, drainage of an anastomotic fistula, etc.

Standard treatment consisting of surgery, antibiotic administration, and general hemodynamic support measures helps to cure secondary peritonitis in 90% of patients.(14)

#### **Evolution, complications and prognosis**

Predictive factors of an unfavorable prognosis are: advanced age; malnutrition; increased APACHE II score and Mannheim Index at the time of admission; preoperative organ dysfunction; absence of improvement in 24-72 hours in case of correct treatment.(15)

Mortality in secondary peritonitis varies according to etiology: in acute appendicitis and perforated ulcer the mortality is 10%, while in the case of postoperative peritonitis it increases to 50-60%.(16,17)

A series of scores are used to assess the severity of peritonitis: Mannheim Peritonitis Index (MPI); Acute Physiology and Chronic Health Evaluation Score II (APACHE II); Multiple Organ Dysfunction (MOD); Sequential Organ Failure Assessment (SOFA); Multiple Organ Dysfunction Score (MODS).(18–23)

The most used scores are MPI (Mannheim Peritonitis Index) and APACHE II. MPI is specific for intra-abdominal infections and can also be used in dynamics. (7)

The evolution of secondary peritonitis can be:

**Favorable** - through the remission of fever, the disappearance of gastric stasis, the resumption of intestinal transit, the improvement of biological parameters, the resumption of oral nutrition, the progressive suppression of drainage.

**Unfavorable** – Occurrence of progressive peritonitis despite all therapeutic measures, which is lethal; The appearance of residual abscesses 8-10 days postoperatively; The occurrence of mechano-inflammatory intestinal occlusion due to agglutination of intestinal loops; The occurrence of mechanical occlusion through clamps.(1)

## **II. Personal contributions.**

### **4. Working hypothesis and general objectives**

Acute peritonitis, as I presented in the general part, is still a topical, often encountered pathology, which constitutes a challenge for the surgeon, very often from the point of view of establishing the cause and therapeutic management, with major implications both on the patient's vital prognosis, his quality of life, and socio-economical.

We carried out two research studies, the first of them using as a substrate the patients hospitalized in the aforementioned surgery clinic, between 2016 and 2019, diagnosed and operated on for secondary acute peritonitis, and the second study using a group of rats that were experimentally induced with acute peritonitis through the perforation of the pylorus and the sigmoid colon.

The main working hypothesis from which we started was that acute peritonitis produces important changes, both from a clinical, biological and cyto-architectural point of view, on the tissues involved in this process. Another secondary working hypothesis was that all these changes occur differently depending on the characteristics of the involved subject (eg age, associated pathologies, biological status, cause of peritonitis or location of peritonitis).

The general objectives of this research consisted in the identification, monitoring and interpretation of some quantitative or descriptive parameters of the studied batches, which were determined dynamically, as well as the implications of some procedures on these parameters.**5. Study I – 4-year retrospective analysis of patients hospitalized with the diagnosis of acute peritonitis in the General Surgery Clinic of the Emergency Clinical Hospital "Bagdasar - Arseni" Bucharest.**

#### **Material and methods**

We carried out a retrospective, observational, descriptive study on 185 patients, hospitalized with the diagnosis of acute peritonitis and operated on, in the general surgery clinic of the Emergency Clinical Hospital "Bagdasar - Arseni" Bucharest between 2016 and 2019.

All anamnestic, clinical and paraclinical information was obtained from the patients' observation sheets, after the approval of the hospital's ethics committee, respecting the patients' rights and the confidentiality of the obtained data. At the same time, the patients hospitalized in

the clinic signed an informed consent by which they agreed to obtain data and take photos and use them for scientific purposes, without affecting their image and integrity.

Inclusion criteria: patients hospitalized and operated on in the General Surgery Clinic of the Emergency Clinical Hospital "Bagdasar Arseni" Bucharest with the diagnosis of acute secondary peritonitis in the period 2016 – 2019.

Exclusion criteria: patients with acute peritonitis who were not hospitalized in the period 2016-2019 in the General Surgery Clinic of the Emergency Clinical Hospital "Bagdasar-Arseni" in Bucharest or who were operated on during this period, but for another pathology; patients diagnosed with primary or tertiary acute peritonitis; patients in whom the diagnosis of acute peritonitis was suspected preoperatively based on the clinical examination and imaging investigations, a diagnosis that was however refuted intraoperatively; patients who presented with symptoms specific to acute peritonitis, but in whom the conservative treatment was effective, with symptom relief, even if they eventually required surgical intervention during another admission; patients diagnosed with acute peritonitis who refused surgery and requested discharge on their own responsibility.

A series of parameters were collected from each patient, which included general characteristics (sex, age, number of days of hospitalization), clinical elements at presentation, associated medical pathology, surgical interventions in the antecedents, medication taken prior to admission, the mechanism of peritonitis production, the type of procedure performed, the postoperative evolution, as well as the complications that occurred. The obtained data were centralized in a working model, which was made in Microsoft Office Excel and which was later used for the statistical analysis of the studied lot.

Among the above parameters, not all of them could be analyzed because in the case of some, not enough data were found to be analyzed from a statistical point of view, the most important example being antibiotic therapy where, for most likely administrative reasons, an important polymorphism of the antibiotics used, both in terms of the substance and the class of antibiotics administered, was recorded, a fact that led to the impossibility of drawing up descriptive and analytical statistics that would present scientific relevance. However, we note that the principles of antibiotic therapy described in the specialized literature were respected

At the same time, we mention the fact that not enough data could be collected regarding the bacteria involved because in a proportion of over 70% of the bacteriology bulletins no germs developed on the cultures analyzed.

A similar situation also occurs with regard to local postoperative complications because, from my own experience, in many cases they can appear after the patient's discharge and their treatment does not require the patient's rehospitalization, as they can be solved in the polyclinic. For this reason, we decided not to develop this chapter, otherwise we would have to present inaccurate data that would have affected the scientific value of this work.

## Results

### Preliminary analysis

During 4 years (2016 - 2019), the period of the study, a number of 185 patients diagnosed with acute peritonitis were hospitalized and operated on. Regarding the gender distribution, the majority of patients 62.16% (115 patients) were male.

The patients in the studied group were aged between 9 and 86 years, with an average age of 51.46 years, the interval with the most patients being represented by those aged between 40 and 50 years, 40 patients being registered here. (Fig 5.2)(Fig 5.3) In our study, there were 90 patients aged over 50 years representing a percentage of 48.64% and a number of 60 patients aged over 65 years representing a percentage of 32.43%.

Regarding the environment of origin, 60.54% of the patients, totaling 112 people, came from the urban environment, the main mode of presentation being in the emergency, meaning 171 patients (94.4%)

At the time of presentation, most of the patients presented a good general condition, being hemodynamically stable (105 patients), and 29 of the patients presented with toxico-septic shock. We note that by general good condition we mean the fact that at the time of presentation the objective clinical examination revealed no signs of sepsis or septic shock.

From the point of view of symptomatology, the most frequent symptom was represented by abdominal pain (as the only symptom) in the case of 50 patients (27%) and by the triad: abdominal pain, nausea and vomiting in the case of 43 patients (23.2%). Regarding the onset of symptoms, most patients, 55 (37.2%) presented 72 hours after the onset and only 13 patients (8.8%) presented less than 6 hours after the onset of symptoms.

Most of the patients included in the study, a number of 103 (50.68%) had no personal pathological history (APP), the most common APP being cardiac, 13 patients (7%) and digestive (gastritis, gastric and duodenal ulcer, colonic polyposis, colonic diverticulosis), 10 patients (5.4%).

More than 90% of patients did not have organ failure at the time of presentation, while 5.41% of patients, totaling 10 cases, at the time of presentation to the emergency room had multiple organ failure (MSOF).

All patients in the study underwent surgery, most of them, 38% (46 patients) within 6-12 hours of presentation to the emergency room. In the case of patients operated on more than 24 hours after admission, these were patients in whom conservative treatment was initially attempted and who presented an unfavorable evolution. The most interventions were represented by appendicectomies, in the case of 51 patients and by suturing the ulcer perforation in the case of 36 patients. Intraperitoneally, in the case of 103 patients (55.7%), generalized peritonitis was found, the appearance of the intraperitoneal fluid being in most cases serocitrin (97 cases, 52.4%), then purulent (69 cases, 37.3%), fecaloid (12 cases, 6.5%), and in 7 cases (3.8%) coleperitoneum was detected. It should be noted that due to the polymorphism of the surgical techniques used, a statistical analysis could not be performed regarding the surgical interventions.

Regarding the cause of acute peritonitis, most cases were represented by acute appendicitis, 51 cases (27.6%), and perforated ulcer 46 cases (24.9%). An important proportion was also represented by perforated or abscessed neoplasms, which were found in 12.4% of cases, representing a number of 23 patients.

The postoperative evolution was favorable in the case of 145 patients, representing 83% of the total number of cases, and unfavorable in the case of 31 patients, representing 17% of the total number of cases.

Surgical re-intervention was not necessary in the case of 173 patients, but in the case of 10 patients a re-intervention was necessary, and in the case of only one patient from the studied group two, respectively 3 re-interventions were necessary.

Also postoperatively there were patients who developed organ failure, thus one patient developed liver failure, six patients developed renal failure, 3 patients developed heart failure and 13 patients developed MSOF.

In order to predict the evolution of the patients in the studied group, the Mannheim index was used, which had values between 0 and 43 with an average of 15.43 and a median of 15. We decided to divide the patients according to the Mannheim index as follows: under 21, between 22 and 29, over 30. Thus, in the group with a value under 21 we had 149 patients of which 15 died, revealing a mortality of 10.06%, in the group with values between 22 and 29 we had 27 patients of which 10 died, revealing a mortality of 37.03% and in the group with values greater than 30 we had 9 patients of which 6 died revealing a mortality of 66.66%.

For better relevance, we decided to group the patients into 4 categories according to the Mannheim index, as follows: < 12, between 12 and 20, between 21 and 27 and >27. Thus, in the group with the value below 12, a number of 75 patients were registered, of which 6 died, revealing a mortality of 8%, in the group with values between 12 and 20, there were 59 patients, of which 8 died, revealing a mortality of 13.55%, in the group with values between 21 and 27, there were 40 patients, of which 10 died, revealing a mortality of 25% and in the group with a value of the Mannheim index above 27 there were 11 patients, 7 of whom died, revealing a mortality of 63.63%.

The average number of hospital days was 9.97 days, with a minimum of 0 and a maximum of 48 days. The minimum number of days was in the case of some patients who died immediately postoperatively.

### **Statistical analysis**

All data were analyzed with IBM SPSS Statistics software (Version 25) and Microsoft Excel 2019 MSO (Version 2301 Build 16.0.16026.20002 64-bit for Windows). Analyzes of these data involved frequency percentages, descriptive statistics, cross-tabulations, chi-square tests, etc.

For a better statistical analysis of the obtained data, we decided to analyze the data according to several statistical hypotheses, thus we developed a set of statistical hypotheses that were to be analyzed. Due to the lack of data, a statistical analysis of all the hypotheses proposed for the analysis was not possible, thus a series of hypotheses were analyzed that revealed either positive statistical relevance, negative statistical relevance, or were null.

Null hypotheses: Sex – Type of pathology; Sex – Evolution; Age – Type of pathology; Environment – Type of pathology; Environment – APP; APP – Type of pathology; APP – Postoperative organ failure; APP – Evolution; Onset symptoms – General condition at presentation; Onset of symptoms – Organ failure at presentation; Onset of symptoms – Postoperative organ failure; Onset symptoms- Evolution; Urea, creatinine at presentation – Postoperative organ failure; Leukocyte count at presentation – Organ failure at presentation; Symptoms – Elapsed time to surgery; Cause – Postoperative organ failure; Cause – Organ failure at presentation; Cause – Intraperitoneal fluid appearance; ALT, postoperative AST – Evolution; Urea, postoperative creatinine – Evolution; Elapsed time until surgery – Postoperative organ failure; Type of pathology – Number of leukocytes at presentation; Pathology type – Postoperative leukocyte count.

Hypotheses with positive statistical correlation: Age – Evolution; Environment – Evolution; Medium – Onset of symptoms; APP – Number of days in hospital; Mannheim Index – Evolution; Hemoglobin at presentation – Evolution; Elapsed time to surgery – Evolution; Cause – Evolution; Type of pathology – Evolution; Peritonitis type – Evolution; Intraperitoneal fluid aspect – Evolution; Cause – Number of days of hospitalization; Organ failure at presentation – Evolution; Postoperative hemoglobin – Evolution.

Hypotheses with negative statistical correlation: ALT, AST – Postoperative organ failure; Postoperative leukocyte count – Evolution. In these two cases, the negative correlation indicates that increased values of AST and ALT are associated with a lower risk of developing postoperative organ failure, and that postoperative leukopenia is associated with an unfavorable outcome.

## **Discussions**

In the USA, the population over 65 years old represents approximately 58-65% of the total number of peritonitis(24,25), in our study, there were 90 patients over 50 years old representing a percentage of 48.64%. Acute peritonitis, in the present study, is associated with an unfavorable evolution in patients over 50 years old, a statement supported by the fact that in the group aged under 50 years a mortality of 5.10% was recorded, and in the group aged over 50 years a mortality of 29.8% was recorded, the mortality in the entire studied group being 16.75%.

In our study, 62.16% of patients were male, a fact comparable to other studies in which 70.6% of patients were male(26) but also different from other studies in which the percentage of male patients was between 43 and 52%(27,28). At the same time, the specialized literature does not record gender as a risk factor in acute peritonitis, (26–28) and in our study there is no correlation between the gender of the patients and their evolution.

Delayed surgical intervention is described as a risk factor in secondary acute peritonitis(29,30), in our study, only 66% of patients, representing a percentage of 35.67%, presented to the doctor in the first 24 hours from the onset of symptoms, of which 7 (7.57%) had an unfavorable evolution. At the same time, regarding the time elapsed from presentation to the emergency room until the moment of surgical intervention, 42.2% of the patients included in the study were operated on within the first 12 hours after presentation.

The serious general condition at presentation, important comorbidities and organ failure are risk factors in acute peritonitis(29–33), in our study 17.7% of patients at the time of

admission to the health unit had toxico-septic shock. Regarding organ failure, a percentage of 9.6% of patients included in the study had organ failure at the time of presentation, of which 55.55% had MSOF. Regarding organ failure developed postoperatively, it occurred in 12.3% of the patients included in the study. Of the patients who presented with postoperative organ failure, 52.52% presented with MSOF.

Acute peritonitis arising from the complications of a malignant tumor pathology is described as a risk factor(34,35), in our study a percentage of 16.8% presented malignant tumor pathology, with a mortality of 29.03%.

The appearance of peritoneal fluid and generalized peritonitis is also a risk factor. Multiple studies associate the fecaloid appearance of the intraperitoneal fluid and generalized peritonitis with a high mortality. (34,36,37) In our study 55.7% of patients presented with generalized peritonitis, and regarding the appearance of the intraperitoneal fluid, it was fecaloid in 6.5% of cases. The fecaloid appearance of the intraperitoneal fluid was associated with 100% mortality.

In the case of patients with localized peritonitis, a mortality of 9.75% was recorded, while in the case of patients with generalized peritonitis the mortality was 22.33%, statistical correlation tests indicating a significant association between the type of peritonitis (localized or generalized) and the evolution of the patients.

Although in the literature anemia is described as a result of sepsis due to the persistence of the inflammatory syndrome, being associated with low levels of sideremia(38–41), we did not find in the literature that anemia represents a risk factor in the evolution of peritonitis. In our study, 14.59% of patients had hemoglobin values below 10g/gl at the time of admission, of which 80% died. Regarding hemoglobin values below 10g/dl postoperatively, they were observed in 21.62% of the patients included in the study, being correlated with a mortality of 37.5%.

Mortality in acute peritonitis is between 6 and 40%(18,26–28,42–44), an important risk factor being organ failure(45) in our study, mortality being 16.75%.

In many studies, Mannheim index values are divided into 3 groups: below 21, associated with low mortality, between 21 and 29 and above 29, associated with a mortality rate of up to 100%(42,46,47), many authors considering that a Mannheim index greater than 26 is associated with high morbidity and mortality.(18,26,27,46,48–53) For better statistical relevance in our study we divided the patients into 4 categories according to the Mannheim index as follows, < 12 associated with a mortality of 8%, between 12 and 20 associated with a mortality of 13.55%, between 21 and 27 associated with a mortality of 25% and >27 associated with a mortality of 63.63%. This indicates that this prediction cannot be applied individually in terms of making therapeutic decisions in a single individual, a fact also confirmed by multicenter studies carried out on large groups of patients. (18,26,53) Contrary to the previously mentioned statements, certain studies support the fact that the Mannheim index can be used as a criterion in choosing the optimal treatment of acute peritonitis (46,47,51), laparoscopic treatment being indicated for a Mannheim index with a value below 29. (26,46, 54,55)

The Mannheim index represents a severity score that is easy to use in the clinic, studies that compared it with the APACHE II score, peritonitis index of altona and sepsis severity score demonstrated its value, being equal or superior in assessing the prognosis.(42,47,49,56,57)

## **6. Study II – Clinical, biological and histopathological elements analyzed dynamically in secondary acute peritonitis. Efficacy of Cefuroxime and Meropenem in the Laboratory Animal with Experimental Secondary Acute Peritonitis**

### **Material and method**

The experimental study was carried out within the National Research Institute for Medical-Military Development "Cantacuzino", Băneasa Department (Romania), Preclinical Testing Unit, being carried out according to the Organization for Economic Cooperation and Development (OECD) norms in good laboratory practices (GLP) and in accordance with Romanian laws in force and internal protocols, with the authorization of the Veterinary Authority and the Ethics Committee of the "Cantacuzino" Institute. The laboratory animal used was the Wistar rat, aged 14-16 weeks and with a body weight (b.w.) of 150-300 g at the start of the study. We used 65 healthy young-adult animals, both female and male, that had not been involved in previous tests.

The animals were divided into seven groups A, B, C, D, E, F, and G. The 5 rats from group A, which represented the control group, had samples collected from the parietal peritoneum, stomach and sigmoid colon, and the 10 rats from each group - B, C, D, E, F and G had a gastric perforation (groups B, D, F) and a perforation at the level of the sigmoid colon (groups C, E, G) when it was defined as T0. General anesthesia of the animals was achieved with a mixture of Ketamine (0.35 mg/kg body) + Aceprosamine (0.3 mg/kg body) + O2 with Isofloran. Postoperatively, the animals in groups B, C, D, E, F and G received treatment with Ketoprofen, and the antibiotic therapy was administered as follows: groups B and C did not receive antibiotic treatment, groups D and E received antibiotic treatment with Cefuroxime 25/kg/24h intravenously(58), and groups F and G received treatment with Meropenem 40 mg/kg intravenously(59).

Five times were defined: T0 – the time when the parietal peritoneum, stomach and sigmoid colon were sampled from all subjects in group A, and gastric perforation occurred to subjects in groups B, D, F and sigmoid perforation was caused to subjects in groups C, E and G, T1 – 24 hours after the occurrence of gastric perforation and sigmoid perforation, T2 – 48 hours after the occurrence of perforation gastric and sigmoid lesions, at which time some of the subjects were sacrificed and histopathological samples were collected, T3 – 72 hours postoperatively and T4 – 96 hours postoperatively, at which time the subjects were sacrificed and histopathological samples were collected.

At time T0, as mentioned above, all subjects in group A were sacrificed and their parietal peritoneum, stomach and sigmoid colon were sampled. The samples taken were processed and stained with Hematoxylin-Eosin and analyzed under an optical microscope.

Subjects in groups B, D and F underwent a median incision through which the peritoneal cavity was penetrated, where a 0.5 cm incision was made at the level of the pylorus followed by hemostasis and parietorrhaphy in anatomical layers. The same was done in the case of subjects from groups C, E and G, except that a 0.5 cm incision was made at the level of the sigmoid colon. No problems were encountered during the procedures, after which the subjects were monitored until awakening from anesthesia.

From time T0 each of the animals that were alive received anti-inflammatory treatment consisting of the intramuscular administration of Ketoprofen 3 mg/kg body weight. Antibiotic



therapy with different drugs, administered as follows: Subjects in groups B and C received no antibiotic, subjects in groups D and E received Cefuroxime 25 mg/kg/24 h intravenously, and subjects in groups F and G received Meropenem 40 mg/kg/24 h intravenously.

By T1, 10 of the subjects in the study groups had died, as follows: four subjects in group B, five subjects in group D, and only one subject in group F.

At T2, subjects with severe general condition were selected from the survivors of groups B, D and F and randomly 5 subjects each from groups C, E, G, and the peritoneal cavity was penetrated by removing the sutures from the parietorrhaphy, to observe local macroscopic pathological changes, then, after resection and sampling of the parietal peritoneum and the stomach and sigmoid colon respectively, the tissue fragments were processed and analyzed under the optical microscope for to detect pathological microscopic changes.

At T3, two of the subjects died, one subject belonging to group B and one subject belonging to group G.

At time T4, the surviving subjects were sacrificed so the peritoneal cavity was penetrated by removing the sutures from the parietorrhaphy, to observe local macroscopic pathological changes, then, after the resection and sampling of the parietal peritoneum and the stomach and sigmoid colon respectively, the tissue fragments were processed and analyzed under the optical microscope to detect pathological microscopic changes.

After sampling all subjects examined at T2 and T4 were euthanized according to internal procedures with anesthetic overdose.

Throughout the study, subjects received water and food ad libitum.

## **Results**

For a better analysis of the results obtained, we decided to divide the analysis of the results into 3 studies as follows:

### **1. Comparative analysis between acute peritonitis due to perforation of the stomach and acute peritonitis due to perforation of the sigmoid colon.**

From a clinical point of view, the evolution was favorable for subjects in group D, in which no death was recorded. In the case of subjects in group C, at time T1 the death of 4 subjects was recorded, and at time T3 the death of one subject. At the same time, the subjects in group B presented the alteration of the general condition, with apathy and loss of appetite, while the subjects in group D presented good general condition with preserved appetite. In terms of body mass, subjects in group D showed weight gain and subjects in group B showed weight loss.

From a macroscopic point of view, at the time of T2 significant gastric distension and the formation of plastrons that covered the lesion in which the omentum, liver and spleen participated and the presence of edema in the intraperitoneal abdominal wall, a significant amount of serocitrine liquid with distended, edematous loops of the small intestine and colic framework were observed in group B. At the level of group D, when entering the peritoneal cavity, the presence of serocitrine liquid in a minimal amount, slightly distended colic framework, at the level of the sigmoid perforation, the plastron, in which the intestinal loops participate, intensely adherent, covering the perforation.

From a microscopic point of view, at time T2, in the case of subjects from group B, thickening and edema between the muscles and the peritoneal sheet can be detected at the level of the peritoneum. At the level of the stomach, the visceral peritoneum is detected, showing the activation of mesothelial cells, edematous gastric and submucosa muscles. In the case of subjects from group D, active mesothelial cells with slight thickening of the parietal peritoneum and active mesothelial cells at the edge of the serosa, mucous membrane with abundant goblet cells are observed in the sigmoid.

At time T4, in the subjects of group B, upon entering the peritoneal cavity, significant gastric distention and the formation of plastrons were detected that covered the gastric lesion in which the omentum, liver and spleen participated, which contained purulent liquid and food debris and edematous abdominal wall, with areas of devitalized tissue, intraperitoneal medium amount of serocitrin fluid, with loops of small intestine and distended colic framework with the appearance of ileus. While in the subjects of group D, in addition to the changes detected at the time of T2, significant distension and edema of the cecum and colic frame are detected.

From a microscopic point of view, at the time of T4, a thickened basement membrane with active fibroblasts and rare mesothelial cells can be observed at the level of batch B at the level of the parietal peritoneum. At the gastric level, the peritoneum detaches from the gastric serosa with the presence of mesothelial cells increased in volume, fragmented gastric smooth muscle, infiltrated with neutrophils and macrophages, with the presence of microhemorrhages and marked hyperemia. While at the level of group C, the peritoneal serosa infiltrated with neutrophils and macrophages, with hyperemia, can be observed at the level of the parietal peritoneum. At the level of the visceral peritoneum of the sigmoid hyperpalsia, with active hyperbasophilic cells with edema and abundant infiltrate with neutrophils and macrophages between the serosa and the smooth muscle.

## **2. Evaluation of antibiotic treatment in acute peritonitis through gastric perforation.**

From a clinical point of view, the subjects in group F evolved favorably, compared to groups B and D, thus at time T1 there were deaths of 4 subjects from group B, 5 subjects from group D and one subject from group F, at time T3, one more death occurred in one subject from group B. Also subjects from group F showed good general condition with preserved appetite. At the same time, subjects in group F gained weight throughout the experiment, in comparison, subjects in groups B and D showed weight loss.

From a macroscopic point of view, in the case of all examined subjects, both at T2 and at T4, significant gastric distension and the formation of plastrons were observed that covered the gastric lesion in which the omentum, liver and spleen participated, containing purulent liquid and food debris. Regarding the changes in the peritoneal cavity, both at T2 and at T4, it was found that there were minimal changes in group F, the subjects showing a favorable evolution compared to those in groups B and D.

At the microscopic examination, although at the level of the visceral peritoneum and at the level of the stomach, no important changes were detected between the subjects of the 2 groups, neither at the time of T2 nor at the time of T4, the changes detected at the level of the parietal peritoneum show a better evolution of group F.

### **3. Evaluation of antibiotic treatment in acute peritonitis due to perforation of the sigmoid colon.**

From a clinical point of view, the subjects in all 3 groups showed favorable evolutions, with only one death recorded in group G at the time of T3. Subjects in all 3 groups showed good general condition and weight gain, except for subjects in group C who at T2 showed a slight decrease in mean weight.

Macroscopically, at the time of T2 in the peritoneal cavity, the presence of intraperitoneal fluid with serocitrin appearance, distended colic frame, sigmoid perforation covered by intensely adherent intestinal loops was found in all groups, without notable differences between the 3 groups.

At time T4, 96 hours from the time of perforation, we sacrificed 5 subjects each from groups C and D and 4 subjects from group G, one subject from group G died at time T3. Intraperitoneally, subjects from group C and E have a minimal amount of serocitrin fluid, distended intestinal loops, much distended, edematous cecum and colic frame. Subjects in group G did not have free intraperitoneal fluid, instead they had distended intestinal loops with the formation of plastrons at the level of the perforation.

At the microscopic examination, at the time of T2, a better evolution of groups E and G was observed, compared to group C, at the same time, group G presenting the least inflammatory changes, at the level of the peritoneum being described its discrete thickening and the presence of active mesothelial cells, and at the level of the sigmoid being described thickened serous with vascular hyperemia at the level of the colic wall muscles and rare active mesothelial cells.

The microscopic analysis of the samples collected at the time of T4 revealed a better evolution of the subjects in group G, thus at the level of the parietal peritoneum there are rare active mesothelial cells, increased in volume, and at the level of the sigmoid no signs of inflammation.

From the above we can deduce the fact that the groups that received antibiotic treatment presented a favorable evolution both from a clinical point of view, of macroscopic intraperitoneal changes and from the point of view of microscopic changes, and that received Meorpenem presented a clearly favorable evolution compared to the group that did not receive antibiotic treatment.

### **Discussions**

In the case of digestive perforation, studies on laboratory animals revealed a mortality of up to 80% 72 hours after the occurrence of the perforation(60) reaching a mortality of 100% (61–63) in our study a mortality of 18.46% was recorded, the majority of deaths (11 subjects) being part of the groups with gastric perforation, most of them being from the group that did not receive treatment and from the group that received received Cefuroxime.(64) In the case of colic perforation, only one subject died, death occurring 72 hours after perforation.(65)

Studies carried out on rats have demonstrated that peritoneal lavage decreases mortality in acute peritonitis, (61)(62) in the absence of any type of treatment, this can reach up to 100% in time intervals between 12 and 52 hours, (61–63) in our study, mortality at 24 hours was 50% in the case of groups B and D, most deaths being recorded in the first 24 hours and 10% in in the case of groups F and G, in the case of group F in the first 24 hours, and in the case of group

G 72 hours postoperatively. (64,65) In the case of all subjects treated with Meropenem, mortality at 24 – 48 hours was 0, explainable in the context in which studies performed on rats demonstrated a mortality at 8 days of 10%. (66)

With the formation of intraperitoneal plastrons, the effects of peritonitis begin to decrease, the clinical evolution being towards an apparent cure(67), in our study, all subjects presented during the exploration of the peritoneal cavity intraperitoneal plastrons, formed by the organs adjacent to the perforation, which had the role of locating the lesions. With the formation of plastrons, a decrease in macroscopic changes in the peritoneal cavity is observed. If at time T2 in the case of all groups the presence of intraperitoneal fluid could be observed, at time T4 the amount of intraperitoneal fluid decreased, in the case of the subjects who received antibiotic therapy, the absence of intraperitoneal fluid was noted at the level of group G, at time T4. (64,65)

Paralytic ileus secondary to acute peritonitis was explained, according to Stokes' law, as a result of serous inflammation(68) in the first phase, then bacterial toxicity and finally intraperitoneal adhesions(69). In subjects with gastric perforation, the presence of paralytic ileus was detected at time T2 in subjects who did not receive treatment (group B) and in subjects who received treatment with cefuroxime (group D). At time T4, the presence of paralytic ileus was detected only in subjects from group B. In subjects with sigmoid perforation, ileus was detected in the case of all subjects both at time T2 and at time T4, with a discrete improvement in the case of subjects who received antibiotic treatment at time T4.(64,65)

Intraperitoneal adhesions are classified according to the "Adhesion grading scale" as follows: Score 0 - no adhesions, Score I - fine adhesions, Score II - tight localized adhesions, Score III - tight viscerovisceral adhesions, Score IV - tight viscerovisceral and visceroparietal adhesions. (70,71) In our study, in the case of each group, we found at time T2 adhesion syndrome with a score between I and II and at time T4 adhesion syndrome with a score between II and III, without notable differences between the groups.

The inflammatory response of the peritoneum occurs through several steps, (72,73), being characterized by the increase in blood supply with the accumulation, with the attraction and infiltration of immune cells, with the accumulation of macrophages, which play a key role in the immune response of the peritoneum, which releases pro- and anti-inflammatory factors. (73,74). In our study, in subjects with gastric perforation, activation of mesothelial cells and accumulation of immune cells was observed in all groups, both in the parietal peritoneum and in the visceral peritoneum of the affected organ. Although no differences were observed between the lesions in the visceral peritoneum between the groups, neither at T2 nor at T4, differences were detected in the parietal peritoneum in terms of the inflammatory process, thus the smallest lesions in the parietal peritoneum were observed in group F. In the case of subjects with sigmoid perforation, mesothelial cell activation and immune cell accumulation were observed in all groups, both in the parietal peritoneum and in the peritoneum visceral tone at the level of the affected organ. The exception was made by group G in which, at the time of T4, a minimal inflammatory reaction was found at the level of the visceral peritoneum and the absence of inflammatory phenomena at the level of the parietal peritoneum. (64,65)

Important microscopic changes at the level of the parietal peritoneum were detected in the case of subjects in which the extravasation of food content from the digestive tube occurred or in the case where the parietal peritoneum participated in the formation of an intraperitoneal

abscess, regardless of the group to which the subjects belonged. At the same time, important inflammatory changes were observed at the level of the affected organ, especially at the level of the perforation. (64,65)

Both Meropenem and Cefuroxime associated or not with Metronidazole are antibiotics that are used successfully in the treatment of acute peritonitis with similar results(75,76). In our study, both from a clinical point of view (evaluation of the general condition), macroscopically and microscopically, a better evolution of the subjects who received antibiotic treatment can be observed, compared to those who did not receive antibiotic treatment, both at T2 and at T4. From a microscopic point of view, it can be observed, especially at the time of T4, that in the case of subjects treated with Meropenem, the changes in the parietal peritoneum were minimal.(64,65)

## **Conclusions and personal contributions**

Following the study that was carried out in the General Surgery Clinic of the Emergency Clinical Hospital "Bagdasar-Arseni" in the period 2016 - 2019, we can draw the following conclusions:

1. In our study, less than half of the patients were over 50 years old and about a third were over 65 years old, so we can conclude that in the studied group acute peritonitis occurs especially at young ages.
2. Advanced age is a risk factor in acute peritonitis, a fact supported by the fact that in our study the mortality in the group of patients aged under 50 years was 5.10%, and in the group aged over 50 years it was 29.8%.
3. Mortality in the present study was 16.75%, a result comparable to the specialized literature.
4. Although 62.16% of the patients included in the study were male, no data were obtained to suggest that gender is a risk factor in acute peritonitis.
5. Although organ failure in acute peritonitis occurs in a relatively small number of cases, it is still a rather serious complication considering that in our study, in more than 50% of cases that developed organ failure, MSOF occurred.
6. Malignant pathology is a risk factor in secondary acute peritonitis, a statement supported by the fact that the mortality rate in the group of patients who presented malignant pathology was 29.03%, and the data analysis demonstrates a correlation between malignant pathology and unfavorable evolution.
7. Stercoral peritonitis represents an important risk factor regarding the evolution of patients with acute peritonitis. In our study all stercoral cuperitonitis patients died.
8. In the case of patients with generalized peritonitis, the mortality was 22.33%, statistical correlation tests indicating a significant association between the type of peritonitis (localized or generalized) and the evolution of the patients.
9. Among the patients with hemoglobin values below 10g/dl at the time of presentation, 80% died, so we can conclude that anemia can represent a risk factor in the evolution of acute peritonitis.
10. The Mannheim index is a useful score in predicting mortality in acute peritonitis. Based on the results obtained in our study we can conclude that there is a significant association between the Mannheim index and the evolution of patients. The Mannheim

index may be a useful predictor of progression, and further analyzes may be beneficial to explore this relationship further.

Following the experimental study carried out on rats that developed acute peritonitis, we mention the following conclusions:

1. In our study, a mortality rate of 18.46% was recorded, the majority of deaths (11 subjects) being part of the groups with gastric perforation, of which the majority were from the group that did not receive treatment and from the group that received Cefuroxime.
2. In the case of all subjects treated with Meropenem, mortality at 24-48 hours was 0, results comparable to those obtained in other studies published in the literature.
3. In the case of all subjects who survived more than 24 hours, when exploring the peritoneal cavity, the formation of intraperitoneal plastrons was observed, which had the role of locating the lesions and subsequently reducing intraperitoneal reactivity. And in this case, there was a better evolution of the subjects in the groups that received treatment with Meropenem.
4. Antibiotic treatment, by reducing bacterial toxicity and the formation of abscesses that localize the lesions, can prevent dynamic ileus or actively participate in its reversal.
5. In our study, in the case of each group, we found at time T2 adhesion syndrome with a score between I and II and at time T4 adhesion syndrome with a score between II and III, without notable differences between the groups.
6. Although histopathological analysis did not show differences between the visceral peritoneum lesions between groups with gastric perforation, neither at T2 nor at T4. At the level of the parietal peritoneum, differences were detected regarding the inflammatory process, thus, at the time of T2, no very large differences were observed between the groups, while at the time of T4, the subjects from the groups that received antibiotic treatment, presented a weaker inflammatory process at the level of the parietal peritoneum, the smallest lesions being observed in the subjects from the group that received treatment with Meropenem.
7. In the case of subjects with sigmoid perforation, the histopathological analysis observed in the case of all groups, the activation of mesothelial cells and the accumulation of immune cells, both at the level of the parietal peritoneum and at the level of the visceral peritoneum at the level of the affected organ, except for the subjects who received treatment with Meropenem, in which case, at the time of T4, a minimal inflammatory reaction was found at the level of the visceral peritoneum and the absence of inflammatory phenomena at the level parietal peritoneum.
8. If there are factors that maintain the lesions (food debris, bacterial inoculation), the inflammatory response will be stronger and will persist for a longer period of time, regardless of the treatment received.
9. In our study, both from a clinical point of view (evaluation of the general condition), macroscopically and microscopically, a better evolution of the subjects who received antibiotic treatment can be observed, compared to those who did not receive antibiotic treatment.

Through the first study, the present work aims to bring into clinical practice a wider use of the Mannheim Index, both in the format presented in the literature and in the format presented in this thesis in Chapter 5, Subchapter 5.3.2, statistical hypothesis number 13. From the data

obtained from the analysis of the studied group as well as from the consultation of the specialized literature, it follows that the Mannheim Index represents an important and reliable predictive factor in terms of the evolution of patients with acute peritonitis secondary care, at the same time being easy to use inclusively in general surgery clinics that have limited diagnostic resources.

At the same time, the first study, through the results regarding the preoperative and postoperative anemic syndrome, in which it is observed that anemia is associated with an unfavorable evolution (Chapter 5, Subchapter 5.3.2, statistical hypotheses 23 and 35), aims to be a basis for other additional studies regarding the role of anemia in the evolution of patients with acute peritonitis.

The second study in the present work (Chapter 6) represents an original study that wants to draw attention to the importance of antibiotic therapy in secondary acute peritonitis, at the same time being a good scientific basis for further studies.

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