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Management of infectious complications in the severely burnt patient

DOCTORAL THESIS SUMMARY

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Main ideas synthesis

In light of the fact that burn patients frequently suffer from infectious complications, which represent the main cause of mortality within the first 24 hours, our working hypothesis is that by conducting rigorous observational studies and critically analyzing the existing literature, we can obtain a deeper understanding of the management of these complications in cases of extensive burn patients.

The fundamental problem we aim to address is the identification of knowledge gaps regarding the management of infectious complications in severely burned patients. While previous research exists in this field, a comprehensive approach is necessary to identify the main unresolved issues and improve current approaches.

Our obejctives are as follows:

1. Identifying the risk factors with prognostic character for the infectious complications at severely burned patients.
2. Analyzing the main types of infectious complications associated with extended burns.
3. Evaluating the efficiency of several management strategies in handling the infectious complications.
4. Identifying the potential new risk factors through observational studies.

Our research methodology consists of collecting and analyzing data from patients with extensive burns, as well as conducting a detailed assessment of previous research. We will employ observational methods to gather relevant data and perform a critical review of the existing literature to understand the current state of knowledge in the field. This combination of observational studies and critical evaluation will allow us to obtain a more comprehensive overview and identify new research directions and management approaches for infectious complications in severely burned patients.

In conclusion, by pursuing this working hypothesis, our aim is to promote an evidence-based research model, with the goal of enhancing the care provided to patients with extensive burns and reducing the impact of infectious complications on their morbidity and mortality.

1. Epidemiology, demographic data, prognostic and prehospital management

Burns represent a significant public health issue, causing a considerable number of deaths and injuries worldwide. They can be caused by various mechanisms, such as flames, hot liquids, hot objects or surfaces, electrocution, chemicals, or radiation, and can lead to severe tissue damage. (Hettiaratchy & Dziewulski, 2004; Jeschke et al., 2020).

In the United States, approximately half a million people suffer from burns each year, and a significant number of them require hospitalization in specialized burn centers. Infections are the leading cause of death in burn injuries, and proper management has led to a decrease in the number of fatalities in recent years.(Lachiewicz et al., 2017; Norbury et al., 2016a).

There are multiple causes of burns, including flames, scalding, workplace accidents, chemicals, electrical current, electric shocks, fireworks, or intentional burns. Individuals at higher risk for burns include the elderly, people with disabilities, and military personnel. Post-burn immunosuppression increases the risk of infections and complicates their treatment.

In the past 10 years, infectious complications in burn patients have been the cause of approximately 42-65% of deaths. It is critically important to understand that multidrug-resistant (MDR) infections present additional risk factors, necessitating the development of prevention strategies for severely burned patients. (Cambiaso-Daniel et al., 2018; Norbury et al., 2016b; Powers, 2003; van Langeveld et al., 2017; Vinaik et al., 2019).

The optimal therapy for patients with severe burns involves a multidisciplinary approach and requires coordinated efforts among various healthcare specialists, including plastic surgeons, nurses, nutritionists, physiotherapists, and occupational therapists. Efficient transport and pre-hospital management are essential for improving the prognosis of burn patients, and transfer to specialized burn centers is often necessary.

2. Evaluation of the burn lesion

Assessing post-burn injuries is essential to make appropriate management decisions in treating these injuries. The skin, the largest organ of the body, protects against fluid loss, infection, and radiation and has multiple functions, including thermoregulation and interpersonal interactions. Post-burn injuries primarily affect the first two layers of the skin: the epidermis and the dermis.

The epidermis, the outermost layer of the skin, is composed of keratinocytes, melanocytes, Langerhans cells, and other inflammatory cells. The epidermis is the most susceptible to injuries and can undergo permanent pigmentation changes following burn injuries. The dermis, a deeper layer, is composed of the papillary dermis and the reticular dermis. It contains capillaries that supply nutrients to dermal cells and plays a role in maintaining the hydration of the skin matrix. The dermis, like other structures derived from the mesoderm, heals not through regeneration but through fibrosis and scarring.

Thermal injuries result in protein denaturation and loss of cellular membrane integrity due to the application of heat at the cellular level. The duration and temperature of contact have a synergistic effect on cellular necrosis. Following a thermal injury, a central area of necrosis called the "coagulation zone" occurs, surrounded by an ischemic stasis zone and a peripheral zone of hyperemia. Necrosis of the stasis zone can be prevented through adequate fluid resuscitation and infection prevention. (Js et al., 1999; Rico et al., 2002)..

The depth of post-burn injuries can vary and may involve one or more layers of the skin, subcutaneous fat, muscles, or even bone structures. There are different degrees of burns, including first-degree burns (superficial), second-degree burns (superficial dermal), second-degree burns (deep dermal), and third-degree burns (full thickness). Accurately assessing the depth of the injury is important for determining the appropriate treatment.

There are several methods for assessing the depth of post-burn injuries, such as thermography, photometry, nuclear imaging, ultrasound, and serial biopsies. However, clinical evaluation performed by a burn specialist remains the gold standard as no technology has proven superiority over clinical assessment thus far.(Shin & Yi, 2016).

There are various mechanisms of thermal injury, including burns by flame and flash, scald burns, contact burns, chemical burns, and electrical burns. Each type of burn has specific characteristics and requires appropriate approaches and treatments.

In conclusion, the assessment of post-burn injuries is a complex and essential process in the management of burn patients. Understanding the physiopathology and mechanisms of thermal injury aids in making treatment decisions and achieving optimal outcomes in the healing of burn injuries.

3. Infection pathogenesis for burn lesions

Infections at the site of post-burn injuries are the result of thermal damage to the skin barrier and the suppression of local and systemic immune responses. The wound surface, especially in the case of deep or full-thickness burns, becomes a conducive environment for the colonization and proliferation of microorganisms. Within the first 48 hours, the wound surface is primarily colonized by Gram-positive bacteria such as Staphylococci. Subsequently, these wounds can be contaminated by various other microorganisms, including Gram-positive bacteria, Gram-negative bacteria, and yeasts. (Church et al., 2006; Erol et al., 2004).

The formation of biofilm is an important process in the pathogenesis of infections at the site of post-burn injuries. Biofilm consists of aggregates of microorganisms attached to the surface and protected within a matrix of polysaccharides. The biofilm acts as an effective barrier against antimicrobial agents and the host's immune system, allowing for persistent colonization and infection of the wounds. Bacteria within the biofilm undergo phenotypic changes, producing altered virulence factors and exhibiting reduced metabolic rate and mobility. Persistent cells within the biofilm exhibit resistance to treatment with antibiotics and antiseptics. (Church et al., 2006; Sutherland, 2001).

Different microorganisms can colonize post-burn injuries, originating from the patient's skin, gastrointestinal tract, respiratory tract, or being transferred through contact with contaminated surfaces or the hands of healthcare personnel. Staphylococcus aureus has long been the primary etiological agent of infections at the site of post-burn injuries. However, currently, Pseudomonas aeruginosa from the patient's gastrointestinal flora and/or the hospital environment is the most common cause of infection. The emergence of antimicrobial resistance complicates the treatment of infections in post-burn injuries.

Pathogenic microorganisms, such as Pseudomonas aeruginosa and Staphylococcus aureus, produce virulence factors that facilitate colonization, evasion of the immune system, and tissue destruction. These bacteria also possess antimicrobial resistance traits, which make infections at the site of post-burn injuries more challenging to treat. (Church et al., 2006).

In conclusion, infections at the site of post-burn injuries are the result of colonization and proliferation of microorganisms in the favorable environment provided by the wound surface and the formation of biofilm. Various bacteria, particularly Pseudomonas aeruginosa and

Staphylococcus aureus, are implicated in infections at the site of post-burn injuries and possess virulence factors that contribute to tissue invasion and antimicrobial resistance. Treating infections at the site of post-burn injuries is challenging due to antimicrobial resistance and biofilm persistence.

4. Sepsis and infections predictibility with the help of biomarkers

Studies have shown that biomarkers, including proteins such as procalcitonin, interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and C-reactive protein (CRP), can be used to predict the risk of infections, sepsis, and clinical outcomes in patients with post-burn injuries.

Biomarkers, including proteins and combinations of variables, can be used to predict the risk of infection, sepsis, multiple organ failure, and survival prognosis. The expression of proinflammatory and anti-inflammatory cytokines, such as TNF-alpha, IL-8, and IL-6, can be utilized to predict the progression of patients and complications associated with burns. (de Bandt et al., 1994; Kraft et al., 2015; Toliver-Kinsky et al., 2018). Additionally, biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), and leptin can be useful in evaluating inflammation and infections in septic burn patients. (El Ayadi et al., 2018; Mann et al., 2011).

Clinical characteristics such as age, burned body surface area, and the presence of inhalation injuries can also be taken into consideration to estimate the prognosis of patients.

Biomarkers can also be used to monitor fluid resuscitation, renal function, and the healing of post-burn injuries. (El Ayadi et al., 2018). The use of biomarkers in managing patients with severe burns can contribute to early intervention, reducing morbidity and mortality, and lowering treatment costs. The addition of proteomic data adds a higher level of precision.(Finnerty et al., 2008).

5. Infections classification in burn patients

Infection of post-burn wounds is a significant issue in the treatment of burn patients as it can delay healing and lead to the formation of additional scar tissue. Invasion of microorganisms into subdermal tissues can cause bacteremia, sepsis, and multiple organ failure syndrome. The clinical diagnosis of post-burn wound infections is based on monitoring vital signs and inspecting the entire surface of the burn during dressing changes. Local signs of infection include the transformation of a partial-thickness injury into a full-thickness injury, rapid spread of cellulitis into the healthy tissue surrounding the burn, rapid separation of necrotic tissue, and tissue necrosis. In the past, post-burn wound infections were classified based on changes in the wound and/or appearance of the eschar, timing of onset, and associated mortality. Effective treatment of burn wound infections involves frequent dressing changes and administration of appropriate antibiotics based on microbiological culture results and susceptibility.

Post-burn wound infections can be classified into several types, including impetigo, cellulitis, and invasive infections. Diagnosis is made by examining the appearance and odor of the wound, but microbiological testing is also necessary to identify the specific pathogen. Patients with signs of systemic infection require additional analyses such as blood cultures, urine cultures, and cultures from the wound site. Effective treatment involves the use of antibiotics based on microbiological culture results and adjusting therapy based on susceptibility.

In addition to post-burn wound infections, patients with severe burns can develop other infectious syndromes. One of these is the hypermetabolic syndrome, characterized by altered inflammatory and immune response, which can lead to infections, multiple organ failure, and death. Other infections encountered in burn patients include respiratory, gastrointestinal, urinary tract, and catheter-related infections. The diagnosis and treatment of these infections vary depending on symptoms, clinical signs, and microbiological culture results.

It is important for burn patients to be carefully monitored for signs of infection and to receive prompt and adequate treatment to prevent serious complications.

6. Prevention and monitoring infectious complications in the severely burn patients

Studies have shown that the use of topical antibiotics in the treatment of severe burn injuries can reduce morbidity and mortality in patients. However, the effectiveness of these antibiotics may vary due to the rapid development of microbial resistance. It is important to establish standardized methods for detecting and monitoring antimicrobial resistance in modern burn units.

Clinical studies have not demonstrated a greater benefit of systemic antibiotic administration in preventing infections in burn patients compared to the use of topical antibiotics in combination with surgical excision. In a study involving burned children, prophylactic antibiotic administration did not prevent the development of post-burn wound infections and actually led to a higher rate of secondary infections and longer hospital stays. Therefore, systemic antibiotic administration should be used selectively and for a short duration of time.

Selective intestinal decontamination can reduce the colonization of post-burn wounds with intestinal bacteria and associated infections. However, decontamination regimens must be carefully selected to avoid disrupting beneficial intestinal flora. Early enteral nutrition and early surgical excision of post-burn wounds can also contribute to reducing burn wound infections.

Prevention of tetanus is a crucial concern in the treatment of burn patients as thermal injuries can create a contaminated open wound. Active and passive immunization should be administered based on the patient's immunization status.

Infection control in burn units involves strict hygiene measures, appropriate isolation of patients and healthcare personnel, monitoring of microbial cultures, and selective use of antibiotics based on antimicrobial resistance. The infection control program should be tailored to the specific needs of the burn unit and aim to reduce and eliminate pathogenic and antibiotic-resistant organisms.

In the future, it is necessary to employ standardized and reproducible methods for monitoring infections in burn wounds, as well as develop specific antibiotic susceptibility tests for burn injuries. The treatment program should include rotation of antimicrobial agents to prevent the development of microbial resistance. Tratamentul complicațiilor infecțioase la pacienții arși

The antibiotic treatment of severely burned patients presents challenges and requires a judicious approach. Prophylactic antibiotic administration is not recommended, and perioperative antibiotic therapy is only accepted in the absence of documented infections. (Church et al., 2006; Lachiewicz et al., 2017; Ramos et al., 2017).

Modern infection prevention protocols are effective in reducing the spread of antibiotic-resistant pathogens in burn units. Antibiotic selection is based on the results of antibiograms, and empirical administration in cases of systemic infections is followed by de-escalation with targeted therapy.

It is important to have the treatment monitored by a clinical pharmacist in order to ensure the effective and safe dosing of antibiotics in these patients. (Martyn, 1986).

Antifungal treatment poses challenges, and the excision of infected tissues and the use of antifungal agents are essential. Aggressive and early excision of burn wounds is crucial for the favorable outcome of patients. (Cambiaso-Daniel et al., 2018; Jaskille et al., 2010).

A key element is the implementation of an antimicrobial stewardship program in a burn center, involving a multidisciplinary approach with plastic surgeons, anesthesiologists, and infectious disease specialists to ensure the best clinical outcomes for the patient and reduce the development of further antibiotic-resistant bacteria. (Lachiewicz et al., 2017).

7. Management of infectious complications with multidrugresistant bacteria in the severely burn patient

Managing complications of multidrug-resistant bacterial infections in severely burned patients is a significant challenge. The most concerning pathogens are the multidrug-resistant strains of Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, and methicillin-resistant Staphylococcus aureus (MRSA). (Kanamori et al., 2017).

Risk factors for acquiring these multidrug-resistant bacteria in burn patients include prolonged hospitalization, prior exposure to antibiotics, and the use of invasive medical devices. Infection prevention is based on strict infection control measures, including hand hygiene, contact isolation, and disinfection of objects and surfaces. (Lachiewicz et al., 2017).

Diagnosing MDR infections in burn patients is challenging and requires careful evaluation. The treatment of MDR infections involves controlling the source of infection, using appropriate antibiotics, and engaging in an antimicrobial stewardship program. There is a growing interest in the development of new antimicrobials for the treatment of MDR infections in burn patients, such as firmicidin, fusidic acid, usnic acid, and phage therapy. However, further research is needed in this field. (Sevgi et al., 2014; Vinaik et al., 2019).

8. Conclusions and personal contributions

8.1. Conclusions

In conclusion, medical advancements in the management of severe burns encompass a wide range of aspects, from innovations in fluid resuscitation to advancements in nutritional and immunological support, pulmonary therapy, and the management of post-burn wounds. Additionally, a central aspect is the rigorous implementation of infection control protocols. (Lee et al., 2014).

In this discussion, it is essential to emphasize that infections are among the most frequent and severe complications that occur in the context of severe burns. There are several risk factors for the development of these infections. Firstly, the integrity of the skin is compromised in burn injuries, removing the natural barrier of protection against pathogens. Secondly, the immune function of the body can be impaired, leading to immunosuppression and increased susceptibility to infections. This risk can be further amplified by inhalation injuries and invasive medical procedures such as vascular access, intubation, and urinary catheterization.

The management of infections in patients with burns is an extremely dynamic and complex process that extends throughout the patient's hospitalization. This process takes into consideration a series of variables, including the specific therapy applied in the burn unit and the individual characteristics of the patient.

An essential part of this procedure is the prompt identification of patients at high risk of developing complications. This identification facilitates timely diagnosis, allowing for the rapid implementation of appropriate therapeutic measures. In this way, both morbidity and mortality are significantly reduced.

The most important therapeutic goal for a severely burned patient is to achieve robust immunity as quickly as possible, thereby preventing most infectious complications. This goal is facilitated by a combination of systematic supportive measures and specific approaches.

The early initiation of enteral nutrition, for example, can play a significant role in improving the overall condition of the patient. Similarly, early complete excision of deep burns followed by grafting is another effective approach that reduces the risk of infection and associated morbidity

and mortality in severely burned patients. Additionally, strict adherence to infection control protocols is crucial, as mentioned in the introduction.

Furthermore, it is important to avoid empirical broad-spectrum antibiotic prophylaxis. Its use is desirable only as perioperative prophylaxis for excision and grafting procedures, to prevent bacterial seeding into the systemic circulation.

Instead, antibiotic therapy should be guided by targeted antimicrobial susceptibility testing, with a significant emphasis on de-escalation of therapy once empiric broad-spectrum coverage has been initiated. Constant reassessment of the patient's condition, vital parameters, and response to treatment is crucial for selecting the most appropriate therapy and achieving the best possible prognosis.

In addition, it is recommended to limit invasive and unnecessary catheterization to reduce the risk of secondary infections. Thus, the effective management of infections in patients with severe burns involves an integrated and holistic approach that extends throughout the entire hospitalization period.

In this regard, the urgent need for continuous improvements in the diagnosis of infections in patients with burns is emphasized. Unfortunately, the clinical symptoms in these patients are not specific, which means that the signs and symptoms that could indicate an infectious syndrome can easily be confused with the perilesional inflammatory signs of the burn. This can delay the establishment of a precise and rapid diagnosis, which is essential to initiate appropriate treatment.

Among the feared etiological agents are the bacteria that make up the ESKAPE group, a collection of pathogens known for their propensity to cause severe infections in patients with extensive burns. These bacteria pose a significant therapeutic challenge due to their rapid ability to develop antibiotic resistance, complicating the management process. As a result, the effectiveness of last-resort antibiotics is alarmingly eroding in the face of these bacteria.

Indeed, we are witnessing a widespread proliferation of these bacterial species, both within healthcare facilities and in the natural environment, a concerning phenomenon that is prompting healthcare professionals to resort to treatment strategies involving older-generation antibiotics such as Colistin. This has pushed the boundaries of antibiotic research in order to counter the ongoing evolution of resistant bacteria.

Moreover, medical staff need to be aware that a considerable percentage, potentially up to three-quarters, of all patients admitted to burn care units, regardless of the severity of burns or associated pathologies, may be contaminated with at least one type of ESKAPE bacteria.

In the context of infections in severely burned patients, it is important to shift our attention to another medical issue they face. In addition to the considerable risk of infection with multidrug-resistant bacteria, burn patients also face an increased risk of fungal infections. Therefore, a comprehensive approach to infections in burn patients must encompass a careful understanding of both bacterial and fungal infections, highlighting the complexity of the challenges these patients encounter.

The approach to fungal infections in the context of severe burns represents a substantial clinical challenge, as they are more commonly observed in patients with a significant percentage of total body surface area burned, those with compromised immune systems, the elderly, or those who have received empiric broad-spectrum antibiotic therapy. In clinical antifungal therapy, it is crucial to make a clear distinction between fungal colonization and true infection.

However, it is regrettable that in the context of burn patients, the presence of clinical symptoms often proves nonspecific, and the sensitivity of diagnostic results varies.

Therefore, a series of strategic measures are necessary. Firstly, it is vital to ensure adequate systemic support to the patient in order to improve immunological competence, thus facilitating a favorable recovery. Additionally, surgical procedures such as early and adequate excision of post-burn eschar followed by effective coverage of resulting defects are key components in reducing the risk associated with fungal infections in severe burns.

Therefore, this complex of factors needs to be carefully considered in the effort to minimize complications and optimize outcomes in the management of fungal infections in patients with severe burns.

8.2. Personal contributions

Performing a review study on the topic of infectious complications in burned patients, including the development of a comprehensive management plan, throughout Chapter 12, from paragraph 13 to the end of the Results section (Grosu-Bularda et al., 2021; LAZARESCU et al., 2021).

Analyzing the observation records and data from Hippocrates of patients hospitalized during the period of 01.05.2016 - 01.05.2018, as well as those from 01.01.2019 - 31.12.2019, to identify the main data regarding fungal infections in severely burned patients, in paragraph 7 of Chapter 11 and paragraph 4 of Chapter 13, with the following conclusions. (Lazarescu et al., 2020):

1. Patients who suffered from Candida spp. infections had an average burned surface area of 47%, and 22% of them had grade III injuries (paragraph 13, Chapter 11).

2. Out of the 26 patients with positive cultures, 16 of them died during the study (paragraph 15, Chapter 11).

3. The predominant comorbidity among patients with positive cultures was arterial hypertension (paragraph 12 and 17, Chapter 11).

4. Four out of five patients with positive cultures for Aspergillus died (paragraph 21, Chapter 11).

5. The average burn surface area in patients with Aspergillus was approximately 72% (paragraph 19, Chapter 11).

6. During the year 2019, the average burn surface area was 39% (paragraph 1, Chapter 13).

7. Fungal colonization can occur at any time during the hospitalization period; therefore, rigorous monitoring is necessary and should be performed periodically throughout the patient's stay (paragraph 7, Chapter 13).

The analysis of observation records and data from the Hippocrates system of patients admitted to the Intensive Care Unit for Severe Burns during the period 01.01.2019-31.12.2019, for the study of the prevalence of bacteria from the ESKAPE group in severely burned patients, led to the following conclusions:

1. 51 patients presented at least one pathogen from the ESKAPE group (paragraph 3, main results subsection, chapter 14).

2. No significant statistical differences were found between the presence and absence of ESKAPE bacteria regarding mortality (paragraph 9, results subsection, chapter 14).

3. It was observed that ESKAPE bacteria have a higher susceptibility to develop antibiotic resistance (paragraph 11, results subsection, chapter 14).

In conclusion, I would like to emphasize once again the need for improved protocols regarding the use of antibiotics both in burn patients and in the treatment of other infectious diseases. This is necessary to avoid the increase of antibiotic resistance. It is also crucial to strictly adhere to hygiene protocols, clinical pathways, and modern recommendations for the treatment of burn patients.

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Publicated papers and posters

Articles

1. Grosu-Bularda, A., **Lazarescu, A.L.**, Andrei, M.-C., Ionescu, D.A., Frunza, A., Grama, S., Stoian, A., Hodea, F.V., Neagu, T.P., Popescu, S.A., Lascar, I., 2021. Infectious Complications in Severely Burned Adult Patients-Diagnostic and Therapeutic Algorithm. Mod. Med. 28. – *în teză Cap. 13, p.104-131* https://medicinamoderna.ro/wp-content/uploads/2021/03/Infectious-Complications-in-Severely-Burned-Adult-Patients-Diagnostic-and-Therapeutic-Algorithm-3.pdf
2. **LAZARESCU, A.-L.**, Grosu-Bularda, A., ANDREI, M.-C., Frunza, A., Grama, S., STOIAN, A., Hodea, F.-V., IONESCU, D., Popescu, S., LASCAR, I., 2021. Burn infections characteristics: A review. Romanian J. Med. Pract. 16, 32–41. https://doi.org/10.37897/RJMP.2021.1.6 – *în teză Cap. 1, p.15; Cap. 5, p.42-53*
3. **Lazarescu, A.L.**, Grosu-Bularda, A., Andrei, M.-C., Grama, S., Frunza, A., Ionescu, D.A., Arghir Popescu, S., Neagu, T.P., Lascar, I., 2020. Fungal Infections in Major Burns - 2 Years Overview. Med. Mod. - Mod. Med. 27, 185–190. - *în teză Cap. 12, pag. 91-103* https://doi.org/10.31689/rmm.2020.27.3.185
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6. Andrei, M.-C., Grosu-Bularda, A., Vermesan, O., Popescu, S. A., Chivu, A., Al-Falah, K., **Lazarescu, L.**, Neagu, T. P., & Lascar, I. (2018). Negative Prognostic Factors in Severe Burns – Implication for Clinical Outcome. *Modern Medicine*, *25*(2). https://medicinamoderna.ro/https-medicinamoderna-ro-negative-prognostic-factors-in-severe-burns-implication-for-clinical-outcome/ - *în teză Cap. 11, pag. 81-90*

Posters

1. Fungal Infections in Major Burns - 2 Years Overview – Lăzărescu A.L., Andrei M.C., Bularda Grosu A., Vermeșan O, Lascăr I., Popescu Ș. A.