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A Nasal Localization of Abrikossof Tumor Observed to Yaounde Reference Hospital

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Abstract

Background/Aim: Abrikossof's tumor or granular cell tumor is a rare tumor. The cervicofacial localization is the most common. The aim of this report case was to show a rare case of nasal localization, to the 48-year old patient, treated in poor medical condition. **Case presentation:** The patient consults late with enormous nasal mass involving for five years. After biopsy and facial CT-scan, a surgical procedure was performed. The evolution was good and the final pathology confirms the diagnosis. The objective of this case report was to show the originality of the presentation and the difficulties for management in poor medical environment. **Conclusion:** Abrikossof's tumor is a rare benign tumor but whose preferential development occurs at the expense of the ENT sphere. Large forms remain the preserve of poor environments. The diagnosis is pathological and the treatment is surgical.

Keywords

Abrikossof Tumor, Nasal Cavity, Yaounde

1. Introduction

Abrikossof's tumor or granular cell tumor is a rare tumor, is a nodular benign tumor. The first description was a tongue description on 1929 by Abrikossof [1]. Any part of the body can be affected, but the most localized is cervicofacial (45% - 65%) [2]. The main facial localization is intra-oral, lips and parotid gland (70%). A case of nasal localization is rarely found in the literature.

It is more common in black people and mainly women are affected.

The anatomopathological examination confirms the diagnosis. We can observe the possibility of local recurrences. The treatment is surgical and guarantees a good evolution.

The interest of this case report is the nasal localization that is rare. The authors also present the difficulties of management in our environment.

2. Observation

This is a 48-year old patient, with no history of alcohol-smoking. He consulted in our department for a large mass evolving for 5 years. The clinical presentation was dominated by an obstructive nasal syndrome (nasal obstruction and hyposmia) without epistaxis.

On physical examination, we had a facial deformity with a large right nasal mass. The mass extended from the nasal pyramid to the philtrum; It invaded the controlateral nasal fossa with left deviation of the columella, and disappearance of the nasolabial fold homolateral The skin opposite was normal.

Endonasal examination found a total filling of the two nasal cavities by a mass of reddish color, and soft consistency; not bleeding on contact. It continued into the oropharynx (**Figure 1** and **Figure 2**)

The CT scan of the facial mass showed a mass of tissue density of the nasal fossae with lysis of the nasal septum and extension towards the three stages of the pharynx (**Figure 3** and **Figure 4**).

A biopsy carried out was in favor of an ulcerated fibro-inflammatory polyp.

A surgical excision by the trans-facial approach (right para-latero-nasal of Moure) was performed (**Figure 5**). The surgical procedure was performing under general anesthesia. The naso or oro-tracheal intubation was not possible, because the tumor was extended at the level of oropharynx. So we did the tracheostomy first under local anesthesia. After incision we did the resection of the mass. The bleeding was not abundant. The follow up was simple, we remove the

Figure 1. Clinical aspect of the patient.

Figure 2. Profile view of the patient.

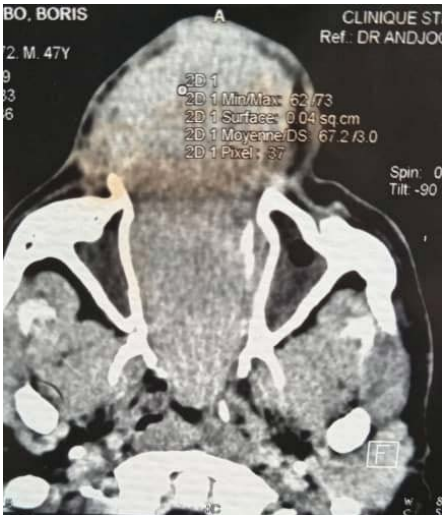

Figure 3. CT view of the nasal tumor nasopharynx and septal lysis.

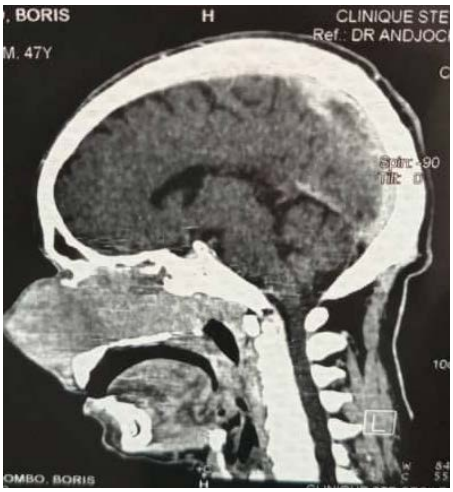

Figure 4. Extension of the mass to the nasopharynx and oropharynx.

compresses inside the post-operative cavity after 3 days, and the patient did the nasal washing with saline water $9_{0/00}$ for two weeks. The duration of admission was for 5 days. Histological analysis concluded in a granular cell tumor (Figure 6). More than a year after surgery the patient is doing well, no signe of recidive (Figure 7).

Figure 5. Per-operative view of the tumor.

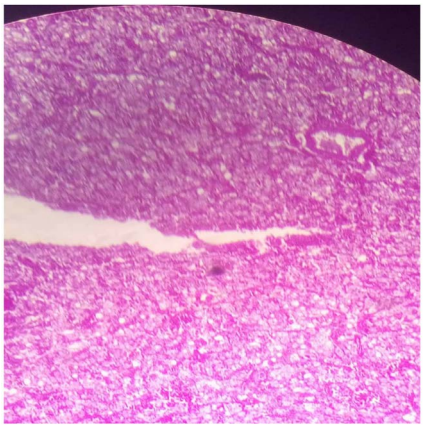

Figure 6. Microscopic view: proliferation in layers of large cells, with microgranular eosinophilic cytoplasm and a round nucleus.

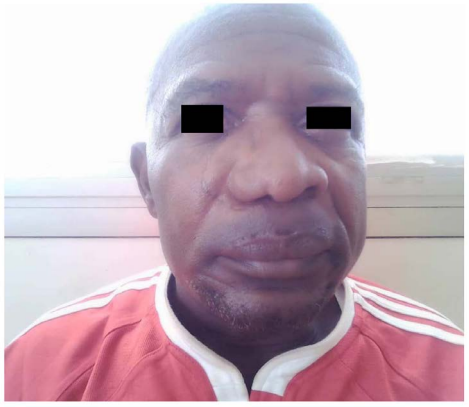

Figure 7. Post-operative aspect of the patient (after 6 month).

3. Discussion

Granular cell tumors or Abrikossof's tumors are rare benign tumors. They represent 0.019% to 0.03% of all tumors [3]. They develop at the expense of any anatomical site but the cervicofacial localization is the most common; particularly lingual [4]. The endonasal localization of Abrikossof tumors is unusual and rarely reported in the literature.

The epidemiological aspects: our patient has 48 years old and was a man. The abrikossof tumor appears most in the women, the female sex is particularly affected with a sex ratio of 2/1 [5]. That was one of the particularities of our case. The age of the patient is similar to the literature review, this affection occur at any age with a peak frequency between 20 - 60 years [6].

Clinically it appears as a protruding nodule of about one to 8 centimeters that is firm to palpation, non-inflammatory. The voluminous form described in our observation is probably due to the delay in diagnosis and management. In literature review, most of case are small most of them are discovered under 2 cm [7] the patients consult early. In our environment the low socio-economic level, ignorance make the patient consult late. And also the nasal localization is less visible than other (oral cavity…).

Surgical treatment allows total removal of the tumor and reduces the risk of recurrence. The voluminous nasal localization also poses a problem of procedure, the enormous size make us to choose the external approach than the endonasal endoscopic procedure. The patient pass through a tracheotomy procedure first, because the extension to the nasopharyx and oropharynx make the normal intubation difficult. Certain forms can also pose problems of reconstruction in the event of a delabrous exercise [6] the patient in our observation was able to benefit from a simple edge-to-edge closure.

The diagnosis is pathological, immunohistochemistry can help to specify the diagnosis, and reveals a nervous origin (Schwann cells) [5].

4. Conclusion

Abrikossof's tumor is a rare ubiquitous benign tumor but whose preferential development occurs at the expense of the ENT sphere. The nasal localization is rare. Large forms remain the preserve of poor environments. The diagnosis is pathological and the treatment is surgical.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Influence of Age on the Clinical and Prognostic Features of Tetanus in Mali

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Abstract

Background: The regression of post-vaccination immunity with age exposes elderly subjects to certain infectious diseases, in particular tetanus. The aim was to compare the clinical and prognostic features of tetanus according to the age of patients. **Methodology**: Analytical study of the files of patients hospitalized for tetanus in the Infectious Diseases Department at Point "G" University Teaching Hospital from 2013 to 2019 with retrospective collection. According to age, three groups of patients were formed: group I (<18 years), group II (18 - 59 years) and group III (≥60 years). The study variables were socio-demographic, clinical and prognostic. The One-way ANOVA and Chi-square statistical tests were applied with a significance level $p = 0.05$. **Results**: In total, 202 cases of tetanus were recorded or 7.3% of admissions. The mean age was 41.9 ± 15.6 years (range, 6 and 85 years) with a sex ratio of 19.2. According to the age grouping, group II was predominant (79.2%) followed by group III (14.9%) with respective mean ages of 39.2 ± 10.6 and 67.3 ± 6.5 and sex ratio of 39 and 29. Workers (33.3%), farmers (25.8%), traders (19.7%) and drivers (7.1%) represented the most important occupations most at risk. Clinically, bad general condition ($p < 0.001$), trismus ($p = 0.001$), dysphagia ($p = 0.009$) and complications during hospitalization ($p = 0.028$) were seen more frequently in group III patients compared to younger ones. From a prognostic point of view, patients in group III were at greater risk to develop a severe form of tetanus ($p = 0.021$) with higher mortality compared to other age groups ($p < 0.001$). **Conclusion**: Tetanus is more prevalent in men. Complications and mortality increase with age. It is important to include booster immunization of adults in existing national programs in order

to reduce disease-related morbidity and mortality in this age group.

Keywords

Tetanus, Elderly, Clinical, Prognosis, Mali

1. Introduction

While tetanus has almost disappeared from northern countries because of vaccination and improved hygiene, it remains a significant public health problem in developing countries where immunization programs are insufficiently implemented [1] [2] [3] [4] [5]. The annual incidence of tetanus is estimated at nearly one million cases [5]. The disease burden is very heavy in resource-limited countries [3] [5] [6] [7]. In fact, in 2015, Sub-Saharan Africa recorded 44% and 36% of deaths related to neonatal tetanus and that of children and adults respectively in the world [8]. Several studies on tetanus have been carried out in Africa but the main emphasis was on epidemiological and prognostic aspects. And it appears that tetanus mainly affects young adult males [7] [9]-[17]. In this sense, Dao *et al.*, in Mali in 2009 found a hospital frequency of 5.9% with a sex ratio of 2.17 and an average age of 39 years [9]. As for Sondo *et al.*, in 2018 in Burkina Faso, the hospital frequency of tetanus was estimated at 2.6% with a sex ratio of 4.1 and an average age of 29.2 years [15].

Tetanus is a bacterial disease caused by Clostridium tetani, a spore-forming, cosmopolitan germ, which secretes a potent neurotoxin. C. tetani spores enter the body through contaminated skin or tissue lesions and sometimes through puncture wounds [2] [3]. It is a serious disease, however preventable by vaccination [3] [5] [6].

It is well known that immunity to the tetanus vaccine acquired in childhood decreases with age, thus exposing adults to the disease [6] [18] [19]. However, there is no vaccine booster program for adults other than women during pregnancy [6]. How significant is the morbidity and mortality from tetanus depending on the patient's age? The influence of age on clinical signs and the fate of tetanus patients in our countries have not yet been addressed, justifying this study that the objective was to perform a comparison of the clinical and prognostic features of tetanus according to the groups of ages.

2. Patients and Methods

This was a retrospective and analytical study using hospital data from January 2013 to December 2019, *i.e.* a period of seven (7) years. The Infectious Diseases Department of the Point "G" University Teaching Hospital in Bamako was the study setting. It's the referral service for infectious pathologies in Mali with an inpatient capacity of 30 beds in addition to a non-functional Intensive Care Unit. Severe tetanus cases requiring intensive care are transferred and managed

in the Intensive Care Department.

All complete records of patients hospitalized for tetanus during the period were included except those patients who died within 24 hours of hospitalization.

The diagnosis was just clinical. Tetanus was defined by a set of signs namely: trismus with the presence of Armengaud's captive tongue depressor sign; generalized or localized contracture; the presence or absence of a gateway; the presence or absence of spontaneous paroxysm, painful or caused by noise or light, the presence or absence of dysphagia [20] [21].

The management consisted of:

- hospitalization with neurosensory isolation and restriction of food intake by the oral route;
- administration of muscle relaxants drugs to fight against muscle spasms;
- administration of antibiotics and tetanus immunoglobulins;
- the application of a vaccination protocol by tetanus toxoid;
- the gateway treatment when it was found.

Three groups of patients were formed according to their age:

- Group I: corresponded to patients under 18 years-old. At this age, the immunity to the tetanus vaccine acquired at birth remains protective;
- Group II: for ages between 18 and 59 years-old;
- Group III: for patients at least 60 years-old.

The study variables were grouped into socio-demographic variables (age, sex, occupation, place of residence); clinical variables (gateway, type of lesion, clinical signs) and development variables (outcome of hospitalization, length of stay).

Regarding clinical signs, the change in clinical state corresponded to a deterioration in the subject's overall state of health [22].

We assessed the clinical severity of tetanus using the Dakar score [23]. Tetanus was considered benign for a Dakar score between 0 and 1. It was moderate if the score varied between 2 - 3 and severe when the score was between 4 and 6.

Data collected was entered using Epidata entry 3.1 software and analyzed with Statistical Package for Social Science (SPSS) version 22 software.

A descriptive analysis first made it possible to appreciate the distribution of the values of variables as well as the parameters of central tendencies. Then, statistical tests were applied with a significance level $p = 0.05$. The 1-way ANOVA test was used to compare means in the three age groups. The chi-square test made it possible to compare the proportions. Fisher's test was used when the theoretical cell size was less than 5. Analyzes were performed on anonymized data collected as part of routine patient care. We obtained an authorization from the Head of Department for the data using and the conduct of the study. No further investigation was conducted.

3. Results

3.1. Main Features

During the period, 202 patients were hospitalized for tetanus out of a total of

2,782 admissions, for a hospital frequency of 7.3%.

The mean age of the patients was 41.9 ± 15.6 years with ranges of 6 years and 85 years. Men represented 95% of the sample (n = 192) avec a sex ratio of 19.2. The mean age of the men was 42.6 ± 14.9 years and that of the women was 27.6 ± 21.5 years ($p < 0.001$). Most of the patients lived in couple (73.8%) and resided in the city of Bamako (70.3%). The occupations most exposed to tetanus were manual workers (33.3%), farmers (25.8%), traders (19.7%) and drivers (7.1%). Before admission to the Infectious Diseases Department, patients were first seen and cared for in another hospital (32.7%) or a referral health center (19.8%). The results are shown in Table 1.

Figure 1 illustrates the distribution of patient by demographic data. In terms of numbers, patients in group II (18 - 59 years old) were the most represented (79.2%) followed by those in group III (60 years and over) (14.9%); and their sex ratio was largely in favor of men, respectively 39 and 29.

Table 1. General characteristics of the sample.

Variables	n (%)
Patient sex (n = 202)	
Male	192 (95.0)
Female	10 (5.0)
Marital status (n = 202)	
In couple	149 (73.8)
Single life	53 (26.2)
Place of residence (n = 202)	
Bamako	142 (70.3)
Outside Bamako	60 (29.7)
Occupation (n = 198)	
Worker	66 (33.3)
Farmer	51 (25.8)
Trader	39 (19.7)
Driver	14 (7.1)
Official	11 (5.6)
Students	6 (3.0)
Housewives	6 (3.0)
Other informal sectors	5 (2.5)
Provenance (n = 202)	
Hospital	66 (32.7)
CsREF*	40 (19.8)
Home	36 (17.8)
Private clinic	28 (14.1)
CSCOM**	18 (9.1)

*CsREF: Referral Health Center; **CSCOM: Community Health Center.

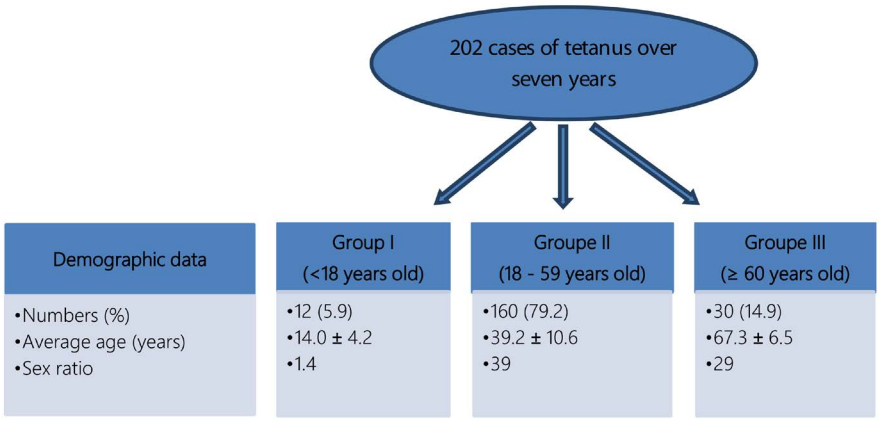

Figure 1. Demographic data of patients by age group.

3.2. Age Influence on Clinical Characteristics of Patients

Clinically, the general condition of the patients gradually deteriorated with age. On admission, bad clinical condition was observed more frequently in group III patients ($p < 0.001$). It was the same for trismus ($p = 0.001$), dysphagia ($p = 0.009$) and the occurrence of complications during hospitalization ($p = 0.028$). Systolic blood pressure ($p = 0.007$), diastolic blood pressure ($p = 0.028$), pulse ($p = 0.029$), and body mass index ($p = 0.001$) were higher in group III patients compared to groups II and I. However, paroxysm, respiratory distress, incubation and invasion times were not significantly influenced by patient age. **Table 2** shows the distribution of clinical signs by age.

3.3. Age Influence on the Prognosis of Tetanus

Table 3 presents elements for assessing the prognosis of patients according to the three age groups. On admission, patients in group III were at greater risk to develop a severe form of tetanus ($p = 0.021$). Patient mortality increased with age and was higher in group III compared to younger patients ($p < 0.001$). Age did not have a statistically significant influence on patient length of stay ($p = 0.116$).

4. Discussion

Tetanus remains a worrying pathology in the referral Department for Infectious Diseases in Mali. It represented 7.3% of all infectious pathologies treated during the period. This frequency varies according to the African studies between 5.3% and 11.8% [9] [14] [24].

Tetanus in Africa remains the preserve of young adults and males [3] [11] [14] [24] [25] [26] and that was the case in our study. The mean age of our patients was 41.9 years with a sex ratio largely predominant for men (20 men for a woman). This observation could be explained by the anti-tetanus immunization policy for girls and pregnant women during antenatal consultations, which provides them with long-term protection compared to men [2] [7] [27]. On the other hand, tetanus is more often seen in elder women in developed countries,

Table 2. Distribution of clinical data according to age groups.

Variables	Groupe I n (%)	Groupe II n (%)	Groupe III n (%)	P
Clinical condition				
Well	9 (75.0)	115 (71.9)	9 (30.0)	
Bad	3 (25.0)	45 (28.1)	21 (70.0)	<0.001
Trismus				
Absent	2 (16.7)	2 (1.2)	0 (0)	
Present	10 (83.3)	158 (98.8)	30 (100)	0.001
Paroxysm				
Absent	2 (16.7)	33 (20.6)	3 (10.0)	
Present	10 (83.3)	127 (79.4)	27 (90.0)	0.386
Dysphagia				
Absent	10 (83.3)	111 (69.4)	13 (43.3)	
Present	2 (16.7)	49 (30.6)	17 (56.7)	0.009
Respiratory distress				
Absente	12 (100)	151 (94.4)	28 (93.3)	
Presente	0 (0)	9 (5.6)	2 (6.7)	0.674
Complications				
Absent	7 (58.3)	77 (48.1)	7 (23.3)	
Present	5 (41.7)	83 (51.9)	23 (76.7)	0.028
Mean values ± standard deviation				
Incubation time (days)	8.8 ± 3.6	13.7 ± 18.3	14.0 ± 17.4	0.692
Invasion time (days)	1.5 ± 1.1	1.7 ± 1.1	1.8 ± 1.2	0.656
Systolic blood pressure*	114.0 ± 13.8	124.4 ± 17.9	137.3 ± 26.6	0.007
Diastolic blood pressure	70.5 ± 12.3	79.7 ± 11.7	84.7 ± 21.3	0.028
Pulse (ppm)**	98.1 ± 16.4	97.1 ± 17.7	106.4 ± 15.9	0.029
FR (cpm)***	28.7 ± 9.3	26.1 ± 6.0	28.4 ± 7.0	0.113
BMI (kg/m^2)	17.9 ± 7.4	22.5 ± 3.4	24.7 ± 4.0	0.001

*Blood pressure unity in mmHg; **ppm = beats per minute; ***cpm = cycle per minute.

Table 3. Distribution of prognostic data according to age groups.

Variables	Groupe I n (%)	Groupe II n (%)	Groupe III n (%)	P
Severity of tetanus (Dakar score)				
Benign (score 0 - 1)	4 (33.3)	48 (30.0)	3 (10.0)	
Moderate (score 2 - 3)	7 (58.3)	94 (58.8)	18 (60.0)	0.991
Severe (score 4 - 6)	1 (8.3)	18 (11.2)	9 (30.0)	0.021
Outcome of hospitalization				
Death	1 (8.3)	70 (43.8)	25 (83.3)	<0.001
Living	11 (91.7)	90 (56.3)	5 (16.7)	
Length of stay (days)	15.3 ± 7.7	11.2 ± 9.5	8.3 ± 13.3	0.116

men being protected by vaccination during required military service [19] [28] [29] [30]. Workers (33.3%), farmers (25.8%), traders (19.7%) and drivers (7.1%) were the socio-professional groups most exposed to tetanus in our study. These are professional activities with a risk of injury, especially when protective measures are not sufficiently applied. They are most commonly exercised by men, making them even more susceptible to tetanus than women [1] [7] [18]. Before admission to the Infectious Diseases department, more than half of our patients came from a referral health center or hospital, for etiological diagnostic problems or technical support. Some patients have even been taken care of beforehand by traditional healers. All of this could contribute to delaying diagnosis and treatment, which are aggravating factors for tetanus in our context [14] [31].

Patients in group III (over 60 years of age) tended to have an altered clinical condition on admission compared to younger patients. In addition, the symptomatology was more evident in these elderly patients through the presence of trismus, the manifestation of dysphagia and the occurrence of complications during hospitalization. A tendency for blood pressure to rise and pulse rate to increase was also noted in those over 60 years of age. These findings have been made by other authors who confirm the vulnerability of this age group compared to younger patients [24].

Aging is synonymous with carrying comorbidities such as diabetes, arterial hypertension, cancer, etc. [24] which are at risk of decompensation due to Clostridium infection and can thus contribute to worsening the clinical condition and prognosis. Although an incubation period of less than seven (7) days and an invasion period of less than 48 hours are generally considered to be indicative of a badprognosis [3] [5] [18], in our study there was no statistically significant difference for these two parameters depending on the age of the patients. The same was true of the paroxysm and respiratory distress. The small sample size in our study could explain these results.

In many countries, the lack of material and human resources in our hospitals contributes to justifying high mortality among tetanus patients [5] [7]. However, age is also a determinant of morbidity and mortality [3]. The aging of people is accompanied by senescence of the anti-tetanus immune system [3] [32] [33] [34] [35] justifying an increase in the incidence of tetanus cases but also the frequency of severe and fatal forms with age [3] [18] [36]. In our study, people over 60 were at greater risk of dying from tetanus than those younger. This result corroborates that of Tanon *et al.*, in the Republic of Côte d'Ivoire in 2017, who found that those over 60 were three times more at risk of dying from tetanus than the younger ones [17]. In Lagos, in 2005, a study on hospital mortality from tetanus came to the same conclusion [25]. Another Nigerian study in 2009 concluded that the only factor for survival during tetanus was young age [26]. There is great interest in stepping up disease prevention measures in favor of the elderly who are moreover vulnerable to other diseases due to age. We would like to emphasize here the interest in introducing the booster or catch-up tetanus vaccination in adults in order to limit the burden of the disease [34] [36]. But

beyond age, several other factors are often cited as contributing to patient mortality in our context, in particular the virulence of the Clostridium strain in question, the severity of the clinical signs, the insufficiency of materiel resources for intubate and ventilate cases of respiratory failure due to dysautonomia, as poverty limits patients' access to intensive care [5] [7].

The main limitation of our study concerns the incompleteness in the registration of patient records. This limit is frequent in retrospective studies.

5. Conclusion

Although vaccination is the best way to avoid tetanus, it remains a major public health problem with regard to the morbidity and mortality caused. In our context, tetanus is found much more in adult men and has a bad prognosis in the elderly. There is an interest in taking age into account in the clinical and prognostic assessment of tetanus cases. To reduce the burden of tetanus in adults, it is imperative to expand booster immunization to these vulnerable age groups through national immunization programs to ensure universal health coverage.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Current Problems of Diagnostics and Treatment of Purulent-Inflammatory Diseases and Sepsis in Medical Practice

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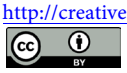

Abstract

Background: Poor treatment of burns can lead to sepsis and even death. Especially promising is the use of the method of fluorescence spectroscopy for its diagnostics. **The aim of the research** is to create a pathogenetic concept as the basis of a diagnostic and treatment model of purulent-inflammatory diseases and sepsis. **Material and methods:** The study lasted from 2001 to 2019 and included 4 stages. The experimental base of luminescent research at all stages was the luminescence laboratory of the Department of Experimental Physics of the Ivan Franko National University of Lviv. The study was performed by using optical monochromators MDR-2 and MDR-12. The excitation of the blood serum was performed with light with a wavelength of 280 nm, which corresponds to the glow region of human serum albumin. **Results:** The main indicators, used for the analysis, were the fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max}). The object of the study was samples of the blood serum of patients of the main and control groups. In the case of the presence of endogenous intoxication in the body, albumin binding centers are blocked by the products of bacterial metabolism and therefore such "pathological" albumin is unable to perform its functions, including transport and detoxification. **Conclusions:** The pathogenetic concept as the basis of the diagnostic and treating model of purulent-inflammatory diseases and sepsis was devised. In particular, the important role of albumin solution infusion in the treatment of the above-mentioned diseases was established.

Keywords

Purulent-Inflammatory Diseases, Sepsis, Burn Injury,

Method of Fluorescent Spectroscopy, Albumin Infusion

1. Introduction

The fundamental problem of modern medical science remains a significant improvement in the immediate and long-term functional and cosmetic results of surgical treatment of patients. Early detection of sources of infection and effective treatment can significantly help to prevent the development of sepsis in patients. Particular attention should be paid to the problems associated with burns. Their solution will be able to play a key role in clarifying and understanding the main processes occurring in the human body in patients with sepsis. The fundamentally important point is the restoration of the skin in a short time after injury, when patients are not yet exhausted by the healing process, and the regenerative properties of their body are still preserved. Therefore, the objective requirement of the time is to develop new modern approaches in this field of medical science, which are associated with the successful development of biomedical research. The use of the method of fluorescence spectroscopy in medical practice is especially promising.

Pathogenesis is the mechanism of the origin and development of diseases and their individual, including specific, manifestations. It can be seen very carefully at different levels: from noticeable changes at the molecular level to possible disturbances in the body as a whole. Based on the obtained results of the study of pathogenesis, it is possible to assess properly the prognosis of the disease and prescribe a reasonable treatment. It is fundamentally important to develop a scientifically sound algorithm for diagnosing diseases and the effective treatment strategy. This makes it possible to develop the unique algorithm for the diagnostics of their diseases and a full-fledged treating strategy.

The understanding of the pathogenesis of sepsis is the key point in finding effective approaches of its prevention and treatment. It develops when the body's response to the infection causes damage to its own organs and tissues and can lead to significant deterioration of a patient's health or even to death [1] [2]. The antigen in burn shock is tissue proteins, destroyed by a thermal agent, which leads to the synthesis of pro-inflammatory cytokines.

Recovery of affected skin with deep and large burns is a difficult problem. Therefore, even with a favorable course of burn disease, this process lasts at least 1 - 2 months after injury. Through the surface of the burn wound there is a loss of water, proteins, electrolytes, and the wound itself remains a source of infection and intoxication and is the main driving force of pathological changes, that occur in the human body. Therefore, the important component of treatment is the need for rapid and safe removal of necrotic tissue, the use of modern methods of antibacterial therapy, timely correction of metabolic processes and the fastest recovery of lost skin. Therefore, in addition to infusion therapy and sur-

gical treatment, the use of skin substitutes for temporary closure of burn wounds is an important area of treatment. An important point is also the choice of the optimal time of recovery of the skin in a short time after injury, when patients are not yet exhausted by a long treatment process, and the regenerative properties of the body are still preserved.

2. Literature Review

In recent years, a lot of attention was paid to improve the diagnostics and treatment of patients with burn injuries. A particular emphasis should be placed on the feasibility of early surgical treatment with the proper restoration of skin integrity after a burn injury. It is characterized with significant volumes of damaged tissues, which should be eliminated, the activation of cellular and humoral phases of nonspecific resistance and the persistence of microflora. Note, that following endogenous intoxication which occurs in this disease, tissue repair in the area of inflammation and restoration of homeostasis is enormously complicated [3] [4]. Early surgical interventions for the prevention and treatment of wound infection, the restoration of anatomical structures and their rehabilitation are widely used. A separate domain is the study of a wound process and the impact of various drugs on it, as well as that of determining the optimal time of the plastic closure of wound defects [5] [6] [7].

But insufficent attention was paid to the problem of complications after burns, *i.e.* sepsis. The changes, occuring in patients with sepsis at the molecular level, are understood poorly. At the same time, they play a key role in understanding the processes, occurring in the human body during sepsis and allow the appointment of effective treatment. This problem is very relevant and needs solving.

At the same time, significant progress was made in recent years in the field of combustiology [8] [9]. The concept of early surgical necrectomies of burn wounds with their primary plasticity is widespread. Means of prevention and treatment of wound infection, restoration of anatomical structures and non-surgical correction in the postoperative period are also being developed. Methods of medical and social rehabilitation of patients are also being improved. Considerable attention was also paid to the problems of the functional state of the internal organs, increasing the body's immunoreactivity and combating wound infection.

The authors [10] [11] proposed a method of collection, cryopreservation and lyophilization of xenografts made of pig skin. Lyophilized xenografts are included in the State Register of Medical Devices and approved for use in medical practice in Ukraine in accordance with the Order of the Ministry of Health of Ukraine from 11 May 1998 №115. It is a mandatory element of wound treatment, the purpose of which is to clean it, remove fragments of necrotic formations, disinfect the skin around the wound, wash the wound surface with antiseptic solutions and apply an aseptic dressing. Today drugs based on silver in the treatment of burns are widely used. A technique for saturating lyophilized xe-

noimplants with silver nanocrystals and using them to treat burn wounds was developed [12].

In patients with superficial burns, silver-rich lyophilized xenoimplants are used to close burn wounds after thorough cleaning under general anesthesia. Wound cleaning is a mandatory element of their treatment, the purpose of which is to remove fragments of necrotic formations, disinfect the skin around the wound, wash the wound surface with antiseptic solutions and apply an aseptic bandage. In patients with burns, lyophilized xenoimplants saturated with silver nanocrystals remain on the wounds for up to 8 - 10 days after applying them to them. This eliminates the need for painful dressings. Wound epithelialization occurs directly under lyophilized xenoimplants. Freeze-dried lyophilized xenoimplants adsorb toxins from the wound surface, reduce the inflammatory process in the wound and revascularize areas of necrosis. Later, lyophilized xenoimplants fall off on their own after wound healing. To date, the clinical effectiveness of the use of xenoimplants saturated with silver nanocrystals in the treatment of patients with burn injuries has been proven.

In the treatment of deep burns in the traditional way, local treatment of burn wounds is aimed at restoring microcirculation, creating antibacterial protection and stimulating reparative processes. After chemical necrectomy and wound cleansing, autodermoplasty should be performed. Wounds that are not covered with autodermografts should be closed with lyophilized xenoimplants rich in silver, which temporarily close the wounds. This reduces pain, water, protein and electrolyte loss from the wound, prevents infection and promotes marginal and islet epithelialization. Under the removed xenoimplants there are pure granular granulations, which are ready to accept autografts. Along with the formation of granulation tissue is an active course of epithelialization of the wound surface.

Deep burns with an area of more than 20% of the body surface often have the following complications: sepsis, erosions and ulcers of the gastrointestinal tract. Immunosuppression, suppression of the cellular immune system and intoxication of the body are also characteristic. Therefore, excision of necrotic tissue significantly improves the patient's condition due to the elimination of the source of infection and intoxication. An open wound surface of a large area leads to depletion of the compensatory capabilities of the human body. Therefore, the technique of early necrectomy with xenodermoplasty prevents progressive intoxication from the affected areas and the development of infection in wounds, reduces the possibility of further progression of burns and leads to the restoration of the skin in the shortest possible time.

Serum albumin composes 60% of total plasma proteins. It plays an important role in maintaining oncotic pressure. It is also involved in metabolic processes and transports of various chemicals. Albumin is a polypeptide, which consists of 585 amino acids with molecular weight 66.000 - 69.000 Da. Albumin synthesis occurs exclusively in the liver. This provides regular replenishment of albumin

in the body, which is regulated by osmoreceptors and is inversely proportional to the level of colloid-oncotic pressure.

The detoxification function of albumin is important. Due to the changes of the conformation of its molecules, albumin interacts with hydrophobic molecules of endotoxins and promotes their excretion from the body. Albumin synthesis may decrease under the influence of infusion of synthetic colloids and albumin. It is also slowed by the influence of stress, sepsis, starvation, hyperthermia, and in elderly people. Hormones insulin, cortisone, testosterone, ACTH, growth factors and thyroid hormone can increase the rate of albumin synthesis by hepatocytes. The half-life of endogenous albumin is 21 days, and that of exogenous albumin is 12 hours. Albumin is mainly an extracellular protein. 40% of albumin is contained in blood plasma and 60% in the depo (40% in the skin, 20% in the muscles of the internal organs) [13]. Albumin enters the interstitium through pores in the endothelium of the capillars and returns to the bloodstream along with the lymph flow. One cycle lasts 15 - 18 hours.

Albumin molecules are able to complex. Diseases, which are accompanied by endogenous intoxication, are characterized with impaired ability of albumin to perform its functions, because some of its binding centers are blocked by toxins. This leads to the deterioration of detoxification capabilities of the body. Although the total concentration of albumin in the body may be within normal limits, its actual "effective" concentration is much lower. Note, that the determination of the "effective" concentration of albumin cannot be performed by modern conventional diagnostic methods, which are currently widely used in the laboratories of health care facilities. Because of the pathogenetic changes of albumin molecules in patients with endogenous intoxication, the effective component of pathogenetic treatment is the use in complex therapy infusions of albumin solution. As mentioned above, the infusion of albumin solution reduces the synthesis of endogenous albumin, but without this infusion, the body will not be able to overcome the infection in case of the presence of endogenous intoxication.

The aim of the research is to create a pathogenetic concept as the basis of a diagnostic and treatment model of purulent-inflammatory diseases and sepsis.

3. Data and Methology

Spectral analysis is one of the most important methods for studying the structure of matter and physical processes, which take place in it, including at the molecular level. Luminescence occurs due to the absorption of light by the system under study due to the transition of its molecules from the excited state to the ground state. The absorption and radiation processes are presented in more details in **Figure 1**. In the initial state (it is also called the ground, unexcited state), the molecule (atom) occupies the energy position with the lowest energy (**Figure 1(a)**). The absorption of light transfers the system from the ground state to the excited states, which, along with the electron state, also have vibrational energy

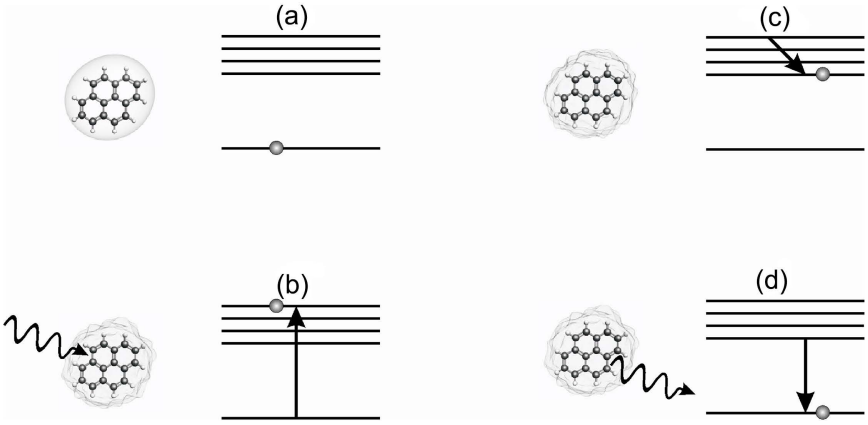

Figure 1. Scheme of luminescence of molecule in the case of irradiation with light.

due to the oscillation of molecules. Therefore, such states are also called electron-oscillating (**Figure 1(b)**). Due to the oscillating motion, the electronic energy of the molecule turns into oscillating; the molecule loses its energy and for about 10 - 12 seconds relaxes to the lowest excited state (**Figure 1(c)**). The molecule transitions from this lowest excited state to the ground state are accompanied by radiation-luminescence (**Figure 1(d)**).

According to the afterglow duration, τ luminescence is divided into two types: fluorescence if $\tau < 10^{-7}$ seconds, *i.e.* the extinction of luminescence occurs very quickly (for the eye, instantly); phosphorescence if $\tau > 10^{-4}$ seconds. In this case, the extinction occurs relatively slowly and is often clearly visible to the naked eye). As part of our own research, we studied radiation with short attenuation times that is fluorescence.

3.1. Data Source

In the framework of this research we used general blood test, general analysis of urine, biochemical blood test, bacterioscopic examination, ultrasonographic examination and the method of fluorescence spectroscopy (MFS). The fundamentally important advantages of the MFS are its simplicity, expressiveness, high sensitivity and accuracy, as well as its ability to control effectively biological objects and environments. Thus, the use of this method is very promising for improving diagnostics in medical practice. Within the framework of MFS, it is possible to study the spectral-fluorescent characteristics of biological objects both in normal and in various pathological conditions. In medical practice since 2000, we have been using this method to study the blood serum (BS) and urine of patients, including those with purulent septic complications and sepsis. The study included several stages.

At the first stage, the behavior of the spectral-fluorescent characteristics of the BS of 100 surgical patients with purulent-inflammatory diseases and sepsis and 40 donors were studied. The clinical basis of the study at this stage was the purulent-septic center of Lviv's municipal clinical hospital of emergency medical

services (Ukraine). The experimental base of luminescent research was the luminescence laboratory of the Department of Experimental Physics of the Ivan Franko National University of Lviv. The study was performed by using optical monochromators MDR-2 and MDR-12. As a source of exciting light, a deuterium lamp DDS-400 with a continuous radiation spectrum in the region λ = 200 - 420 nm was used. The excitation of the BS was performed with light with a wavelength of 280 nm, which corresponds to the glow region of human serum albumin. The main indicators, used for the analysis of fluorescence spectra of BS, were the fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max}). BS of patients is a mixture of normal (concentration X) and blocked by toxins (concentration 1-X) molecules of albumin. In this case, ΔE_a (**Figure 1(d)**) is the difference between the energies of the excited and ground states of normal albumin molecules, and ΔE_t, respectively, for toxin-blocked albumin molecules. In this case, $\Delta E_a \geq \Delta E_t$.

3.2. Research Results

For purulent-inflammatory diseases, three characteristic types of changes of the spectral-fluorescent characteristics of BS were identified, which correspond to aseptic, preseptic and septic pathologies [14]. **Figure 2** and **Table 1** represent the results of the study of the fluorescence spectra of the BS of the donor and the patient with severe sepsis, caused by purulent epiduritis of the lumbosacral spine and massive

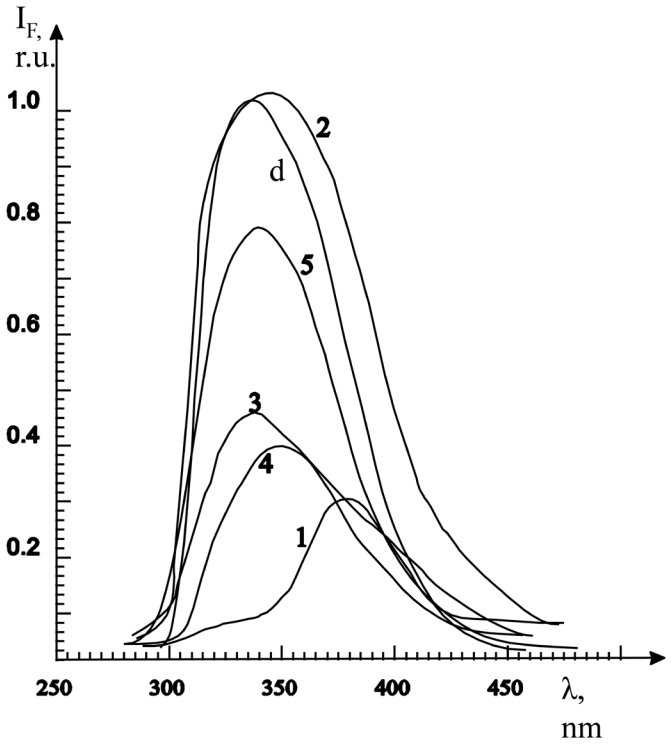

Figure 2. Fluorescence spectra of blood serum of septic patient: 1—28.12.; 2—04.01.; 3—12.02.; 4—19.03. 5—04.06. and donor of BS (340 nm—"normal peak", 380 nm—"septic peak").

retroperitoneal intrapelvic phlegmon. She was treated in the hospital from 28 December 2001 till 15 April 2002. At the time of hospitalization (28 December 2001) she was in a critically serious condition with verified bacteraemia (blood culture of 28 December 2001—*Staphylococcus aureus*). This figure shows that the maximum of the fluorescence band of the patient's BS is shifted to the long-wavelength region by $\Delta\lambda = 40$ nm (curve 1) relative to the fluorescence band of the donor, and the fluorescence intensity was 0.3 * I_F of the donor's BS. This contribution is connected with the glow of albumin molecules, blocked by toxins. At the same time, in the region of 330 nm, luminescence intensity due to the contribution of full-fledged albumin molecules is very small. This indicates that the predominant contribution to the intensity of the BS of this patient in a serious condition is made by pathological albumin molecules. The obtained result for the spectral-fluorescent characteristics of the BS at this time indicates a severe septic condition of the patient.

Note, that the survival of the patients in such a serious condition is possible only if $X \geq X^*$ (X^*—is the limit value of the concentration of complete albumin, enough to ensure the survival of patients with sepsis).

After surgical treatment and intensive antiseptic therapy and ongoing bacteraemia (blood culture of 4 January 2002—*Staphylococcus aureus*), a significant improvement and stabilization of the patient's condition was noted: analysis of the fluorescence spectra of the patient's BS on the seventh postoperative day revealed that the shift of her fluorescence band changed significantly and was $\Delta\lambda = 7$ nm (**Figure 2**, curve 2). At the same time, the intensity of the patient's fluorescence band increased significantly and quite unexpectedly to 1.07 * I_F. Because of subcompensated changes in the absolute quantitative and qualitative content of BS proteins at the time of examination (biochemical studies on 2-4 January 2002: total protein and protein fractions were at the lower limit of normal), the rapid increase in the fluorescence band of the BS of patient in this case cannot be interpreted by absolute hypoproteinemia that typically causes a weakening of the concentration quenching of fluorescence, which is characteristic of protein fluorescence. The only possible explanation for the phenomenon of increasing fluorescence band intensity of the BS of this patient registered above may be the presence of transient hypervolemia during this period of treatment: the volume of daily intravenous infusions during this treatment period was 8 - 10 liters.

Under such circumstances, a natural increase in the fluid component of the BS leads to pseudohypoproteinemia—a laboratory phenomenon which is not a

Table 1. Changes of the spectral-fluorescent characteristics of the patient 1 with sepsis.

N	d	1	2	3	4	5
Date	28.12	28.12	04.01	12.02	19.03	04.06
λ_{max}	340	380	345	337	349	340
I_F	1.0	0.3	1.07	0.46	0.39	0.79

standard biuret reaction and can be differentiated from true hypoproteinemia only by special techniques and the normogram of Phillips and van Slyke [14] [15].

Note, that the detected changes in the spectral-fluorescent characteristics of BS in patients with sepsis in most cases were pre-manifest: they were usually recorded 24 - 48 hours before the appearance of obvious clinical and laboratory signs of significant change in the general somatic status of patients.

Further studies of the fluorescence spectra of this patient showed, that bacteremia was not overcome. Although (see **Figure 2**, curves 3, 4) the long-wave septic peak disappeared only a further long process of treatment under the influence of complex therapy led to a significant suppression of bacteremia and a significant improvement in the patient's condition (**Figure 2**, curve 5) and she was discharged from the hospital in satisfactory condition.

In our opinion, the forced excessive therapeutic dilution of the blood during this period caused a weakening of the concentration quenching of the fluorescence of the BS of this patient and caused an increase in the intensity of the fluorescence bands of her BS. Undoubtedly, the above-mentioned significant increase in the intensity of the fluorescence band of her BS from 4 January 2002 was influenced by the weakening of septic symptoms.

Thus, according to our studies of the fluorescence spectra of the BS of the above patient, note, that the decrease in intensity and shift of the fluorescence band are due to the presence of advanced septic process and correlate with integrated indicators of clinical severity and bacteremia. The dynamics of changes in the spectral-fluorescent characteristics of the BS of the mentioned patient quite objectively reflects the course of sepsis and correlates with the effectiveness of treatment tactics.

Note, that for the first time we obtained fundamental results for the fluorescence spectra of a patient with sepsis and studied the dynamics of their changes during her recovery [15] [16]. They became a reference point for our further studies of the fluorescence spectra of BS of patients with purulent-inflammatory diseases and sepsis. Note, that the results for the spectral-fluorescence characteristics of two more patients with sepsis for convenience, we will discuss later during the analysis of the corresponding results, obtained by us for patients with burns.

The dilution of BS with distilled water causes an increase of the fluorescence intensity of BS (**Figure 3**). Note, that the dilution of BS with a solution of albumin has little effect on the spectral-fluorescence characteristics of these solutions. However, the position of the fluorescence bands does not change. Changes in fluorescence spectra during the dilution of BS with distilled water have a specific character and form the basis for the development of the fluorescent method to diagnose various diseases accompanied by hypoproteinemia and hypoalbuminemia and various treatments (study of the effects of infusion therapy). This made it possible to model the effect of infusion therapy on the spectral-fluorescence characteristics of BS of patients.

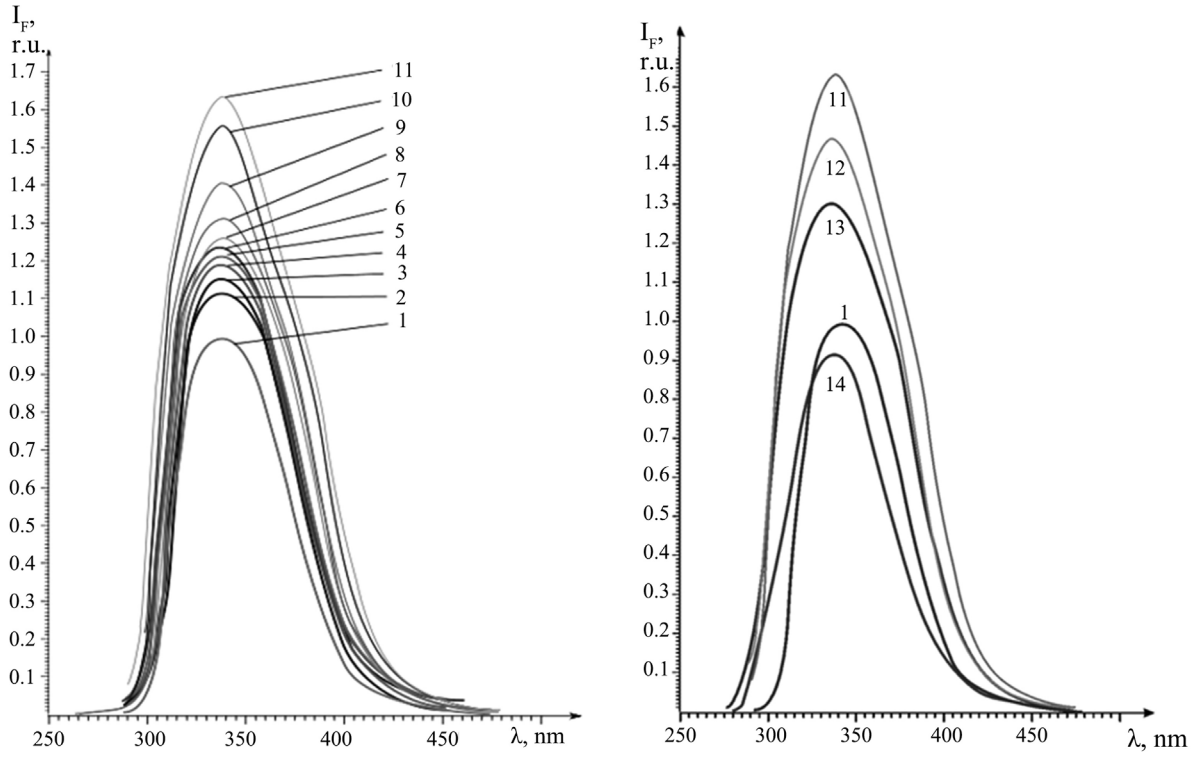

Figure 3. Effect of dilution with distilled water (DW) on the fluorescence spectra of donor blood serum (BS) (1—BS 2—90% BS, 3—80% BS, 4—70% BS, 5—60% BS, 6—50% BS, 7—40% BS, 8—30% BS, 20% BS, 10—10% BS, 11—5% BS, 12—DW: $I_F = 0$).

Our *in vitro* studies of the spectral-fluorescence characteristics of standard dilutions of the donor BS with distilled water (see **Figure 3**) confirmed the correctness of our proposed explanation of the registered phenomenon of fluorescence band increase in the BS of a patient with sepsis (**Figure 2**, curve 2).

After all, the decrease in the content of BS in the samples after the addition of distilled water also leads to a significant increase in the intensity of the fluorescence bands.

Dilution of BS by bacterial culture of *Staphylococcus aureus* (**Figure 4**, **Figure 5**) causes gradually decreases of I_F with increasing content of bacterial culture in solution. There is also a long-wavelength shift of the fluorescence bands (λ_{max}) of these dilutions [17]. Note, that the detected effect of changing the spectral-fluorescent characteristics of dilutions of BS by bacterial culture is due to the influence of bacteria and products of their metabolism on the molecules of serum albumin. Note, that changes of the fluorescence spectra of BS during dilution of BS by bacterial cultures have a specific character (**Figure 4**, **Figure 5**) and form the basis for the development of the fluorescent method for early diagnosis of sepsis by studying the spectral-fluorescent model of sepsis *in vivo* [16]. The behavior of the spectral-fluorescent characteristics of dilutions of BS with sugar broth has similar character.

At the fourth stage of the study, the main task was to develop the optimal treatment tactics and methods of effective control of the treatment process for

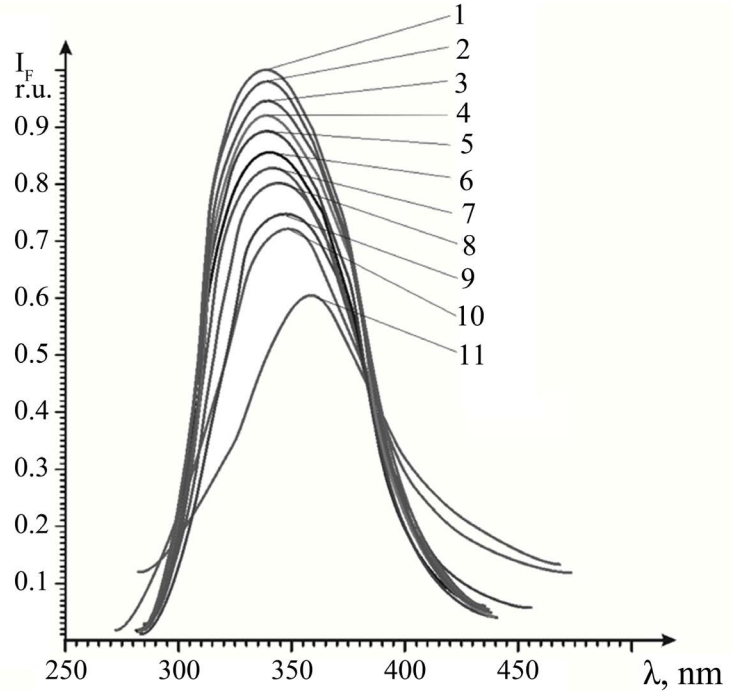

Figure 4. Effect of dilution non-centrifuged (NCF) crops on fluorescence spectra of donor blood serum (BS) (1—blood serum (BS) 2—90% BS 3—80% BS, 4—70% BS, 5—60% BS, 6—50% BS, 7—40% BS, 8—30% BS, 9—20% BS, 10—10% BS, 11—NCF crops). λ_{ex} = 280 nm.

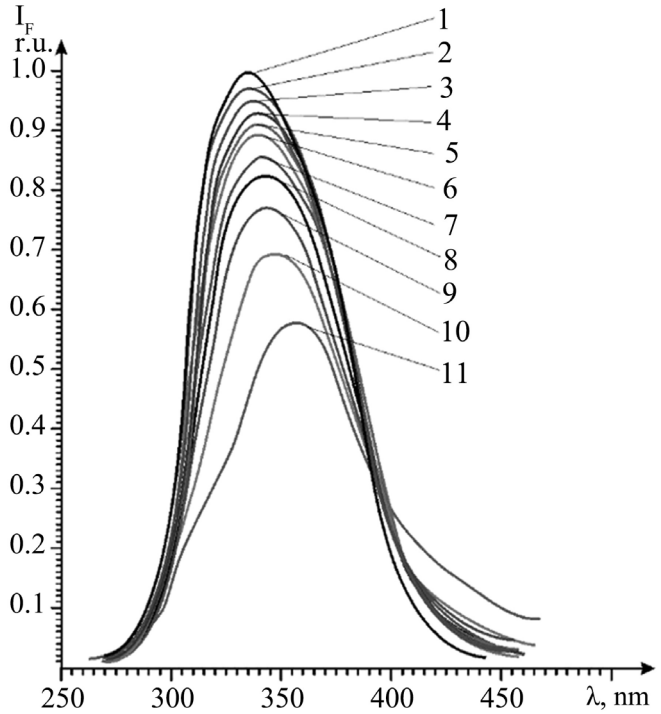

Figure 5. Effect of dilution centrifuged (CF) crops on fluorescence spectra of donor blood serum (BS) (1—blood serum (BS) 2—90% BS 3—80% BS, 4—70% BS, 5—60% BS, 6—50% BS, 7—40% BS, 8—30% BS, 9—20% BS, 10—10% BS, 11—CF crops). λ_{ex} = 280 nm.

the patients with burn injuries. The clinical base of the study was the burn department of Lviv Communal City Clinical Hospital No 8. The research lasted in 2015-2019.

The main study group consisted of 20 patients. The criteria for selecting patients for follow-up were the presence of superficial and deep burns flame and boiling water burns, including head and neck burns. In the study, we included patients mostly without comorbidities aged 20 - 60 years for the purity of the experiment, because the presence of these comorbidities can dramatically change the behavior of spectral fluorescence parameters of serum.

The control group consisted of 25 healthy individuals (donors) without chronic diseases. For patients and donors within the MFS, a study of samples of their BS was conducted. The comparison group consisted of 25 patients in serious condition, whose BS was not tested by using MFS. But therapeutic tactics with donor albumin solution was also used for these patients. In this study, the classification of burns depending on the etiological factor, depth, area and location of the lesion was used for both groups of patients. The data of laboratory examinations (general analysis of blood and urine, biochemical analysis of blood, bacterioscopic examination) and the results of instrumental methods of examination were analyzed. In the course of the research, we also discussed clinical and anamnestic data and analyzed the spectral-fluorescent characteristics of the BS of patients of the main group, obtained dynamically within the framework of MFS. All the patients in the hospital underwent the appropriate surgical treatment of affected burn surfaces, followed by wound closure with lyophilized xenografts. The wounds were epithelialized partly under dry skin, partly under dry necrosis and applicators. Residual wounds were epithelialized under dry applicators. Patients also received anti-inflammatory treatment, antibiotic and infusion therapy, including with the use of albumin solution and desensitizing therapy. The main regularities of the behavior of the spectral-fluorescent characteristics of the BS of patients with burn trauma were studied and the problems of their treatment were discussed [18] [19] [20] [21]. However, at the same time, the problem of purulent-septic complications in patients with burns was not discussed.

Now we shall discuss the results of the study of the spectral-fluorescent characteristics of the BS of patients with burn injury with septic complications. **Figure 6** presents the results of the research in the dynamics of fluorescence spectra and **Table 2** contains data for the spectral-fluorescent characteristics of the BS of the patient with burn injury with the area of the burn surface 38%, admitted to the hospital on 27 June 2015.

He was immediately prescribed appropriate treatment, including antibiotic therapy and infusion therapy with the volume of 2 - 3 liters daily. Staphyloccus aureus 10^5 and Pseudomonas aeruginosa 10^6 were verified on the basis of a microbiological study. Due to the infusion therapy, the fluorescence intensity of BS during the first 6 days did not decrease significantly (I_F = 0.88 r.u.), that correlated with the results of *in vitro* studies. There was also no shift in the fluorescence

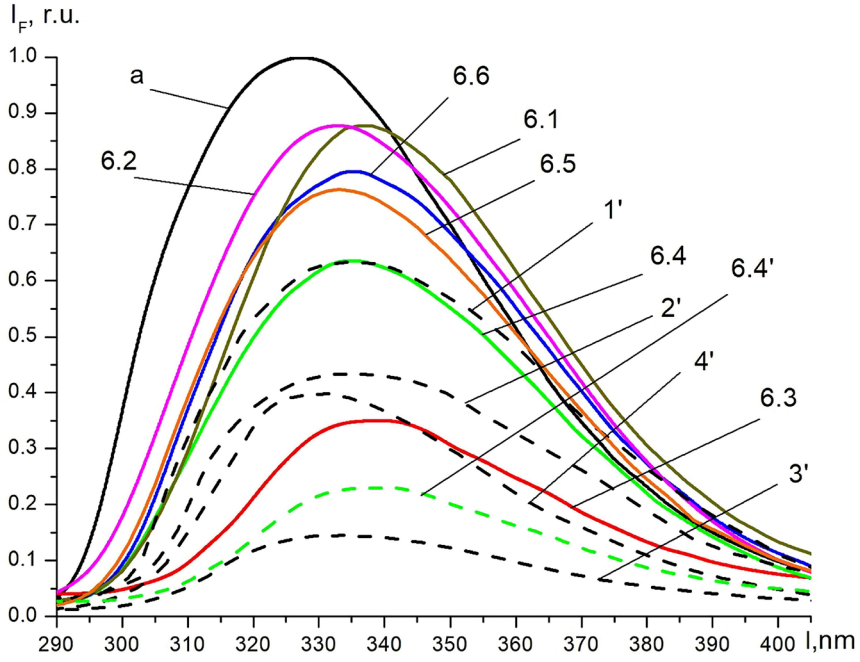

Figure 6. FS of BS of patient 6 with a burn injury, who was hospitalized in Communal City Clinical Hospital №8, Lviv in 2015 in dynamics during treatment (6.1—3.07., 6.2—8.07., 6.3—13.07., 6.4—17.07., 6.4'—17.07., 6.5—20.07., 6.6—24.07.) and a patient with sepsis, who was treated in 2002 in Ambulance hospital (1'—03.06., 2'—05.06., 3'—06.06., 4'—07.06., 5'—10.06) and 20% albumin solution (a), λ_{ex} = 280 nm.

Table 2. Changes of the spectral-fluorescent characteristics of the patient 6 with burn injury.

№	a	6.1	6.2	6.3	6.4	6.4'	6.5	6.6	1'	2'	3'	4'	5'
Date	3.07	3.07	8.07	13.07	17.07	17.07	20.07	24.07	3.06	5.06	6.06	7.06	10.06
λ_{max}	327	336.1	332.2	341.1	335.1	341.1	333.1	335.1	335.2	335.2	334.1	331.6	331
I_F	1	0.88	0.88	0.35	0.64	0.27	0.76	0.80	0.63	0.43	0.14	0.4	0.76

spectra of the BS in the long-wavelength region, despite the verification of two pathogens in the patient. The examination of the fluorescence spectra of the BS of this patient on 13 July 2015 (Figure 6, curve 6.3) showed a significant decrease in its I_F to 0.35 r.u. and a shift of the fluorescence band in the long-wavelength region by 9 nm. The deterioration of this patient's clinical condition was also revealed. This indicated the deepening of endogenous intoxication in him.

The treatment process was corrected by using the infusion of 20% donor albumin solution (100 ml 8 times on different days). Subsequent sampling of BS revealed a gradual normalization of the spectral-fluorescent characteristics of the BS of the patient (see Table 2). Therefore, he was discharged from the hospital in a satisfactory condition on 24 of July 2015. Figure 6 shows that the spectral-fluorescence characteristics of this patient are qualitatively correlated with the corresponding results of the patient with sepsis, presented in the same figure

by dashed curves (curves 1' - 5'). This patient was treated in the hospital in 2002. In order to correct the treatment process of a patient with a burn injury, information about the behavior of the spectral-fluorescent characteristics of a patient with sepsis played a significant role (Figure 6). Without the correction of the treatment process, the condition of the above-mentioned patient with burn injury could continue to deteriorate (Figure 6, curve 6.4') with subsequent transition to a severe septic condition, as it was in case of the patient with sepsis. At the same time, information about the behavior of the spectral-fluorescent characteristics of the patient with sepsis played a significant role in correcting the treatment process of a patient with a burn injury (Figure 6).

The behavior of the spectral-fluorescent characteristics of patients with sepsis, even after burn injuries, is determined by the contributions of two types of albumin molecules: complete and "blocked by toxins". Figure 7 shows, that most of the albumin molecules of a patient with severe sepsis (curve 1) are blocked with toxins (long-wave septic peak). Only a small number of complete molecules of albumin provide support for the vital functions of the patient's body (fluorescence in the region of 330 nm). Earlier it was noted, that in such a serious condition of the patient the synthesis of albumin was very slow. However, if this patient (Figure 2) had been given an infusion of 20% albumin solution, a more noticeable peak in the fluorescence spectra could have appeared in the region of 330 nm that would lead to the improvement of her condition. But this is only

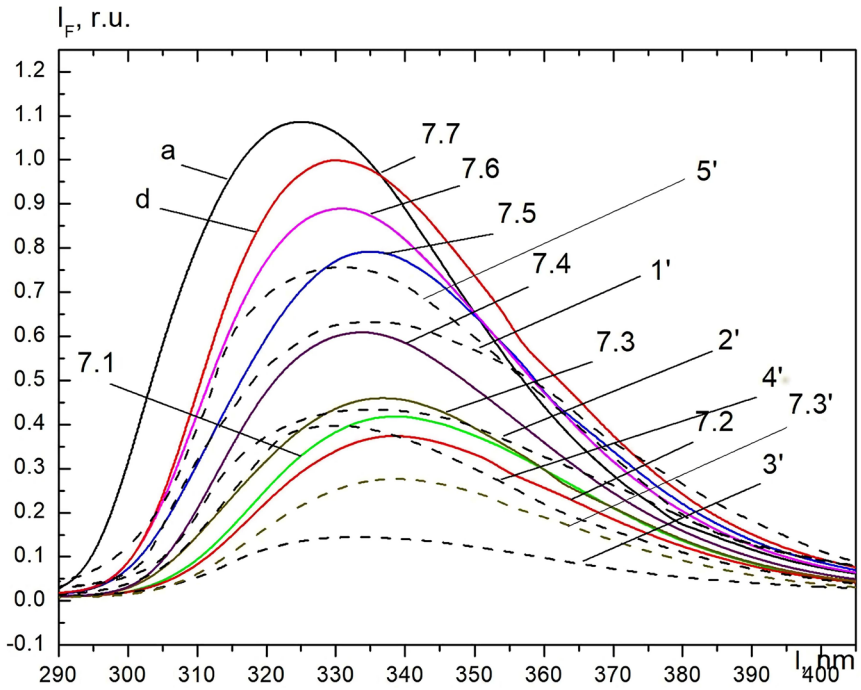

Figure 7. FS of BS of patient 7 with a burn trauma, who was hospitalized in Communal City Clinical Hospital №8, Lviv in 2017 in the dynamics during treatment (7.1—9.02., 7.2—14.02., 7.3—22.02., 7.3'—22.02., 7.4—27.02., 7.5—03.03., 7.6—10.03., 7.7—31.03), and a patient with sepsis, who was treated in 2002 in Ambulance Hospital (1'—3.06., 2'—5.06; 3'—6.06; 4'—7.06, 5'—10.06) and 20% albumin solution (a), λ_{ex} = 280 nm.

our assumption. Strictly speaking about this patient, it was not proven what changes would occur in the fluorescence spectrum during the infusion of 20% albumin solution. This may be the subject of our further studies of the spectral-fluorescent characteristics of patients with sepsis after a burn injury in such a severe condition.

The results of the research of fluorescence spectra of the patient with the burn injury with the burn surface area 28%, who was hospitalized in February 2017, in the dynamics, are presented in **Figure 7**, and the data for the spectral-fluorescent characteristics of his BS are depicted in **Table 3**.

He was immediately given appropriate treatment, including antibiotic and infusion therapy of up to 3 liters daily, as well as infusions of 10% donor albumin (February 6 and 10) in amount 100 ml. The condition of this patient was much more severe than the previous one. Despite intensive treatment, his condition deteriorated markedly during the first 5 days. This is evidenced by the decrease in fluorescence intensity and a slight long-wavelength shift (**Figure 7**, curves 7.1, 7.2).

Compared with the previous patient in this case, most likely, there was a more noticeable endogenous intoxication. Therefore, the correction of the treatment process was performed for him, including the infusion of 10% solution of albumin (February 15, 18, 26 and March 2 in the amount 100 - 150 ml).

It is obvious that the intake of a sufficient amount of albumin significantly improved the work of the body's detoxification systems with the subsequent normalization of the body's synthesis of endogenous albumin. As a result, the fluorescence intensity of the patient's BS gradually increased, and the long-wave shift leveled off. After that, the patient was discharged from the hospital in a satisfactory condition. Without correction of the treatment process, the patient's condition could have deteriorated (**Figure 7**, curve 7.3') towards a subsequent transition to the severe septic condition, as it was as in case of the patient with sepsis.

Our results for the spectral-fluorescence characteristics of the above-mentioned patient with burn injury correlate well with the corresponding results (**Figure 7**, curves 1' - 5') for a patient with sepsis, treated in hospital in 2002. Regardless of the etiological factors of sepsis, the pathogenetic mechanisms of septic complications are unified. Serum albumin molecules have the ability to complexation. In case of the presence of endogenous intoxication in the body, they are blocked by the products of bacterial metabolism. Understanding the microscopic mechanisms

Table 3. Changes of the spectral-fluorescent characteristics of the patient 7 with burn injury.

№	a	d	7.1	7.2	7.3	7.3'	7.4	7.5	7.6	7.7	1'	2'	3'	4'	5'
Date	9.02	9.02	9.02	14.02	22.02	22.02	27.02	03.03	10.03	31.03	3.06	5.06	6.06	7.06	10.06
λ_{max}	330.1	333.1	335.1	339.1	337	337	334	335.1	331.1	332.0	335.2	335.2	334.1	331.6	331
I_F	1	1	0.41	0.37	0.46	0.27	0.61	0.79	0.89	0.95	0.63	0.43	0.14	0.40	0.76

of the theory of pathological albumin formation is the basis for the development of pathogenetic treatment tactics.

The most optimal approach for the detection of septic conditions in patients is the study of the spectral-fluorescent characteristics of their BS in the frame of the method of fluorescence spectroscopy. There is a high risk of septic condition in patients with burn injuries in two cases: in patients with the large area and depth of burn trauma and in the case of inadequate treatment at the initial stage of the disease. Therefore, the key thesis of successful treatment is the comprehensive approach to prevent the development of bacteraemia owing to the early surgical treatment and comprehensive therapy. The fundamental idea of successful completion of the treatment process is constant monitoring within the method of fluorescence spectroscopy of the treatment process with the possibility of its correction. In the treatment process, the intensity and position of the maximum fluorescence of the BS of patients are the indicators of fundamental importance. The lower the fluorescence intensity, the higher the probability of exitus letalis.

To illustrate the above considerations, we present the results of the studies of the spectral-fluorescent characteristics of the BS of the patient with sepsis and diabetes mellitus (Figure 8, Table 4), who was treated at the hospital in 2002.

The patient's condition deteriorated steadily during the follow-up period, despite surgery and intensive antibiotic therapy that may be explained by the presence of a number of severe comorbidities and her advanced age. The negative dynamics of this patient's condition is reflected by the unfavorable dynamics of the parameters of the spectral-fluorescent characteristics of her BS: a constant decrease in the intensity of the fluorescence bands (Figure 8, curves 1, 2, 3).

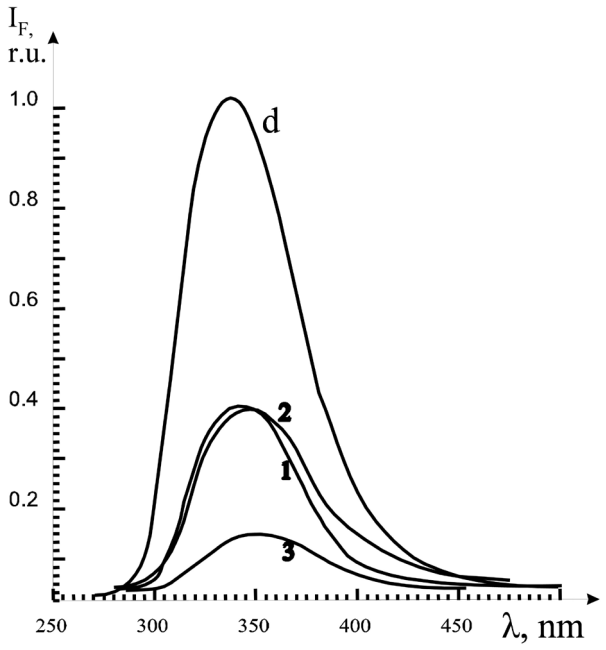

Figure 8. Fluorescence spectra of BS of patient with sepsis and diabetes: 1—03.06; 2—05.06; 3—06.06 and donor BS. λ_{ex} = 280 nm.

Table 4. Changes of the spectral-fluorescent characteristics of the patient with sepsis and diabetes.

N	d	1	2	3
Date	03.06	03.06	05.06	06.06
λ_{max}	338	342	347	351
I_F	1.0	0.41	0.40	0.15

It is logical to assume that it is appropriate to use the infusion of albumin solution to prevent the deterioration of the patient's condition. Obviously, such a treatment procedure should be performed. However, unfortunately, this idea was not implemented in her treatment. We do not have a reliable answer about the possibility of recovery of this patient using the infusion of albumin solution. Unfortunately, the mentioned patient died as a result of the advanced process of the generalization of infection and multiorgan failure. The dynamics of changes in the spectral-fluorescent characteristics of the BS of patients with sepsis objectively reflects the clinical features of the disease, which significantly depends on the quality of diagnosis and correlates with the effectiveness of treatment tactics.

In conclusion, it is important to note that the dynamics of changes in the spectral-fluorescent characteristics of the BS of patients with sepsis during treatment objectively reflects the clinical features of the disease. Successful completion of the treatment process significantly depends on the quality of diagnosis and monitoring and correlates with the effectiveness of treatment tactics. For successful and effective management of the treatment process within the MFS, it is very important to have portable equipment for the study of fluorescence spectra, as well as reliable financial support of the treatment process. If the septic process becomes uncontrollable and cannot be treated, the probability of patient's survival is low. But the use of MFS in the treatment can help to prevent this. There is enough time to adjust the treatment process and help the patient survive. Concomitant diseases that are incompatible with life can become an obstacle to this.

In conclusion, we would like to concentratre on the problems that need to be solved in order to improve properly the treatment process of patients with burn injuries to prevent the development of the septic process. It is necessary to conduct a clinical and laboratory examination of the patient, prescribe antibiotic and infusion therapy, including the use of albumin solution. It is fundamentally important to carry out early surgical treatment to prevent the development of endogenous intoxication of the body. It is important to sow bacteria in order to verify and study their sensitivity to antibiotic therapy. Empirically, it is advisable to prescribe broad-spectrum antibiotics and wait until the results of crops. This algorithm is optimal for the correction of antibiotic therapy. The authors of the research [22] on the basis of a multicentric study demonstrated the effectiveness of the fluorescent method for the diagnosis of bacterial contamination of wounds. The accuracy of this method has been found to be higher than standard

research methods, which are widely used in the routine practice of health care facilities. In this study, the fluorescent method allowed to change treatment tactics in 69% of patients and improve the provision of medical services to patients.

In the critical situation, the fluorescence intensity of albumin molecules is of fundamental importance. The most fundamental is the registration in time of the threatening moment which requires a rapid correction of treatment tactics. If the choice of antibiotic was not correct, it is necessary to replace antibiotics in accordance with the results of the determination of sensitivity according to the antibioticogram. In healthy people, up to 6% (average 4% - 5.8%) of albumin molecules are glycosylated, while in patients with diabetes such molecules are more than 9% (9% - 12%). The albumin glycosylation of more than 12% indicates the presence of decompensated diabetes mellitus. This reduces the amount of albumin, which is able to perform a detoxifying function, which slows down the healing process of wounds in patients with diabetes. Such patients have a predisposition to the prolonged course of purulent-septic complications and the likelihood of exitus letalis (**Figure 8**).

Given our successful experience of using infusion therapy with albumin solution for the treatment of patients of the main group with burn injuries, we applied this experience to the comparison group. Consider in more details several clinical cases of patients from the comparison group in serious condition, which deserve attention. The 38-year-old patient was admitted to the burn department on 29 September, 2018 with superficial and deep flame burns (70% of the head, torso, both upper and lower extremities) and second-degree burn shock. The daily volume of infusion therapy was 3700 - 4000 ml. The patient also had severe septicotoxemia, according to laboratory examination, mild anemia and hypoproteinemia. The patient received antibacterial, anti-inflammatory therapy and infusion of albumin solution for 6 times (three times - 20% and 6 times - 10%). The patient also underwent surgery—necrectomy and free autodermoplasty. During the treatment, the patient's health was closely monitored and treatment tactics was adjusted. After 41 days, the patient was discharged in satisfactory condition under the supervision of a surgeon at the place of residence.

It is necessary to dwell in more detail on the peculiarities of the course of burn injury of another patient, 28 years. The patient was hospitalized in the burn department on 20 June, 2018 with IIB degree gas flames up to 50% of the surface of the head, neck, torso, upper and lower extremities. The patient also had a first-degree airway burn and a second-degree burn shock. He was hospitalized in serious condition. Patient received antibacterial, antiplatelet therapy. As part of the infusion therapy, he also received infusions of 20% albumin solution (100 ml three times). The patient also underwent two surgeries—necrectomy (27 June, 2018) and free autodermoplasty (12 July, 2018). The patient was hospitalized for 40 bed days and was discharged home on 30 July, 2018 in satisfactory condition. Note that the above patients were in a condition very close to septic.

A 38-year-old patient's was treated in the hospital from the 30 August to the 13 November, 2019. At the time of admission, the patient's condition was se-

rious. The main diagnosis was second-degree (type A and B) flame burn of 35% of the head, neck, back and both upper limbs, second-degree burn shock. The patient had a fever and endogenous intoxication. The general blood test revealed leukocytosis with the increased number of rod granulocytes and the increased rate of erythrocyte sedimentation. The patient underwent a successful surgical treatment. He received an anti-inflammatory, antibacterial, anticoagulant, antifungal and hormonal therapy, infusions of albumin solution. Total amount of albumin solution was 700 ml. The patient also received erythromass (4 times) and native plasma (5 times). The daily infusion volume was more than 3000 ml. The patient underwent successful surgical treatment—staged necrectomies, xenoplasty with lyophilized xenoimplants saturated with silver nanocrystals and autodermoplasty. The patient's condition was under reliable monitoring. Infusions of albumin solution were provided in the most critical periods of the patient's condition. They made it possible to balance the amount of complete albumin in the BS and improve the patient's condition. After successful completion of the treatment process (75 bed days), the patient was discharged from the hospital in satisfactory condition.

Thus, this section, based on the results of the study of septic complications of patients with surgical profile, illustrated the successful experience of using MFS to diagnose, control and improve the treatment of patients with burn injuries in a condition close to septic. It is shown, that the experience and skills gained in this case significantly helped to improve treatment tactics in the presence of septic complications in patients with burn injuries. Fundamentally important in the future are thorough studies within the MFS of different scenarios for the development of septic complications in severe forms of burns. The results obtained in our study showed that the method of fluorescent spectroscopy had sensitivity 100% and specificity 88.0%.

4. Conclusions

The pathogenetic concept of diagnostic and treatment model of purulent-inflammatory diseases and sepsis is presented. It is based on the fact, that in diseases, which are accompanied by endogenous intoxication, part of the albumin molecules in the patient's blood is blocked by toxins. As a result, there are two types of albumin molecules in the blood of patients: normal and blocked by toxins. This leads to a deterioration of the detoxification capabilities of the body. For diagnosis, especially early, monitoring and correction of the treatment process, the method of fluorescence spectroscopy is proposed. It has been established that the spectral-fluorescent characteristics of the serum of patients with purulent-septic complications were universal markers of the severity of the patients' condition. The peculiarities of the behavior of these markers for various specific diseases were illustrated. At the same time, some changes of the spectral-fluorescent characteristics of the patients' blood serum were registered 24 - 48 hours before the emergence of obvious clinical and laboratory signs of the pa-

tients' general somatic condition. The results obtained with the help of MFS are significantly ahead of the results of other research methods, which are now routinely widely used for diagnosis in health care facilities.

In order to overcome optimally endogenous intoxication, it is proposed to use infusions of albumin solution to increase the content of complete serum albumin in patients with endogenous intoxication. It is shown, that the scenarios of sepsis, including in the case of burns, depend on the severity of the disease. The features of the pathogenesis of sepsis do not depend on its etiological factors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Comparison of Nasal and Frontal BIS Monitoring in Neurosurgery: Does the Site of Sensor Placement Affect the BIS Values?

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Abstract

Background and Goal of Study: Intraoperative awareness is a serious but preventable complication of general anaesthesia. Bispectral index (BIS) is the most widely used method monitoring anaesthesia depth. BIS monitoring requires attachment of forehead sensors, which poses a challenge when the surgical field involves the forehead. We aimed to compare the gold standard forehead position of BIS sensors with an alternative position across the nasal dorsum for neurosurgical procedures. **Materials and Methods:** After ethical committee approval and informed consent were obtained, 62 patients were enrolled in this prospective observational study. Frontal and nasal BIS values were compared in all patients. **Results and Discussion:** The mean BIS value from frontal versus nasal sensors was 49 ± 22 and 49 ± 21 respectively (n: 62). These values were statistically correlated (ICC 0.78, $p < 0.001$) indicating that nasal BIS measurement does not present a disadvantage for routine use when needed. **Conclusion:** Our data reveal that for measuring anesthesia depth, BIS sensor placement on the nasal dorsum shows comparable efficiency in comparison to standard frontal measurements

Keywords

BIS, Neuromonitoring, Neurosurgery

1. Introduction

Intraoperative awareness, with or without recall, continues to be a topic of clinical significance and neurophysiological interest [1]. The unintended experience

and memory of surgical or procedural events can be devastating for patients and remains an active area of study. Intraoperative awareness also has consequences for the anesthetist. A recent examination by the American Society of Anesthesiologists' (ASA) Closed Claim Project revealed that 2% of all claims were for awareness [2] Such claims are frequently successful, and poor anesthetic technique is often blamed. Hence, monitoring the depth of anesthesia has become increasingly necessary. Bispectral index (BIS) monitoring is a useful adjunct to monitoring the depth of anesthesia and reducing the risk of awareness for high-risk groups. BIS-guided anaesthesia compared to clinical signs may reduce the risk of intraoperative awareness and improve early recovery times in people undergoing surgery under general anaesthesia [3]. A frontotemporal placement of electrodes is now considered to be the gold standard for BIS monitoring [4]. However, in some neurosurgical cases the surgical incision site may compromise this placement. Here, we aimed to compare the gold standard forehead position of BIS sensors with an alternative position across the nasal dorsum for neurosurgical procedures.

2. Methods

After ethical committee approval (Ankara University School of Medicine on October 21, 2016) informed consent was obtained giving adequate information concerning the study, providing adequate opportunity for the patient to consider all options, responding to the patient's questions, ensuring that the patient has comprehended this information, obtaining patient's voluntary agreement. 62 patients who were scheduled for an elective operation under general anesthesia at the neurosurgical unit in Ankara University School of Medicine were enrolled in this prospective observational study. The inclusion criteria were ASA I-III patients between 18 - 80 years of age undergoing elective neurosurgical operations with no contraindications for the placement of electrodes (BISTM Quatro Sensors, Aspect Medical Systems, Newton, MA, USA) over the forehead and nasal dorsum (e.g., the boundary area being too close to the surgical site or having skin infections). Patients with disabling central nervous system or cerebrovascular disease, those currently taking psychiatric medication, and those with a history of neurosurgical intervention were excluded. Standard monitoring was performed upon arrival in the operating room (non-invasive blood pressure measurements, electrocardiography, oxygen saturation, and TOF).

Statistical Analysis: The sample size was calculated using equivalence testing and Bland-Altman analysis. Numerical data were summarized as mean ± standard deviation and median (minimum-maximum), whereas frequencies and percentages were used for categorical data. Consistency between frontal and nasal measurements was evaluated with intraclass correlation coefficient (ICC). When consistency between multiple repeated measurements were considered, a three level linear mixed effects model was fitted taking BIS values as dependent variable and patients, repeated measurements nested within frontal/nasal were

taken as random effects. Variance components then used to calculate ICC. Bootstrap method with 10,000 samples was used to obtain 95% confidence intervals (CI). Based on the guideline given by Koo and Li (2016), ICC values below 0.5 considered as poor, 0.50 to 0.75 as moderate, 0.75 to 0.90 as good, and above 0.90 as excellent. For all statistical calculations IBM SPSS Statistics version 20.0 and R version 4.0.0. (package rmcorr) were used and p value < 0.05 is accepted statistical significant [5].

Before the induction of anesthesia, two BIS sensors (BIS™ Quatro Sensors, Aspect Medical Systems, Newton, MA, USA) were adhered to each patient: one across the forehead and the other across the nasal bridge. Each sensor was attached to its own BIS monitor (BIS-Vista™ monitors, Aspect Medical Systems, Newton, MA, USA). Nasal sensors were placed on the same side of the face with circle 1 on the nasal dorsum, circle 2 on the nasofacial angle, circle 4 on zygomatic bone, and circle 3 on the ipsilateral temporal area (**Figure 1**).

Before induction of anesthesia, all patients were sedated with 1 mcg/kg fentanyl. Anesthesia was induced with 2.5 mg/kg propofol, and 1 mg/kg of rocuronium was administered as a muscle relaxant. Anesthesia was then maintained with 100 - 200 mcg/kg/min propofol and 0.25 - 1 mcg/kg/min remifentanil with a target frontal BIS value of 40 - 60. During the procedure, BIS values were collected from the two different positions before the induction of anesthesia, at loss of the eyelash reflex, after intubation, after the first surgical incision, every 15 minutes during the intraoperative period, and at spontaneous eye opening upon emergence from anesthesia.

The TIVA infusion was stopped after skin closure, and sugammadex (dose was according to the TOF value) was administered to antagonize any residual neuromuscular block when the frontal BIS score was >70. All patients were then extubated when the TOF values were >90. All patients were transferred to the PACU after the first postoperative neurological examination.

3. Results

The patients' demographic and surgical data are summarized in **Table 1**. There were significant correlations between the frontal and nasal BIS values at all time

Figure 1. Nasal and fronatal BIS sensor placement.

Table 1. Patient demographics.

Age (yr)	46.25 ± 15.36
Gender (F/M)	28/34
ASA I-II	29/33
Height (cm)	165.49 ± 8.17
Weight (kg)	64.80 ± 11.53
BMI (kg/m^2)	23.49 ± 3.05
Operation (n: 62)	Spinal (31) and cranial (31)

points. At the same time, according to the correlation coefficient, correlation was stronger during induction and awakening (**Table 2**, **Figure 2**, **Figure 3**). None of the patient interviews indicated awareness. One patient reported dreaming.

4. Discussion

The nasal BIS values were significantly correlated with the gold standard frontal BIS values at all time points. The difference between BIS values obtained from the forehead and nasal areas were considered identical, especially at the beginning-induction phase and during the awakening, emergence and early recovery period. Correlation was the similar during the maintenance period. The ICC was 0.78 indicating a good correlation between frontal and nasal sensors.

EEG activity is not homogeneous across the scalp even in normal awake or anaesthetized patients. Thus, the lack of EEG homogeneity in some clinical situations—including the artifact-free conditions of the present study—is not particularly surprising. The ability of the BIS algorithm such as other EEG-signal treatments to identify these local variations is of interest for potential clinical applications [6].

A few studies [6] [7] [8] have proposed that the BIS score is a topographic-dependent variable in light of the heterogeneous EEG findings in BIS sensors placed on non-frontal areas. Lee *et al.* compared frontal BIS monitoring with mandibular electrode position and reported strong correlations between frontal and mandibular sensor placement [6]. Unlike the frontal or occipital area, no EEG is generated under the mandible and thus detectable EEG or BIS is likely conducted from other parts of cerebral cortex. The exact locations remain unknown and warrant further study.

Another study [8] compared occipital and frontal placements. Here, occipital placement showed a +10 BIS score bias under deep anesthesia and a −10 BIS bias before induction. Although the nature of the BIS algorithm is proprietary, this result may be due to the predominance of the posterior alpha (α) waves in the awake brain and the generation of delta (δ) and theta (θ) activity under deep propofol anesthesia. In another study, Shiraishi *et al.* [9] compared BIS values obtained from frontal and occipital areas during propofol/fentanyl anesthesia. The BIS values in this study showed a strong correlation between frontal and

Table 2. ICC and 95% CI for pointwise and multiple repeated measurements.

Time	ICC (95% CI)
Premedication	0.731 (0.685 - 0.776)
Intubation	0.424 (0.376 - 0.4726)
Intraoperative	0.771 (0.62 - 0.862)
Extubation	0.805 (0.677 - 0.883)
PACU	0.620 (0.369 - 0.771)

ICC: Intraclass correlation coefficients, CI: confidence intervals.

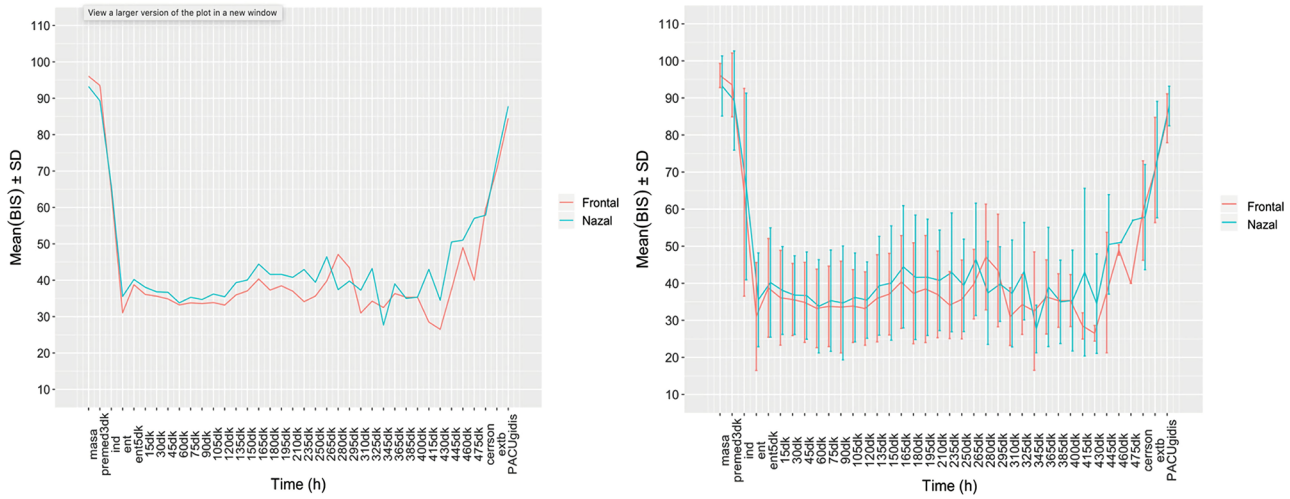

Figure 2. Relationship between nasal and frontal BIS measurements.

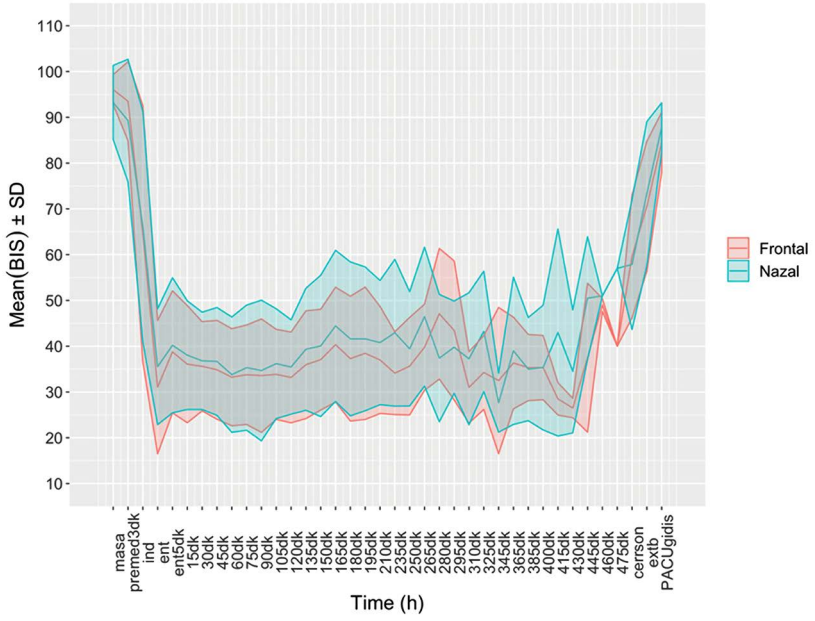

Figure 3. Relationship between nasal and frontal BIS measurements.

occipital montages (r(2) = 0.96; P = 0.03). However, this study had weak correlation between two positions during awakening (r = 0.391) and LOC (r = 0.341)

time points when no correlation at all was detected during emergence time point. These results are different from ours and show the significant correlation between nasal and frontal BIS values during all time points.

In neurosurgery, the recommended placement of electrodes for monitoring depth of anesthesia during surgery sometimes conflicts with the surgical site or patient positioning. Therefore, we conducted this study to evaluate the agreement and correlation of BIS values recorded from the standard frontal area as well as alternative nasal areas in neurosurgery patients. The nasal location of BIS electrodes has been previously demonstrated to be better in terms of correlation and application than occipital positioning, which is often of extreme usefulness for neurosurgical cases.

One limitation of our study is that we did not exclude drugs that could lead to false BIS values. Furthermore, BIS-VISTA does not generate raw EEG tracing for analysis, and thus we could not confirm whether the actual EEG recordings were identical. Although the BIS algorithm has not been formally validated, actual EEG recordings at each electrode on the frontal and nasal positions help confirm the accuracy and characteristics of the EEG signal arising from the nasal dorsum.

5. Conclusion

Our data reveal that BIS sensor placement on the nasal dorsum has comparable efficiency as standard front placement for measuring anesthesia depth (ICC 0.78, $p < 0.001$), especially during the most variable periods of the surgery. This relationship is held regardless of the site of neurosurgical procedure (both cranial or vertebral). Thus, the nasal dorsum is a good and safe alternative when sensor positioning might interfere with the surgical site.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Current Concepts in the Diagnosis and Management of Pulmonary Embolism

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Abstract

Acute pulmonary embolism (PE) is one of the most common causes of cardiovascular death. Most often acute PE is associated with under diagnosis, misdiagnosis and delay in diagnosis and management leading to high morbidity and mortality. PE outcomes will improve with proper evaluation of clinical symptoms and signs, relevant diagnostic tests, identifying high-risk patients suitable for early re-perfusion with I.V. or catheter-directed thrombolytic therapy or surgical embolectomy and in some cases additional use of mechanical circulatory support. During clinical evaluation modified Geneva score, Well's score, and Simplified pulmonary embolism severity index (sPESI) scores are useful in assessing PE and its adverse outcomes. Hestia criteria are useful in identifying suitable for outpatient management of PE. Long-term management of PE involves identifying patients prone for recurrence and CTPE with appropriate long-term prophylaxis using oral anticoagulants.

Keywords

Pulmonary Embolism, Management of PE

1. Introduction

Acute pulmonary embolism (PE) is due to Deep Vein Thrombosis (DVT) embolism, *i.e.* blood clot or part of it breaks off from the vein. DVT is a formation of thrombosis in the deep vein of the lower extremity or pelvis either partially or blocking blood flow [1]. Acute PE ranges from asymptomatic, incidentally discovered sub-segmental thrombi to massive PE complicated by cardiogenic shock and multi-organ dysfunction. The most common PE source is lower extremity sites and unusual sites are the right heart, upper extremity, renal veins, iliac veins and hepatic veins.

Sudden occlusion of the pulmonary artery and its branches results in abrupt

increase of pulmonary vascular resistance to a level of afterload that cannot be matched by the RV causing RV dysfunction, failure, and sometimes sudden death due to Electro-mechanical dissociation. Clinical symptoms and signs of PE depend on the extent and duration of the pulmonary artery obstruction and pre-existing cardiopulmonary status.

Epidemiology

PE is the 3rd most common cause of cardiovascular death [2]. It constitutes approximately 100,000 to 180,000 deaths/annum in USA. Vein thrombus-embolism (VTE) mortality was observed in more than 370,000 people of 6 European countries annually, which is more than the reported combined mortality from AIDS, breast cancer, prostate cancer and traffic accidents. Clinical spectrum of PE varies from asymptomatic to complete cardiovascular collapse. Autopsy based study of 1000 patients observed 15.9% was the reported incidence of PE in India. PE is underestimated, underdiagnosed and undertreated in most patients, and it was estimated that only 8% of patients were exactly diagnosed as a case of PE before death. Untreated DVT/PE has serious long term consequences like recurrent VTE, post-thrombotic syndrome, venous ulceration and chronic thromboembolic pulmonary hypertension (Figure 1). Every effort should be made to clear the clot as early as possible to improve acute hemodynamic status by reversing acute and sub-acute RV dysfunction, chronic thrombotic pulmonary embolism (CTPE), and lowering the mortality rate. CT-PE is a serious complication of PE occurs in 4% of patients and if untreated, associated with a 90% mortality rate.

2. Classification, Assessment of Clinical (Pre-Test) Probability and Risk stratification

PE patients can be categorized as low-risk PE, sub-massive PE, and massive PE. Low-risk PE constitutes 55% of PE patients carries a good prognosis with a

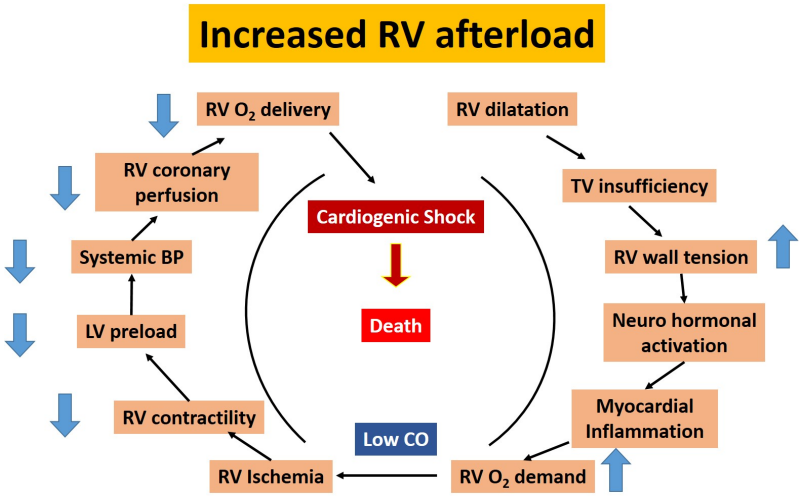


Figure 1. Key factors contributing to hemodynamic collapse and death in acute pulmonary embolism.

mortality of 1%, sub-massive PE was observed in 40% of patients with a mortality of 21% at three months. In contrast, massive PE was observed on average of 5% of PE patients with 58% mortality at three months [3].

Pulmonary embolism can be predicted clinically using wells score and revised Geneva score in a clinically suspected PE case to plan appropriate strategies for treating PE (Table 1).

The spiral of hemodynamic collapse in acute PE (Figure 1): ESC 2019 PE guidelines.

Risk assessment of PE:

PE patients can be classified (Table 2) as a high-risk, intermediate-risk and low-risk group. High-risk group patients are with hemodynamic instability in contrast to the other two groups. Low-risk patients are without elevated Troponin-I, RV dysfunction, and PESI III to IV or SPESI ≥ 1. Intermediate risk group patients have increased troponin I or RV dysfunction with PESI III to IV or SPESI ≥ 1.

Table 3: Simplified pulmonary embolism severity index (PESI) [4].

Patients with none of the clinical variable (*i.e.*, the total score of 0) are considered as low risk and have mortality and pulmonary embolism-related complication rates significantly lower as those with a score of ≥1.

Table 1. Pulmonary embolism can be predicted clinically using wells score and revised Geneva score.

Revised Geneva Score		Wells Score	
Variable	**Points**	**Variable**	**Points**
Predisposing factors		**Predisposing factors**	
Age > 65 years	+1		
Previous DVT or PE	+3	Previous DVT or PE	+1.5
Surgery or fracture within one month	+2	Recent surgery or immobilization	+1.5
Active malignancy	+2	Cancer	+1
Symptoms		Symptoms	
Unilateral lower limb pain	+3		
Hemoptysis	+2	Hemoptysis	+1
Clinical Signs		Clinical Signs	
Heart rate		Heart rate	
75 - 94 beats/min	+3	>100 beats/min	+1.5
±95 beats/min	+5		
Pain on lower limb deep vein at palpitation and unilateral edema	+4	Clinical signs of DVT	+3
		Clinical Judgement	
		Alternative diagnosis less likely than PE	+3
Clinical Probability	**Total**	**Clinical Probability (3 levels)**	**Total**
Low	0 - 3	Low	0 - 1
Intermediate	4 - 10	Intermediate	2 - 6
High	±11	High	± 7
		Clinical Probability (2 levels)	**Total**
		PE unlikely	0 - 4
		PE likely	> 4

Table 2. Classification of PE by American heart association (2011) and European society of cardiology (2019).

AHA CLASSIFICATION (2011)	ESC CLASSIFICATION (2019)*
MASSIVE PE	**HIGH-RISK PE**
Hypotension, defined as a systolic blood pressure < 90 mm Hg, a drop of >40 mm Hg for at least 15 minutes, or need for vasopressor support	One of the following clinical presentations: cardiac arrest, obstructive shock, persistent hypotension (systolic BP < 90 mmHg or a systolic BP drop > _40 mmHg for >15 min
SUBMASSIVE PE	**INTERMEDIATE RISK PE**
Acute PE without systemic hypotension (systolic blood pressure > 90 mm Hg) but with either RV dysfunction or myocardial necrosis[3]	Acute PE without systemic hypotension (systolic blood pressure > 90 mm Hg) but with either RV dysfunction or elevated cardiac troponin levels[3] Additionally, include PESI/sPESI criteria.
LOW-RISK PE	**LOW-RISK PE**
Acute PE and the absence of the clinical markers of adverse prognosis that define massive or sub-massive PE[3]	No RV dysfunction/no elevated cardiac troponins/normal PESI

Table 3. Simplified pulmonary embolism severity index.

Variable	Points
Age > 80 years	1
History of cancer	1
History of heart failure or chronic lung disease	1
The pulse rate of ≥110 bpm	1
Systolic blood pressure < 100 mmHg	1
Oxygen saturation < 90% on room air	1

3. Diagnosis and Management of PE

Management of PE depends upon early diagnosis and assessing risk status to decide appropriate re-perfusion and anticoagulant therapy on fast track basis to reduce mortality and morbidity associated with misdiagnosis and delay in the treatment of PE (Figure 2).

3.1. Plasma D-Dimer

Plasma D-Dimer is the degradation product of cross-linked fibrin. ELISA derived assays have the highest sensitivity, its measurement recommended in out-patient/emergency department patients with low or intermediate clinical probability, or PE unlikely to reduce the need for unnecessary imaging and irradiation.

3.2. Troponin

Elevated plasma troponin (Trop-T/I) concentrations on admission may be associated with a worse prognosis in the acute phase of PE. Elevated Trop-T/I levels

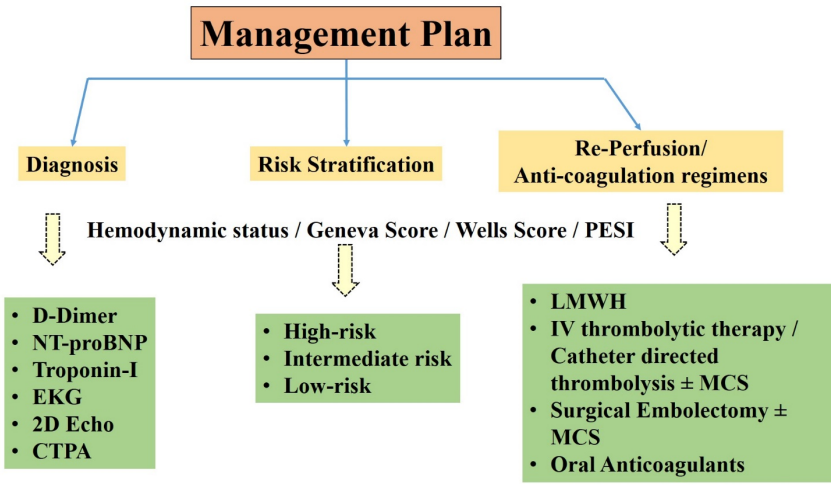


Figure 2. Management of PE.

are observed in approximately 50% of the patients with acute PE, associated with an increased risk of death and significant adverse events in the acute phase. A meta-analysis showed that elevated troponin concentrations were associated with an increased risk of mortality, both in unselected patients (OR 5.2, 95% CI 3.3 - 8.4) and in those who were hemodynamically stable at presentation (OR 5.9, 95% CI 2.7 - 13.0) [5].

3.3. BNP and proBNP

Elevated BNP or NT-proBNP levels associated with low specificity and positive predictive value for increased mortality rate in hemodynamically stable patients with PE, but low levels of BNP or NT-proBNP will exclude an unfavorable early clinical outcome, with high sensitivity and a negative predictive value. A meta-analysis of 13 studies showed 51% of 1132 patients with acute PE with elevated brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP levels contributed to high risk of early death and a complicated in-hospital Course [5].

3.4. EKG

EKG findings vary from patient to patient. Characteristic findings are—sinus tachycardia, T-wave changes, ST-segment changes, right axis deviation, S1-Q3-T3, RBBB and P-pulmonale.

3.5. Chest X-Ray (Figure 3)

Primarily to exclude other diagnoses like pneumonia, pneumothorax, CHF, tumour, and rib fracture, which are also helpful in interpreting the V/Q scan. PE can present with radio-graphical signs on chest X-ray like (https://radiopaedia.org/articles/pulmonary-embolism)—Fleischner sign: Enlarged pulmonary artery, Hampton's Hump: peripheral wedge of airspace opacity and implies lung infarction, Westermark sign: regional oligemia and highest positive predictive value, Knuckle sign: abrupt tapering or cutoff of a pulmonary

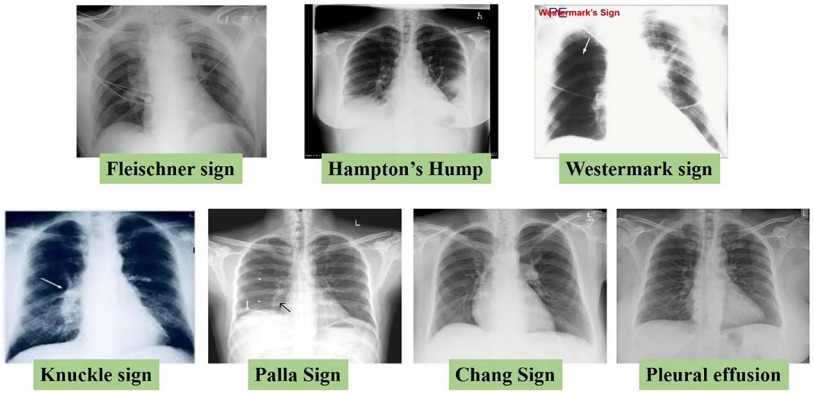


Figure 3. Different radio-graphical signs on chest X-ray of PE (https://radiopaedia.org/articles/pulmonary-embolism).

artery secondary to an embolus, Palla Sign: enlarged right descending pulmonary artery, Chang Sign: dilated right descending pulmonary artery with sudden cut-off, and in some cases Pleural effusion evident (35%).

3.6. Echocardiogram

Transesophageal Echocardiography (TEE) more sensitive than Transthoracic Echocardiography (TTE). It may demonstrate intra-cardiac, main pulmonary artery, and its main branches clots, RV enlargement and signs of right ventricular dysfunction. TTE should be performed to all patients with PE, and feasible in patients with stable hemodynamic status (**Figure 4(a)** & **Figure 4(b)**).

Echocardiographic RV/LV ratio ≥ 0.9 shown to be an independent predictor of hospital mortality. Registry of 1416 patients showed mortality rate is 1.9% if the RV/LV ratio is of <0.9, and 6.6% if the RV/LV ratio is of ≥0.9. Retrospective analysis of 120 patients with hemodynamically stable PE based on chest CT showed mortality at 3 months: 17% if RV/LV ≥ 1.5, 8% if 1 ≤ RV/LV < 1.5 and 0% if RV/LV 1.0 [6].

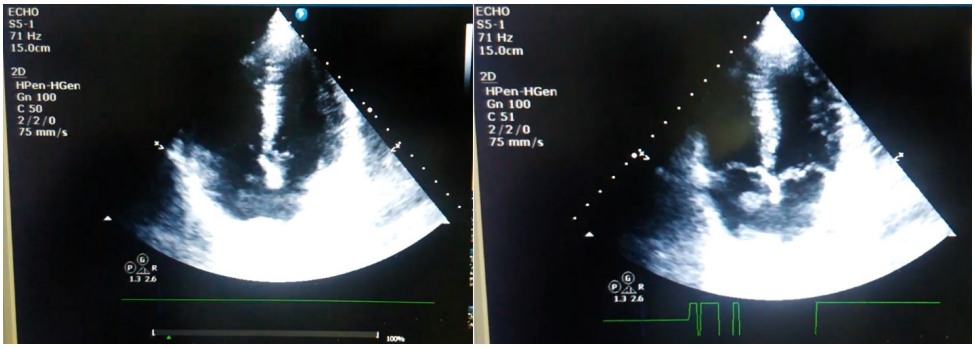
3.7. Computed Tomography Pulmonary Angiography (CTPA)

It has an excellent accuracy in diagnosing PE and may provide alternative diagnoses if PE is excluded with short acquisition time. Main disadvantages of CTPA are exposure to radiation and contrast related problems. CT identifies proximal PE, which is more often associated with the hemodynamic imbalance and not very accurate in diagnosing peripheral PE. CT can show enlarged right ventricle and estimation of the right ventricle and left ventricle ratio (**Figure 5**).

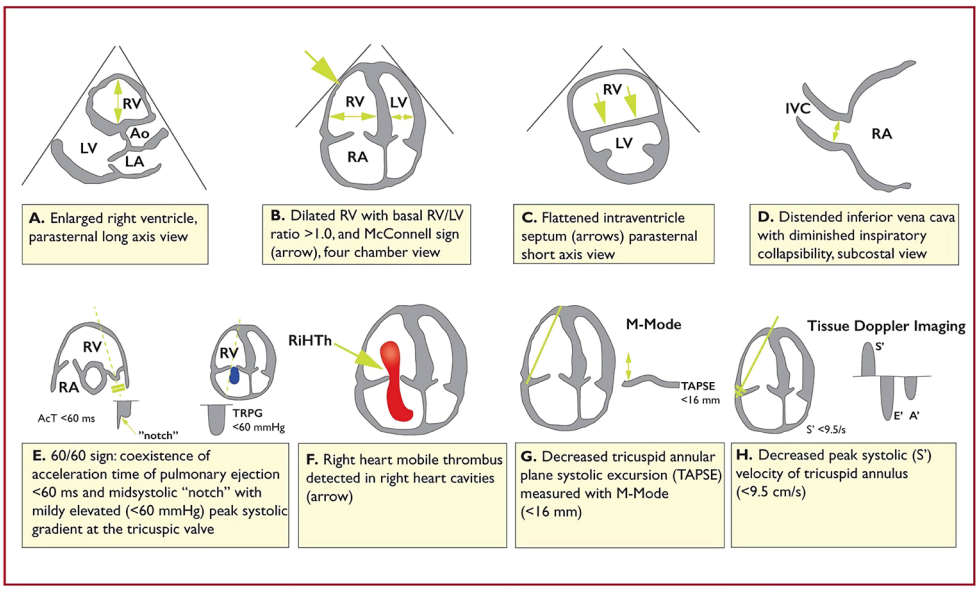
CT scan showing right pulmonary thrombus with RV enlargement (RV/LV ratio > 1) suggestive of massive pulmonary embolism (PE)

3.8. Planar V/Q Scan

Is useful in diagnosing PE but available in limited centres, relatively expensive, no contraindications, inconclusive in 50% cases, and cannot provide the alternative diagnosis.



(a)



(b)

Figure 4. (a) Trans-esophageal Echocardiography (TEE), Trans-thoracic Echocardiography (TTE); (b) Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload (ESC-2019). A' = peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging; AcT = right ventricular outflow Doppler acceleration time; Ao = aorta; E' = peak early diastolic velocity of tricuspid annulus by tissue Doppler imaging; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium; RiHTh = right heart thrombus (or thrombi); RV = right ventricle/ventricular; S' = peak systolic velocity of tricuspid annulus by tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid valve peak systolic gradient.

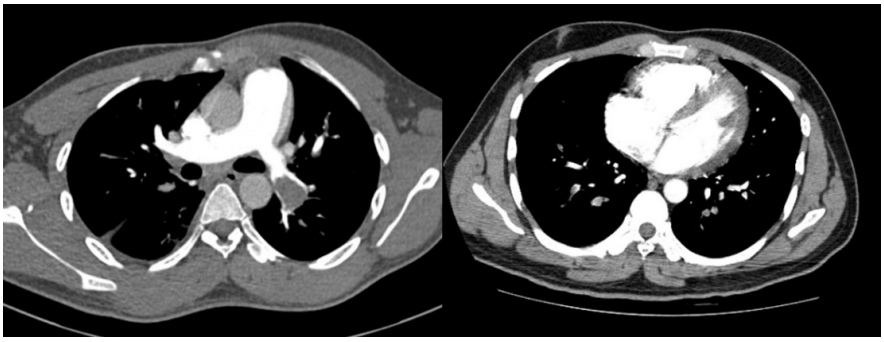


Figure 5. Computed tomography pulmonary angiography for PE.

3.9. Compression Ultrasonography Lower Limb (CUS)

If CUS shows proximal DVT in a patient with clinical suspicion of PE, PE diagnosis is acceptable, and if it shows only a distal DVT, further testing should be considered to confirm PE.

3.10. Pulmonary Angiogram (PA)

Most specific test, can detect even small emboli, presents like intraluminal filling defects, and vascular cutoffs. It is associated with a 0.5% mortality rate.

Bedside echo or emergency CTPA helps categorize and assess risk based on evidence of RV enlargement/RV dysfunction and make the alternative diagnosis. It would be preferable to start low molecular weight heparin (LMWH) in patients with suspected high-risk PE to avoid delay in starting therapy while carrying routine investigations. LMWH or Fondaparinux (Table 4) is recommended (preferred over unfractionated heparin (UFH)) for most patients as the anticoagulation is mandatory to all. Patients When oral anticoagulation is started, in a patient with PE who is eligible for a NOAC (Apixaban, Dabigatran, Edoxaban, or Rivaroxaban), a NOAC is recommended in preference to a Vitamin K Antagonist (VKA).

Table 4 of LMWH and oral anticoagulation.

VKA anticoagulation initiation should be overlapped with parenteral anticoagulation until an INR of 2.5 (range 2.0 - 3.0) is reached. NOACs should be avoided in patients with severe renal impairment, during pregnancy or lactation, and in patients with antiphospholipid antibody syndrome.

4. Management of PE

High-risk or massive PE seen in 5% of patients presenting with acute PE is

Table 4. Recommended LMWH and oral anti-coagulant doses based European society of cardiology 2019 guidelines.

	Dosage	Interval
Enoxaparin	1.0 mg/kg	Every 12 h
	Or	
	1.5 mg/kg	Once daily
Tonzaparin	175 IU/kg	Once daily
Dalteparin	100 IU/kg	Every 12 h
	Or	
	200 IU/kg	Once daily
Nadroparin	86 IU/kg	Every 12 h
	Or	
	171 IU/kg	Once daily
Fondaparinux	5 mg (body weight < 50 kg);	
	7.5 mg (body weight 50 - 100 kg);	Once daily
	100 mg (body weight > 100 kg);	

associated with at least 15% risk of in-hospital death, particularly during the first hours after admission (Figure 6). The crucial determining factor in PE management is the presence and severity of RV systolic dysfunction resulting from acute pressure load. These patients should be treated with reperfusion treatment and hemodynamic support. Thrombolytic therapy of PE is well tolerated with

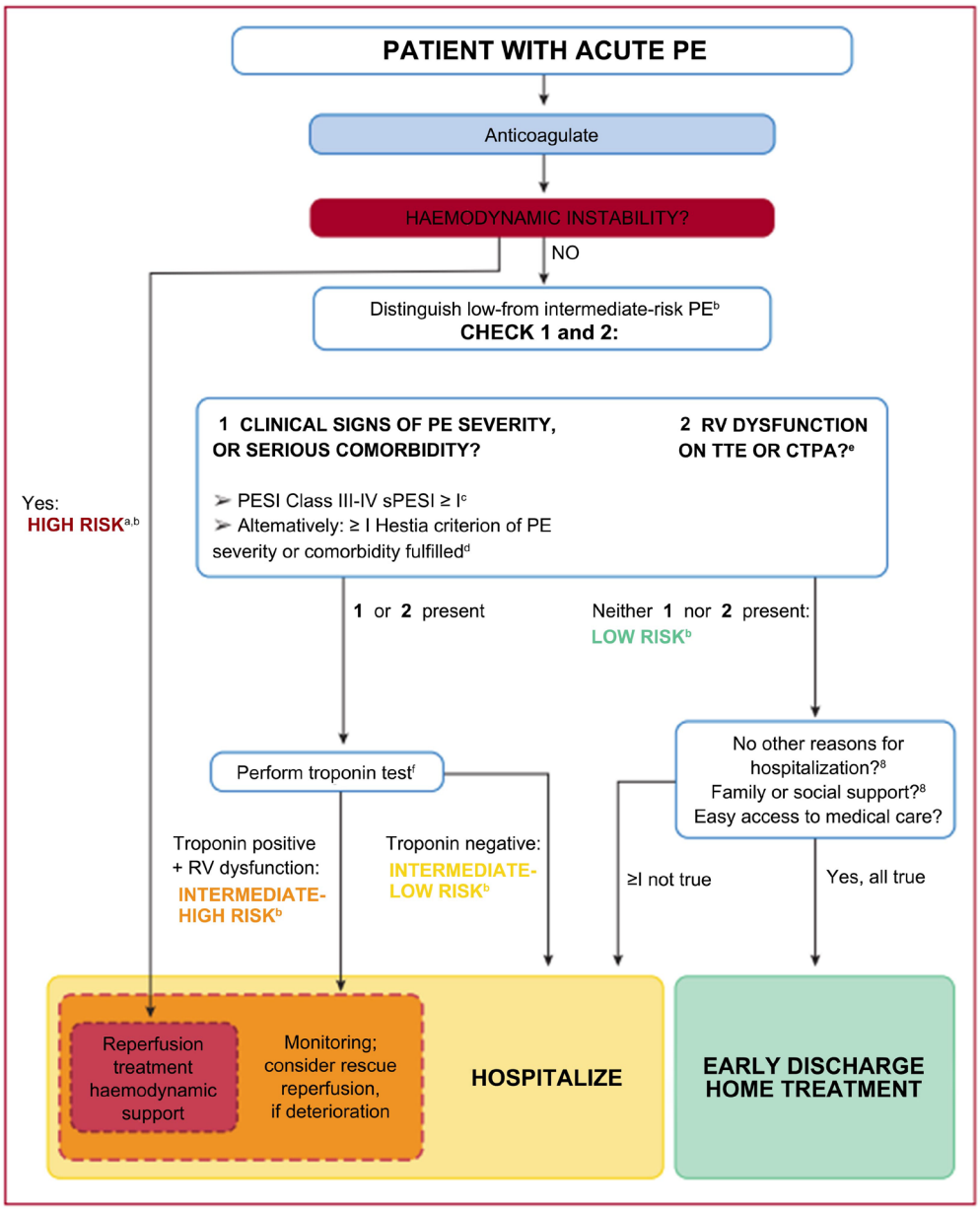


Figure 6. Risk-adjusted management strategy for acute pulmonary embolism (ESC-2019). CTPA = computed tomography pulmonary angiography/angiogram; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram. [a]emergency management algorithm. [b]high, intermediate-high-, intermediate-low-, and low-risk PE. [c]Cancer, heart failure and chronic lung disease are included in the PESI and sPESI. [d]the Hestia criteria. [e]Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE. [f]A cardiac troponin test may already have been performed during initial diagnostic work-up. [g]Included in the Hestia criteria.

excellent prognosis and carries a risk of significant bleeding 1.8% - 6.3% and Intra Cerebral haemorrhage (ICH) 1.2%. It produces faster clot lysing, dissolves obstruction, reverses RV failure, dissolves much of source, and decreases recurrence risk.

Risk-adjusted management strategy for acute PE

Efficacy and safety of systemic thrombolysis in acute PE well proven in Meta-analysis with the reduction in all-cause mortality, PE mortality, PE recurrence with low bleeding complications. Therapeutic doses and contraindications are given in Table 5.

Plasminogen Activator Italian Multicenter Study II (PAIMS-II) included 36 patients with acute PE treated with rtPA 10 mg bolus followed by 90 mg over 2 hours' period and showed reduced angiographic severity of PE, mean pulmonary artery pressure, and increase of the cardiac index [7]. A randomized, double-blind trial assessing RV function and pulmonary function compared Alteplase Vs Heparin which included 101 stable patients with acute PE showed improvement of RV function, reduction in RV dimensions, improvement of pulmonary function and no PE occurrence in rtPA group [8]. Another randomized control trial of rtPA (n = 22) vs Urokinase (n = 23) showed clot lysis in 82% of rtPA vs 48% Urokinase treated patients [9]. A European multicenter, double-blind trial showed a decrease in pulmonary vascular resistance at 2hours, *i.e.* 18% ± 22% in Urokinase vs 36% ± 17% in Alteplase treated patients [10]. RCT of STK vs Alteplase in massive PE with 50 patients showed significant RV ejection fraction and fall of PVR in Alteplase group compared to STK [11].

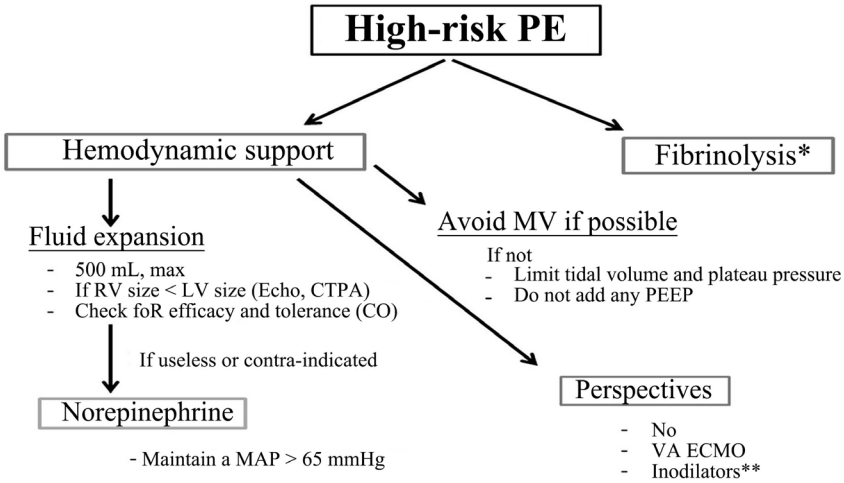
Table 5. Therapeutic doses and contraindications for acute PE.

Molecule	Regimen	Contraindications to fibrinolysis
Recombinant tissue-type plasminogen (rtPA)	100 mg over 2 h 0.6 mg/kg over 15 min (maximum dose 50 mg)	**Absolute:** ➢ History of hemorrhagic stroke or stroke of unknown origin ➢ Ischemic stroke in previous 6 months ➢ CNS neoplasm ➢ Major trauma, surgery, or head injury in previous 3 weeks ➢ Bleeding diathesis ➢ Active bleeding
Streptokinase	250,000 IU as a loading over 30 min, followed by 100,000 IU/h over 12 - 24 h Accelerated regimen: 1.5 million IU over 2 h	
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12 - 24 h Accelerated regimen: 3 million IU over 2 h	**Relative:** ➢ Transient ischemic attack in previous 6 months ➢ Oral anticoagulation ➢ Pregnancy or first postpartum week ➢ Non-compressible puncture sites ➢ Traumatic resuscitation ➢ Refractory hypertension (systolic BP > 180 mmHg) ➢ Advanced liver disease ➢ Infective endocarditis ➢ Active peptic ulcer

All patients with massive PE should be tried with fluid expansion if no significant IVC and RV dilatation followed by IV Nor-epinephrine and IV Dobutamine infusion for hypotension correction inotropy. Volume loading saline or ringer's lactate up to 500 ml over 15 to 30 minutes can be considered in patients with average to low central venous pressure. It sometimes can be over distending the RV, worsen ventricular interdependence and reduce CO. Mechanical ventilation with Positive End Expiratory Pressure (PEEP) is to be avoided as far as possible which may worsen the clinical condition, and try to limit tidal volume plateau pressure due to decreasing venous return. Some high-risk PE patients may get benefited with additional mechanical circulatory support like ECMO along with thrombolysis treatment; catheter-directed PE therapy and surgical pulmonary embolectomy.

Rescue thrombolysis therapy is recommended for patients with hemodynamic deterioration in anticoagulation therapy. Alternatively, these patients can be treated with surgical embolectomy or catheter-directed thrombolysis or interventions percutaneously. Routine treatment is not recommended for intermediate or low-risk PE patients. Percutaneous catheter-directed thrombolysis treatment should be considered for high-risk PE patients whose thrombolytic therapy is contraindicated or has failed. ECMO should be considered in combination with surgical embolectomy or catheter-directed therapy in patients with high-risk PE associated with refractory collapse or cardiac arrest (Figure 7).

No clinical benefit of VA-ECMO in patients with PE unless combined with surgical embolectomy or catheter-directed therapies. Catheter-directed thrombolysis includes CDT, lytic assisted devices—pharmaco mechanical, sonic assisted, Mechanical thrombectomy devices like simple suction ± clot fragmentation, and large bore aspiration.



RV right ventricle, LV left ventricle, computed tomography pulmonary angiography (CTPA), cardiac output (CO), mechanical ventilation (MV), nitric oxide inhalation (NO), veno-arterial extracorporeal membrane oxygenation (VA ECMO)

Figure 7. Proposal for hemodynamic management in high-risk PE (Meyer G, *Ann. Intensive Care* 2016).

Surgical embolectomy is indicated in patients with massive PE with contraindication to thrombolytic therapy, failed thrombolytic treatment, pregnancy, right heart failure or cardiogenic shock.

European Society of Cardiology (ESC) 2019 guidelines recommended Hestia exclusion criteria for choosing outpatient management of PE (Table 6).

5. Risk Factors Associated with Recurrent Venous Thromboembolism (VTE) and Anticoagulant-Related Bleeding (Table 7)

Long-term PE management after discharge depends on the possibility of recurrent

Table 6. Hestia exclusion criteria for choosing outpatient management of PE by ESC 2019.

Criterion/question
Is the patient hemodynamically unstable?
Is thrombolysis or embolectomy necessary?
Active bleeding or high-risk of bleeding?
More than 24 h of oxygen supply to maintain oxygen saturation > 90%?
Is PE diagnosed during anticoagulation treatment?
Severe pain needing I.V. pain medication for >24 h?
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, no support system)?
Does the patient have a creatinine clearance < 30 mL/min?
Does the patient have severe liver impairment?
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?
If at least one of the questions is answered with "yes", the patient can't discharged early.

Table 7. Risk factors associated with recurrent VTE and anticoagulant-related bleeding.

Recurrent VTE	Serious or fatal bleeding	Both recurrent VTE and severe bleeding
Initial unprovoked VTE	Low platelet count	Increased age
Initial proximal DVT or PE	Previous bleeding	Cancer
Thrombophilia	Recent major bleeding	Immobilization
Residual proximal thrombosis	Previous stroke	Recent surgery (transient)
Male sex	Hepatic failure	Severe renal impairment
Elevated D-dimer concentrations	Diabetes	
When not receiving anticoagulation	Abnormal prothrombin time	
Pregnancy	Thrombocytopenia	
Anticoagulation lasting < 3 months	Poor anticoagulant control	
	Comorbidity	
	Anemia	

PE, fatal bleeding and balancing the risk vs benefit of preventing recurrence vs bleeding related events. Standard anticoagulation therapy for at least three months is recommended to all patients, and it can be stopped after three months for patients with 1st PE/VTE secondary to major transient/reversible risk factor.

Indefinite duration is recommended for recurrent VTE (*i.e.* with at least one previous PE or DVT) not related to a significant transient or reversible risk factor and patients with antiphospholipid antibody syndrome. It would be preferable to assess drug tolerance and adherence, hepatic and renal function, and the bleeding risk at regular intervals during follow-up. For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first six months over VKAs. Edoxaban and Rivaroxaban in patients without gastrointestinal cancer should be considered as an alternative treatment to LMWH. Routine use of IVC filter is not recommended, indicated to PE patients with absolute contraindication to anticoagulation and in case of PE recurrence despite therapeutic anticoagulation [5].

In a pregnant patient with suspected PE, venous CUS should be considered to avoid unnecessary irradiation. Perfusion scan or CTPA should be considered to rule out suspected PE. LMWH therapy should be considered for all pregnant women with PE, thrombolytic therapy or surgical embolectomy should be recommended for patients with high-risk PE. NOACs should be avoided during pregnancy or lactation period [5].

6. Pulmonary Embolism Response Team (PERT) Approach

With the prompt response, PE management with Pulmonary Embolism Response Team (PERT) improves patient outcomes using collaborative, multidisciplinary teams with the best therapeutic options available with well-ordination protocol-based services (**Figure 8**). It was observed that with PERT based management reduces delay in diagnosis and treatment, reducing mortality by choosing the best possible therapeutic options.

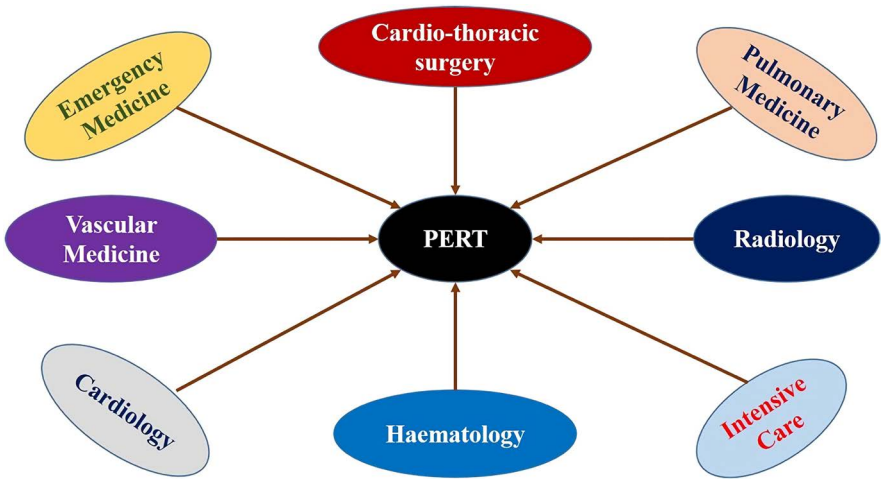


Figure 8. Pulmonary embolism response team.

7. Conclusion

VTE clinically presenting as DVT or PE, is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke. Thrombolytic therapy is recommended in all patients with high risk PE, unless contraindicated. Routine use of primary systemic thrombolysis is not recommended in patients with intermediate-or low-risk PE. The assembly of a PERT can offer a way to expeditiously and simultaneously engage multiple experts to generate a thoughtful, coordinated, and comprehensive treatment plan for patients with PE.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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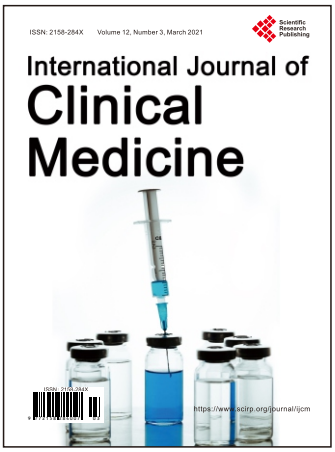

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