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## PROGNOSTIC FACTORS OF INTRACRANIAL PURULENT-SEPTIC COMPLICATIONS OF COMBAT-RELATED GUNSHOT PENETRATING SKULL AND BRAIN WOUNDS

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**Ключевые слова:** гнойно-септические осложнения, интракраниальные осложнения, черепно-мозговые ранения, боевые огнестрельные ранения, факторы прогноза, антибактериальная терапия, летальность, исходы

**Abstract.** Prognostic factors of intracranial purulent-septic complications of combat-related gunshot penetrating skull and brain wounds. Sirko A.G., Dzyak L.A., Pylypenko G.S., Yovenko I.O., Skrypnik A.A. Purpose – to analyze the structure of intracranial purulent-septic complications (IPSC), determine the factors influencing development of purulent-septic complications in patients with combat-related gunshot penetrating skull and brain wounds (CRPSBW), determine the effect of intracranial PSC on patients' outcomes. A prospective analysis of results of examination and treatment of 121 patients was performed. All patients had gunshot penetrating skull and brain wounds sustained in combat conditions during a local armed conflict in the Eastern Ukraine. Evaluation of treatment outcome included analysis of mortality in 1 month (survived/died) and dichotomous Glasgow Outcome Scale (GOS) score in 12 months (favorable/unfavorable outcome). 121 wounded men aged 18 to 56 (average, 34.1±9.1) were included in the study. Intracranial purulent-septic complications (IPSC) were diagnosed in 14 (11.6%) gunshot CRPSBW patients. The following prognostic factors had statistically significant correlation with the risk of intracranial purulent-septic complications development: wound liquorrhea on admission ( $p = 0.043$ ), intraventricular hemorrhage ( $p = 0.007$ ), bone fragments left in the wound ( $p = 0.0152$ ), and duration of inflow-outflow wound drainage for more than 3 days ( $p = 0.0123$ ). Intracranial PSC patients had mortality rate of 50%, and only 14.3% of those patients had a favorable outcome according to GOS score in one year. Presence of intracranial PSC had statistically significant association with mortality rate ( $p = 0.0091$ ) and GOS score in one year ( $p = 0.0001$ ).

**Реферат.** Прогностичні фактори розвитку внутрішньочерепних гнійно-септичних ускладнень бойових вогнепальних проникаючих поранень черепа і головного мозку. Сірко А.Г., Дзяк Л.А., Пилипенко Г.С., Йовенко І.О., Скрипник О.О. Мета – провести аналіз структури внутрішньочерепних гнійно-септичних ускладнень (ВГСУ); визначити фактори, що впливають на розвиток гнійно-септичних ускладнень у пацієнтів з бойовими вогнепальними проникаючими пораненнями черепа і головного мозку; визначити вплив внутрішньочерепних ГСУ на результати лікування пацієнтів. Проведено проспективний аналіз результатів обстеження та лікування 121 пораненого. Всі постраждали мали вогнепальні проникаючі поранення черепа і головного мозку, отримані в бойових умовах у ході локального збройного конфлікту на сході України. Оцінка результату лікування включала аналіз летальності через 1 міс. (вижив / помер) і дихотомічну оцінку за

шкалою виходів Глазго (ШВГ) через 12 міс. (сприятливий / несприятливий результат). У дослідження включено 121 поранений чоловік у віці від 18 до 56 років (у середньому –  $34,1 \pm 9,1$  року). Внутрішньочерепні гнійно-септичні ускладнення (ВГСУ) діагностовано в 14 (11,6%) поранених з вогнепальними проникаючими черепно-мозковими пораненнями. Статистично значуще корелювали з ризиком розвитку внутрішньочерепних гнійно-септичних ускладнень такі прогностичні фактори: наявність рани та ліквореї при надходженні ( $p = 0,043$ ), наявність внутрішньошлуночкового крововиливу ( $p = 0,007$ ), залишені кісткові фрагменти в рані ( $p = 0,0152$ ) і тривалість припливно-відливного дренивання рани більше 3-х діб ( $p = 0,0123$ ). Летальність серед пацієнтів з внутрішньочерепними ГСУ становила 50%, а сприятливий результат за ШВГ через рік мали тільки 14,3% поранених з внутрішньочерепними ГСУ. Наявність внутрішньочерепних ГСУ статистично значущо була пов'язана з летальністю пацієнтів ( $p = 0,0091$ ) і оцінкою за ШВГ через рік ( $p = 0,0001$ ).

In available literature data, infectious complications are considered among other important prognostic factors of mortality and disability [12, 15]. The most frequent complications in neurosurgical patients are pulmonary embolism (PE) (7%), liquorrhea (8.6%), and meningitis (9.1%) [17].

B. Aarabi [3], after examining surgical outcomes in 435 patients with craniocerebral wounds during the Iran-Iraq war, concluded that the two main factors of mortality in the group were low Glasgow Coma Scale (GCS) score and presence of infection. Mortality in this series was 16.3%. 53 of 71 (74.7%) had GCS from 3 to 8. 35 of 71 (49.3%) had an infection as a main adverse factor (25 cases of meningitis and 10 cases of sepsis).

It should be noted that, during the Vietnamese and Korean Wars, extensive surgical treatment of brain wounds was applied. M. Carey et al. reported on the results of treatment of 103 American soldiers who sustained brain injuries during the Vietnam War. Severe brain wounds, meningitis, and PE were the main causes of late mortality. 34% of the injured had brain wound treatment complications, such as left bone fragments (16%), infection (15%), liquorrhea, and wound breakdown (2%) [5]. "Aggressive" surgical tactics was associated with high postoperative mortality, development of persistent neurologic impairment and post-traumatic epilepsy in a significant number of patients [20].

On the contrary, during the Libyan-Israeli conflict, a sparing surgical tactics was applied. When using sparing tactics, mortality remained approximately the same, but the incidence of post-traumatic epilepsy significantly decreased [4].

A compromise during the Afghan and Iraq campaigns was the widespread use of decompressive craniotomy in combination with minimal surgical brain wound treatment and hermetic closure of dura mater defect [21]. The advantages of such surgical tactics were so obvious that they allowed Stephens et al. [7] to call the last decade military field surgery the "era of decompressive trepanation."

According to some authors [9], decompressive craniotomy must be an operation of choice in patients with craniocerebral wounds. Timely decom-

pressive trepanation not only made it possible to effectively control ICP, but also to perform complete surgical treatment with necrotic tissue and foreign bodies removal, which eventually significantly reduce the incidence of infectious complications [11].

During the Afghan campaign, military neurosurgeons encountered the problem of treating post-traumatic meningitis caused by *Acinetobacter calcoaceticus* and *Acinetobacter baumannii*, microorganisms with extremely rapid development of multi-resistance to antibiotics, including carbapenems [13]. In addition to complete surgical wound treatment with necrotic tissue and foreign bodies removal, the second important decision to effectively reduce complications after craniocerebral wounds was primary sealing of dura mater and skull soft tissues wounds. It was especially important in cases with wounds infection or colonization with *Acinetobacter baumannii* strains [22].

The disappointing results of treatment of combat-related penetrating skull and brain wounds (CRPSBW) are presented in a retrospective analysis, which included 102 patients with head wounds, who were treated in various medical institutions in the Egyptian province of North Sinai from 2011 to 2018. 50 patients (49%) had Glasgow Outcome Scale (GOS) score 1 (died), 12 patients (11.8%) had GOS 2 (stable vegetative state), and 40 (39.2%) survived, having varying degrees of disability as of the time of the last examination. The authors identified 3 adverse prognostic factors of gunshot skull and brain wounds. A dangerous anatomical area, where the presence of injury was a predictor of mortality, was identified. The boundaries of this area are callosal convolution superiorly, C2 body inferiorly, tentorium and postcranial fossa posteriorly, and anterior commissure anteriorly. Two-sided fixed mydriasis and low Glasgow Coma Scale score on admission were also recognized as independent predictors of mortality and unsatisfactory treatment outcome. The authors provide an analysis of complications in 52 survived patients [12]. Wound liquorrhea was registered in 3 patients (5.8%), which in all cases was associated with hydrocephalus and was treated with CSF drainage. Various central nervous system

infections occurred in 9 patients (17.3%), each underwent surgical treatment. Brain abscesses were present in 2 patients, meningitis – in 3, and wound infection in 4 patients.

Thus, the outcome of gunshot penetrating head wounds primarily depends on severity of structural destruction of brain substance, which is manifested by low Glasgow Coma Scale score on admission as well as presence and severity of intracranial septic complications [3, 5, 12, 22].

The purpose of the study is to analyze the structure of intracranial purulent-septic complications (IPSC), determine the factors influencing development of purulent-septic complications in patients with combat-related gunshot penetrating skull and brain wounds, determine the effect of intracranial PSC on patients' outcomes.

#### MATERIALS AND METHODS OF RESEARCH

Results of examination and treatment of 121 wounded were analyzed prospectively. Patients admitted to Neurosurgical Clinic at Public Institution, Mechnikov Dnipropetrovsk Regional Clinical Hospital (Mechnikov Hospital), Dnipro, Ukraine from May 25, 2014 to December 31, 2017 inclusively were included to the study. All patients had gunshot penetrating skull and brain wounds sustained in combat conditions during a local armed conflict in the Eastern Ukraine.

The patients were delivered to Mechnikov Hospital in the course of combat-related actions by aircrafts or ground vehicles from military hospitals (MH). Upon admission, all patients were examined by anesthesiology and intensive care physicians, neurosurgeons, surgeons, and traumatologists. If necessary, related specialists were also engaged: vascular surgeons, thoracic surgeons, maxillo-facial surgeons, ENT specialists and urologists. Consciousness after primary resuscitation was assessed based on Glasgow Coma Scale (GCS). Patients' condition on admission was assessed based on Injury Severity Score (ISS). Brain, neck, chest, abdomen, and pelvis HCT was performed in all patients. Brain HCT was performed using Optima CT660 helical computed tomograph (GE Healthcare, USA).

Neurosurgical interventions in the MH were performed in 44 (36.4%) patients. Primarily, 77 (63.6%) patients were operated in Mechnikov Hospital. Neurosurgical interventions in hemodynamically stable patients were performed immediately upon admission. For hemodynamically unstable patients, the surgery was postponed until the stabilization of condition. The surgery had the following objectives: bleeding arrest, intracranial hypertension and infectious complications prevention.

12 key stages of gunshot CRPSBW surgery included:

1. Treatment of wounds entrance and exit.
2. Intracranial pressure (ICP) sensor installation (if indicated).
3. Skull trepanation (resection, osteoplastic trepanation, decompressive craniectomy – on indications).
4. Bone fragments removal.
5. Injuring projectile and its fragments removal.
6. Brain detritus, contusion lesions, and brain crushing (debridement) removal.
7. Intracranial hematomas (epidural, subdural, intracerebral hematomas, intraventricular hemorrhage) removal.
8. Bleeding (from bone, cranial dura mater, sinuses, wounds) arrest.
9. Skull base (bones and dura mater) defects plastic reconstruction.
10. Inflow-outflow drainage system installation in the brain wound (on indications).
11. Duraplasty.
12. Craniofacial reconstruction. Plastic wound closure.

The "brain" stage of the surgery was performed using OPMI VARIO 700 microscope (Carl Zeiss, Oberkochen, Germany). Follow-up brain HCT was performed in all patients within 24 hours after the surgery. Subsequently, the frequency of repeated brain HCTs depended on behavior of neurological condition and dislocation syndrome based on previous HCTs.

Ultimate goals of intensive therapy in the patients were: stabilizing or improving neurological condition; decreasing severity of midline shift according to HCT; maintaining systolic blood pressure of 100 mmHg or higher for patients aged 50-69 and 110 mmHg or higher for patients aged 15-49 or 70+; eliminating hypoxia — avoiding  $\text{PaO}_2 < 60$  mmHg or  $\text{SatO}_2 < 90\%$ ; maintaining adequate cerebral perfusion pressure (between 60 and 70 mmHg); monitoring and adjusting intracranial hypertension (not higher than 22 mmHg) [14]. Prevention of infections in combat-related skull and brain wounds was performed in accordance with the U.S. military medicine recommendations on selection and duration of antimicrobial therapy [15].

The incidence of intracranial PSC development in gunshot CRPSBW patients, mortality and long-term outcomes in the presence of PSC were studied. Evaluation of treatment outcome included analysis of mortality in 1 month (survived/died) and dichotomous Glasgow Outcome Scale (GOS) score in 12

months (favorable/unfavorable outcome). Favorable outcome included the following: good recovery and moderate disability; unfavorable outcome – severe disability, vegetative state and death. Outcome evaluation according to GOS was performed using the standard method [8, 23]. Special attention was paid to the determination of factors that are statistically significant for development of intracranial purulent-septic complications.

#### Statistical analysis of outcomes.

We analyzed dependence of development of purulent-septic complications in patients with gunshot craniocerebral wounds on various groups of variables. The groups of variables included clinical and computed tomographic data and nature of therapeutic measures taken. For all variables, Spearman's rank correlation coefficient was used. Significant correlations ( $p < 0.05$ ) were subsequently subjected to more detailed analysis. For numerical (ordinal or stream) variables, the Mann-Whitney U test was used; for categorical variables, the exact F-test was applied. For statistically significant clinical factors, the odds ratio with a 95% CI was used. All data were analyzed using a statistical data processing software package, Statistica 64, version 12.

#### RESULTS AND DISCUSSION

121 patients aged 18 to 56 (average,  $34.1 \pm 9.1$ ) were included in the study. Upon admission, consciousness level according to the Glasgow Coma Scale varied from 3 to 15 (average,  $10 \pm 4$ ), and patients' condition according to ISS varied from 16 to 57 (average,  $27.7 \pm 7.6$ ).

In 101 (83.5%) patients wounds were caused by mine blast fragments, in 20 (16.5%) patients – by small-arm bullets. The most frequent were non-perforating and ricochet wounds, which were detected in 73 (60.3%) and 29 (24%) patients, respectively. Penetrating wounds occurred in 14 (11.6%) and gutter wounds – in 5 (4.1%) patients. Almost half of the patients (50.4%) were diagnosed with isolated wounds. 55 (45.5%) patients were diagnosed with combined wounds. In such cases skull and brain wounds were combined with extracranial wounds (face, body, limbs, chest, abdominal cavity, and pelvic organs). High percentage of combined wounds is associated with high frequency of use of modern mine blasting devices. 5 (4.1%) patients had combined wounds (damages), where, along with mechanical injuries from the injuring shell, there were scalp and face burns of varying severity. Such injuries were typically caused by mine explosion in the immediate vicinity of the victim.

Foreign bodies of metal density (bullets/fragments) in cranial cavity were found in 73 (60.3%) patients before surgery and 29 (24%) patients after surgery. Bone fragments in cranial cavity were found in 117 (96.7%) patients before surgery and 15 (12.4%) patients after surgery. Thus, during surgical treatment of brain wound, it was possible to isolate bone fragments in 84.3% of patients and metal density foreign bodies in 36.3% of patients. This is due to the nature of spread of such foreign bodies in brain wound. Low kinetic energy bone fragments were located in the first sections of wound channel at a depth of 5 cm and were easily accessible during surgical treatment. At the same time, metal density foreign bodies with high kinetic energy often penetrated to a greater depth, up to the opposite bone, and often ricocheted. The search and removal of metallic foreign bodies in such cases are associated with additional brain matter injury and was not performed by us.

Intracranial purulent-septic complications (IPSC) were diagnosed in 14 (11.6%) patients with gunshot CRPSBW. Isolated meningocephalitis was detected in 8 patients, meningoencephalitis combined with ventriculitis – in 3 patients, meningoencephalitis combined with ventriculitis and subdural empyema – in 2 patients. In one patient, recurrent meningoencephalitis was complicated by multiple brain abscesses.

According to the results of bacteriological CSF examination, in 12 cases it was possible to identify the pathogen. *Acinetobacter baumannii* was inoculated from CSF in 5 cases, the following pathogens of *Klebsiella pneumoniae* and *St. Epidermidis* were found in 2 patients. In 1 case, the following pathogens were detected: *Pseudomonas aeruginosa*, *Enterobacter agglomerans*, *Enterococcus faecalis*.

Clinical profile of IPSC group patients is shown in Table 1.

Presence of intracranial PSC had statistically significant association with mortality rate ( $p = 0.0091$ ) and GOS score in one year ( $p = 0.0001$ ). So, mortality in PSC patients was 50%; in patients without PSC – 17%. Only 14.3% of patients with PSC and 72% of patients without intracranial PSC had favorable outcome according to GOS in one year. Calculated odds ratios showed that, one month after the injury, patients without PSC had 3.55 times higher chances to survive (OR (95% CI) = 4.94 (1.54–15.83)). Moreover, patients without PSC in one year had good outcome 15.4 times more often (OR (95% CI) = 15.4 (3.2–73)).

Table 1

**Clinical profile of IPSC group patients**

Characteristics	N of patients (%)
<b>Patients' characteristics</b>	
1	Brain crushing 14 (100%)
2	Transventricular wound 2 (14.3%)
3	Intraventricular hemorrhage 7 (50%)
4	Wound liquorrhea on admission 10 (71.4%)
5	Skull base fracture 6 (42.9%)
6	Foreign metal bodies in the brain before surgery 8 (57.1%)
7	Foreign bodies (bone fragments) in the brain before surgery 14 (100%)
8	Combined craniocerebral wounds 4 (28.6%)
<b>Neurosurgical procedures</b>	
9	Craniotomy 4 (28.6%)
10	Craniectomy 10 (71.4%)
11	Debridement 14 (100%)
12	Ventriculostomy in the acute period 4 (28.6%)
13	Inflow-outflow drainage of brain wound 13 (92.5%)
14	Skull base plastic repair 3 (21.4%)
15	Repeated surgery in the acute period 7 (50%)
<b>Intensive therapy</b>	
16	Posthemorrhagic anemia 11 (78.6%)
17	Massive hemotransfusion 6 (42.8%)
18	Coagulopathy 2 (14.3%)
19	Long-term ALV — artificial lung ventilation (> 3 days) 12 (85.7%)
20	Long stay in intensive care unit (ICU) (> 3 days) 14 (100%)
21	Vasopressor support 5 (35.7%)
22	PE (pulmonary embolism) 0 (0%)
23	Seizures 2 (14.3%)
24	SIRS (Systemic Inflammation Response Syndrome) 12 (85.7%)
25	MODS (Multiple Organ Dysfunction Syndrome) 7 (50%)
26	APACHE II (score) 6.7±3.6 (1–13)
<b>Infectious complications</b>	
27	Respiratory 8 (57.1%)
28	Urinary tract infection 1 (7.1%)
29	Wound infection 7 (50%)
30	Meningocephalitis 14 (100%)
<b>Treatment outcomes</b>	
31	Mortality 7 (50%)
32	Favorable outcome according to GOS at 1 year 2 (14.3%)

Statistically significant correlation with the risk of intracranial purulent-septic complications was found in the following four clinical characteristics: wound liquorrhea on admission, intraventricular

hemorrhage according to brain HCT, bone fragments left in the wound, and duration of inflow-outflow drainage of the wound for more than 3 days (Tab. 2, 3).

Table 2

**Relationship of clinical characteristics with development of intracranial purulent-septic complications**

Clinical characteristics	Purulent-septic complications		p criterion (value)
	N of patients (%)		
	absent	present	
<b>N of patients</b>	<b>106</b>	<b>14</b>	
<b>GCS on admission</b>			<b>0.39</b>
≤ 8	40 (37.4)	7 (50)	
> 8	67 (62.6)	7 (50)	
<b>Presence of wound liquorrhea on admission</b>			<b>0.043</b>
present	43 (40.2)	10 (71.4)	
absent	64 (59.8)	4 (28.6)	
<b>Skull base fracture</b>			<b>0.55</b>
present	35 (32.7)	6 (42.9)	
absent	72 (67.3)	8 (57.1)	
<b>IVH (intraventricular hemorrhage)</b>			<b>0.007</b>
present	17 (15.9)	7 (50)	
absent	90 (84.1)	7 (50)	
<b>Drainage application and duration</b>			<b>0.0123</b>
≤ 3 days	93 (86.9)	8 (57.1)	
more than 3 days	14 (13.1)	6 (42.9)	
<b>Bone fragments left in the brain</b>			<b>0.0152</b>
present	10 (9.3)	5 (35.7)	
absent	97 (90.7)	9 (64.3)	
<b>Metallic foreign bodies left in the brain</b>			<b>0.74</b>
present	25 (23.4)	4 (28.6)	
absent	82 (76.6)	10 (71.4)	

Using the Mann-Whitney U test, the dependence of risk of purulent-septic complications development on the following numerical variables was studied: patient's age and time from the moment of the injury

to the delivery to a regional clinical hospital. Neither age ( $p=0.96$ ) nor the duration of evacuation ( $p=0.36$ ) were the statistically significant risk factors for development of purulent-septic complications.



**Odds ratios and 95% CIs for clinical characteristics associated with risk of IPSC development**

Characteristics	OR frequency (95% CI)
	Risk of purulent-septic complications
Presence of wound liquorrhea on admission	3.72 (1.1–12.6)
Intraventricular hemorrhage	5.29 (1.6–17.0)
Duration of brain wound drainage over three days	4.98 (1.5–16.5)
Bone fragments left in the brain	5.4 (1.5–19.2)

The role of bone fragments left in the brain in the development of wound infection was indicated by many authors [1, 2, 16, 18]. Experimental studies by Pitlyk et al. revealed that such bone fragments did not increase the infection rate itself, but when scalp or hair accompanied such fragments the rate was 10 times higher [19].

M. Carey et al. [5] noted that half of all bone fragments removed from the wound during repeated treatment were contaminated by bacteria. Removal of bones left in the brain caused some accidental complications but undoubtedly prevented the development of late brain abscesses, which developed only in 2 patients.

In his study of 379 patients wounded during the Iran-Iraq war, Aarabi [2] showed more CNS infections in patients with bone fragments left, but the correlation was not statistically significant.

In an earlier study of Cosar A. et al. [6], bone and metal fragments left after the initial surgery were found in 130 (32.5%) of 400 patients. According to the authors, fragments left in the brain did not increase the risk of infection and were only removed in case of infection development. Presence of cerebrospinal fluid fistula was associated with high incidence of infection, which is confirmed by our data. Presence of diffuse brain damage, CNS infections, and involvement of ventricular system in the wound process were associated with poor outcome.

Aarabi reported a 20-fold higher infection rate in the presence of cerebrospinal fluid fistula compared with those who did not have such injury [1, 2]. Other authors reported higher infection rate associated with cerebrospinal fluid fistula, rhinorrhea, and otorrhea [16, 18].

Meirowsky et al. [16] diagnosed CSF fistulae in 101 of 1,113 Vietnamese war participants with CBF disorder, caused by gunfire. Infection developed in fifty (49.5%) of those patients. Among 1,032 patients who did not have CSF fistula, infection only developed in 47 (4.6%).

Ventricular system wound belongs to extremely severe type of craniocerebral wounds, which causes mortality in 32.8% [10] of patients. Cerebral edema (50%), brainstem injury, and intracranial infection (13.6%) are the main causes of death in ventricular wounds.

An analysis of prognostic factors of intracranial infectious complications development makes it possible to create adequate therapeutic tactics and plan surgical intervention. The maximum and soonest possible removal of foreign bodies, closure of cerebral wound to prevent early liquorrhea, and the shortest possible inflow-outflow drainage should contribute to the reduced incidence of intracranial purulent-septic complications. This problem requires further review.

**CONCLUSIONS**

1. Intracranial purulent-septic complications (IPSC) were diagnosed in 11.6% of gunshot CRPSBW patients. Isolated meningocephalitis was detected in 8 patients, meningocephalitis combined with ventriculitis – in 3 patients, meningocephalitis combined with ventriculitis and subdural empyema – in 2 patients. In one patient, recurrent meningocephalitis was complicated by multiple brain abscesses.

2. Wound liquorrhea on admission, intraventricular hemorrhage, bone fragments left in the wound, and duration of inflow-outflow wound drainage for more than 3 days have statistically significant correlation with the risk of intracranial purulent-septic complications.

3. Presence of intracranial PSC has statistically significant association with mortality rate ( $p=0.0091$ ) and GOS score ( $p=0.0001$ ) one year after the injury.

Conflict of interest. The authors declare no conflict of interest. All treatment approaches and conclusions are the authors' personal opinions and do not reflect the official policy or position of the Ukrainian army, armed forces, or government.

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