

## The role of the Kazan surgical school in better understanding of sepsis

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### Abstract

The work aims to give a clinical assessment of the scientific research of representatives of the Kazan surgical school in the 40–60s of the last century on the problem of sepsis and to consider the practical significance of the results obtained in the light of modern concepts about the purulent-septic disease, as well as to study the effectiveness of the methods used to reduce mortality in wound sepsis. The representatives of the Kazan surgical school were among the first physicians in the national medical society to substantiate the key role of the local focus/foci and generalization of infection in the development of sepsis. They first laid the foundations for the prevention of generalization of infection from the primary focus — as the main factor for developing sepsis. Their data on the role of bacteremia in the etiology of sepsis and the prevention of fulminant sepsis are still relevant. These achievements remain priorities for the domestic surgical school and have become part and parcel of the international guidelines 2016 on sepsis (“Sepsis-3”).

**Keywords:** the Kazan surgical school, focus of infection, generalization of infection, sepsis.

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Representatives of the Kazan Surgical School were among the first among the doctors from national medical schools to elaborate on the leading role of the primary focus (foci) and infection generalization in the development of sepsis. They first laid the foundation for the prevention of infection generalization from the primary focus as the main factor in sepsis development. Their information on the role of bacteremia in the etiology of sepsis and the prevention of fulminant forms of this disease has not lost its relevance to date. These achievements are a priority for national surgery and significantly supplement the international recommendations of 2016 on the concern of sepsis (“Sepsis-3”).

To this day, sepsis remains the most difficult problem of modern clinical medicine, as it is an infectious pathological condition that threatens life owing to septic shock and multiple organ failure [1, 2]. This complication is a common pathological condition in different age groups and is accompanied by high mortality, especially in septic shock (60%–80% of cases) [1–3]. Particularly, sepsis with a fulminant clinical course is dangerous and is characterized by refractoriness to the generally accepted modern intensive care [4]. The treatment of each “septic patient” incurs extensive cost [1].

It should be recognized that among national medical schools, the Moscow Medical School with prominent representatives such as N.V. Davydovsky, V.G. Talalaev, V.I. Struchkov, and A.I. Abrikosov contributed to a certain extent to the development of topical issues of the etiology and pathogenesis of purulent-septic diseases in the 40s–60s of the last century. The works of these scientists are well known and extensively used by clinicians in everyday practice. However, the practical significance of the scientific achievements of the Kazan Surgical School for the aforementioned period remains unexplored and for this reason essentially forgotten or little known to clinicians; however, the achievements of this school are no less significant than those of the Moscow Medical School.

In the 40s–60s of the last century, one of the most authoritative representatives of the Kazan Surgical School and an academician of the Academy of Medical Sciences of the USSR, Professor A.V. Vishnevsky mainly engaged in the widespread substantiation and introduction of local infiltration anesthesia into clinical practice. The author, at the same time, paid great attention to the study of the therapeutic effect of procaine blocks in acute inflammatory processes (such as boils, carbuncles,

and peritonitis). Based on numerous clinical observations, A.V. Vishnevsky [5] completely rejected the erroneous and generally accepted opinion regarding the possible spread of infection when performing local infiltration anesthesia and using procaine blocks in patients with purulent inflammatory processes. At the same time, based on a large clinical material, the author confirmed the absence of any complications, both when providing local anesthesia and when using procaine blocks [5].

A.V. Vishnevsky found that “severe acute peritonitis, different in etiology, proceeded favorably even where, according to the general opinion, it was difficult to count on it” [5]. In addition, according to A.V. Vishnevsky, the therapeutic effect in such situations is mediated by neurotrophic factors, which was confirmed by the study conducted by A.D. Speransky. Notably, the therapeutic effect of procaine blocks in many inflammatory diseases occurs quickly and clearly, which, according to A.V. Vishnevsky, is convincing evidence regarding the pathogenetic role of the neurotrophic component in inflammation. This is expressed by a change in the course of the inflammatory process and is accompanied, as a rule, by a decrease in tissue edema and accelerated abscess formation or in rapid mortification (death) of cellulose [5].

A.V. Vishnevsky revealed that when used in an abscessed form of inflammation, novocaine blockade creates conditions for a faster resolution of this purulent focus that is, delimiting the site of inflammation with purulent fusion. However, the blockade does not always eliminate the purulent process. Recovery occurs after the opening and drainage of the purulent focus. Otherwise, after a while, a new recurrence of infection occurs [5]. Thus, the use of a blockade, e.g., in general purulent sepsis, will be useful if abscesses can not only be opened up but also be drained. Along with this, the blockade can be used in those cases when the purulent infection progresses, despite draining purulent focus (fistula). Features shown blockade in sepsis, when it develops from capillary thrombophlebitis [5].

When case blockade was used as a method of “wide novocainization of the limb,” A.V. Vishnevsky viewed this procedure as a means of preventing and treating the inflammatory processes in the wound. This is especially true for cases with no question of immediate amputation of the injured limb. A wounded patient usually arrives at the place of final wound treatment with a pronounced inflammatory reaction to one degree or another. According to the author, at this stage of infection onset, it is possible to stop the development of infection, without affecting the pathogen itself. In practice, of course, this does not in any

way eliminate the need for primary wound care. In this situation, the effect of the blockade must be considered as the action of an additional favorable treatment that expands the therapeutic possibilities in the fight against further complications resulting from the infection.

All this, as a whole, serves to eliminate the further development of an acute inflammatory process, stopping it until it leaves the stage of serous tissue permeation. As for the abscessing forms, they “go” to a faster limitation, suppuration, and resolution. An abscess that has not undergone a spontaneous opening must be opened; otherwise, the pus in it will “open” a new cycle of infection in a few days [5].

While evaluating the scientific research conducted by A.V. Vishnevsky in the light of modern concepts, we should note the author’s priority in understanding the role of the primary purulent focus in the development of sepsis. In addition, it is essential to decipher the spectrum of the pathogenetic action of procaine blocks and their practical significance for the prevention and treatment of acute inflammatory processes of various severity, including those complicated by abscess formation and sepsis.

Scientific works of A.V. Vishnevsky have gained worldwide recognition. Among all the scientists of that period, who highly appreciated the novelty of scientific contributions by A.V. Vishnevsky, was the outstanding French surgeon Rene Leriche who published several articles in French and German on the high therapeutic effectiveness of procaine blocks in purulent inflammatory complications [5]. It should be borne in mind that A.V. Vishnevsky only partially coincided with the period of initial use of antibiotics in clinical practice, in particular penicillin. Thus, it is not surprising that the author did not present any results on the use of antibiotics in the treatment of pyoinflammatory complications. This insufficiency in data was subsequently successfully compensated for by the scientists of the Kazan Surgical School [6].

An invaluable contribution to the understanding of sepsis in the 40s–50s of the 20th century was made by the scientists of the Kazan Surgical School, headed by Professor N.V. Sokolov. Microbiological studies on the pus from the primary focus were conducted in 111 patients who were wounded and treated in evacuation hospitals and in 81 patients with sepsis treated at a clinic. *Staphylococcus* spp. were detected in the pus of 47 (42.3%) wounded patients, *Streptococcus* spp. in 19 (17.1%), mixed microflora in 44 (39.6%), including various combinations of *Staphylococcus* spp. and *Streptococcus* spp., *Staphylococcus* spp. and *Clostridium*

*perfringens*, *Staphylococcus* spp. and *Pseudomonas aeruginosa*. The pus from wounds of 37, 10, 3, and 31 patients from a clinical setting was found to have *Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli*, and mixed microflora, respectively [6]. For microflora examination, blood from 100 patients was assessed, and blood from 65, 24, 2, and 9 patients was found to have *Staphylococcus* spp., *Streptococcus* spp., mixed microflora, and no microflora.

In addition, Blood for microflora was examined in 85 wounded evacuation hospitals. Of these patients, 57 (67.1%) had *Staphylococcus* spp., 18 (21.1%) had *Streptococcus* spp., and 10 (11.8%) had no microorganisms. However, in this last group of wounded patients, blood tests for microflora detection were conducted only once, and five of them died because of the fulminant form of sepsis. Thus, in relation to *Streptococcus* spp. in the blood and the focus there was a complete parallelism. *Staphylococcus aureus* was observed in isolated cases of many wounded patients but was found only in a purulent focus. However, even where *Staphylococcus* was identified in a purulent focus with a mixed flora, it was found only singly in the blood of these wounded [6]. The ratio of the microflora in the focus and blood in patients in the clinical setting was approximately the same as that in the wounded from evacuation hospitals [6].

Based on the study of the microbiological landscape, N.V. Sokolov [6] proposed the following classification for sepsis. Based on the nature of the course, sepsis was classified as (1) fulminant, (2) acutely protracted, and (3) cachectic (which is not an independent form, but the final stage of acutely protracted sepsis). The author substantiated the refusal to recognize a special form of subacute sepsis and even its chronic form [1], despite the fact that many of his fellow researchers recognized the identifying these two forms (e.g., Strazhesko N.D., Talalaev V.G., and Shlapobersky V.Ya.) [6].

Currently, although subacute and chronic forms of sepsis are still recognized [1], most other national and foreign authors completely deny the existence of these forms [2–4].

The fulminant form is characterized by a bright, fleeting clinical picture (within 6–12 hours) with progressive intoxication. According to N.V. Sokolov [6], fulminant form of sepsis occurs in 3.4%–8.5% of cases, often resulting in death. The author indicates that with the different forms of sepsis, the overall mortality in the 50s of the last century ranged from 20% to 25% [6].

With further advancements in medical science, together with the change in the concept of sepsis, ideas regarding sepsis pathogenesis were also

transformed. When the etiological significance of microorganisms for the development of sepsis was proven, studies were aimed at establishing the role of microflora in the primary focus [6]. The development and characteristics of the course of sepsis and the severity of morphological changes were associated with the virulence of the microbe. The importance of the macro-organism was left in the “shadow.” The microflora in the focus and blood of wounded patients in clinical settings and in evacuation hospitals was found to be similar.

There was a misconception regarding the multiplication of microorganisms in the blood of patients with sepsis. Initially, sepsis was identified with bacteremia, and after considerable observation and research, no basis for this correlation was proved. One of the first researchers, N.V. Sokolov [6] proved that bacteremia might occur during any suppurative process, while sepsis will not develop at the same time. Conversely, bacteria in the blood might not be detected even following a systematic study, and the patient dies with severe sepsis. These data were confirmed later in studies by other authors [2–4]. According to some scientists, bacteremia occurs in 30%–50% of patients with sepsis [2, 3, 7].

The initial stage of scientific research by Professor N.V. Sokolov, the leading surgeon of the evacuation hospital and surgical clinic of Kazan during the period of the Great Patriotic War (1941–1945), was completely focused on providing emergency surgical care to the wounded arriving at evacuation hospitals with purulent-septic complications after gunshot wounds (such as phlegmon of soft tissues, osteomyelitis, and purulent pleurisy). In addition, the research focused on the search and development of methods for the prevention and treatment of wound sepsis, especially its fulminant form, and other purulent-septic complications to reduce mortality.

The next stage of scientific research by Professor N.V. Sokolov and his students (including Takhonova T.P. and Medvedovskaya G.D.) during the post-war period, in particular, the second half of 1945 and the 50s–60s of the last century, was aimed at delineating the topical issues of pathogenesis sepsis and other purulent-septic complications. It was also aimed at the search and development of effective methods to treat purulent-septic complications, introduce them into practice, and evaluate the results of the use of blood transfusions in patients with sepsis.

It was during the period of rave reviews about the effectiveness of blood transfusion that Professor N.V. Sokolov was one of the first in the national literature to point out the danger of whole blood transfusion during the acute stage of sepsis, espe-

cially in the fulminant form, and in large doses (up to 1 L). To confirm the correctness of this indication, the author cited deaths of patients with sepsis after repeated transfusion of 1 L or more whole blood [6]. At the same time, the author proposed using blood plasma transfusion in small volumes (200–250 mL) for the treatment of patients with sepsis every 3–4 days.

The scientific research conducted by N.V. Sokolov and his students was extremely broad and dealt with various aspects of sepsis. In particular, it was found that in cocci infections, microbes can be eliminated from the blood relatively quickly (even within few minutes) by leukocytes, the lysing properties of blood plasma, the reticuloendothelial system of the liver, and subsequent excretion by the kidneys [6]. Microbiological studies revealed that during sepsis, cocci microbes multiply not in the circulating blood but in the primary purulent focus and secondary metastatic foci. The blood poured into the tissues and cavities can become a good environment for the growth of microorganisms.

Purulent microbes affect the body via the release of endotoxins and exotoxins. The causative agents of infection enter the bloodstream from the primary purulent focus by penetrating through the walls of blood vessels, most often through a thrombus, an obstructing vessel, and through the wall of lymphatic capillaries. In most cases, the blood is quickly freed of microorganisms, and in other, more rare cases, they settle in tissues and organs, creating conditions for development into metastatic foci [6].

The aforementioned results serve as a convincing evidence for the exit of the Kazan Surgical School, headed by academician A.V. Vishnevsky and Professor N.V. Sokolov, back in the 40s–60s of the last century to the forefront in the study of the problem of sepsis. During this period, several original scientific findings were reported that have not lost their significance to this day. In particular, over the past century, it was possible to identify the role of the primary focus of infection, which corresponds to a type of “spark” from which one of the most dangerous types of pathological condition, surgical sepsis “ignites,” and was possible to identify the main causative agents of infection and their associations [6]. The monograph “Surgical sepsis” [6] by Professor N.V. Sokolov outlines personal clinical observations of patients with a fulminant form of sepsis; these are so vivid and instructive that they leave an indelible mark on the soul of every modern surgeon on the problem of sepsis, which is practically still insufficiently studied.

N.V. Sokolov in his book expressed dissatisfaction with the results of treatment of sepsis, with

mortality in various disease forms ranging from 20% to 30%. At the same time, in case of gunshot wounds of various localizations complicated by sepsis, the overall mortality rate averaged to 35.6% [6]. The overall, average mortality among the observed patients with sepsis in the clinic was 27.1%. However, if all the observed patients with sepsis were divided into groups receiving and not receiving penicillin, then the mortality in the former group was only 15.1% [6]. These data allowed N.V. Sokolov to conclude that the use of antibiotics, in particular penicillin, is of undoubted importance for reducing mortality in sepsis.

We must not forget the fact that immediately before the start of the Great Patriotic War, the overall mortality rate among patients with surgical sepsis was 72%–75% [6]. Over the past two decades of the XX century, mortality in patients with sepsis was  $\geq 60\%$  [1–3, 7, 8]. Such results cannot be considered reassuring. Representatives of the Kazan Surgical School saw an improvement in the results of patients with sepsis following treatment and the possibility of reducing mortality, first of all in the prevention of infection generalization from the focus (foci), considering this as a leading factor in the development of sepsis.

Long-term studies of prominent representatives of the Kazan Surgical School, based on a large amount of factual material, testify to their high scientific level and can deservedly supplement some information on the problem of sepsis owing to the wider use of methods for preventing generalization of infection from the focus (foci) (Sepsis-3) [7]. The practical significance of the study results obtained by the Kazan Surgical School is confirmed, primarily by their focus on achieving one goal—saving several lives of the wounded and civilians with sepsis and its complications.

## CONCLUSIONS

1. During the Great Patriotic War and the post-war period, representatives of the Kazan Surgical School, headed by academician A.V. Vishnevsky and Professor N.V. Sokolov, demonstrated considerable readiness to provide highly qualified surgical care to individuals with wounds and with varying severity of injury as well as to achieve a significant reduction in mortality among patients with wound-associated sepsis.

2. The provision of highly qualified surgical care to the wounded was facilitated by timely; high-quality rehabilitation of the primary focus of infection; prevention of infection generalization; the use of blood transfusions according to indications; and the introduction of antibiotics, in particular penicillin and other therapeutic agents into practice.

**Author contributions.** V.E.V. — a detailed analysis of the scientific works of academician A.V. Vishnevsky on the problem of sepsis, clinical features, diagnostics, and treatment tactics in patients with sepsis based on the works of N.V. Sokolova, head of work; S.V.V. — study of scientific developments on the problem of sepsis, generalization of modern achievements on the problem of sepsis ("Sepsis-3"), assessment of the scientific achievements of the Kazan Surgical School.

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