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CLINICAL STUDY

A response to infection in patients with severe sepsis – do we need a "Stage-Directed Therapy Concept"?

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Abstract: Excessive forms of the response of organism to infection play an important role in the pathogenesis of severe sepsis. They may consist of either local pro-inflammatory response with a massive release of cytokines into the systemic circulation, or may be presented as an excessive systemic anti-inflammatory response. In the first case, the result is a systemic pro-inflammatory state, characterised by natural stages of the inflammatory response, in which dysfunction of macrocirculation is followed by microcirculation derangement and mitochondrial alteration at the end. These mechanisms are responsible for the development of remote organs failure. The result in the second case is a deactivation of local immunocompetent cells, which results in the risk of uncontrollable growth of microorganisms, especially in organs with an impaired antimicrobial barrier. This may explain the clinically observed recurrence of septic episodes, when a resolution of infection at one site is later replaced with an outbreak of sepsis from another site. A number of therapeutic interventions aimed on the management of causes and consequences of systemic pro-inflammatory state was clinically tested (e.g. antibiotics, goal directed hemodynamic support and inhibitors of coagulation) with surprisingly different effectiveness. The cause of this difference may lie, apart from the frequently discussed inhomogeneity of the studied patient population, also in an incorrect timing of the therapeutic interventions, which does not respect natural stages of the inflammatory response *(Fig. 1, Ref. 40).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: infection, inflammatory response, severe sepsis, therapeutic intervention.

The current knowledge enables us to define sepsis as a disease caused by *the response of the organism to infection* (1). The primary aim of the organism's response to infection is always a defence targeted to eliminate invasive microorganisms. However, there are differences in its clinical manifestations – from benign forms, which we often don't even notify (e.g. minor inflammatory affection of the skin) up to malign forms associated with haemodynamic instability and progression to multi-organ failure (so called *severe sepsis*). The anticipated course of the response to infection in an individual patient still remains a mystery. However, it is apparent that its extent and intensity are significantly influenced by the predisposing factors (age, gender, concomitant diseases, genetic predisposition), location of infection and the amount of microorganisms as well as their virulence (2). Iatrogenic mechanisms may also play an important role, e.g. traumatic mode of artificial lung ventilation in a patient with an acute lung injury (3)

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The aim of this brief review is to describe response of the organism to the infection, its natural stages and possible causes of different effectiveness of the same therapeutic interventions in patients suffering from severe sepsis**.**

Physiology of the organism's response to infection

The response of organism to infection may be described on two levels – *local* and *systemic*.

Local response to infection occurs at the site of tissue invasion by microorganisms (4). The mechanisms are stereotype, they have the characteristic of innate (=inborn) immune response and the responsible structures are cells with nonspecific immunity, especially macrophages. These, following an interaction with microorganisms, or with parts of their bodies (e.g. endotoxin) produce chemokines, pro-inflammatory cytokines and other active substances that mediate chemotaxis of phagocytes (mainly polymorphonuclears - PMN) and consequently also a *purposeful sequence of processes* necessary for safe elimination of microorganisms:

1) *initial vasodilatation with deceleration of the blood flow and temporary activation of fibrinolysis*, which are aimed at facilitation of phagocyte migration into the site of tissue damage and support of interaction between PMN and the endothelium (5–7),

2) *activation of endothelium and PMN* in the expression of molecules (so called selectins and integrins), which enable their mutual interaction (rolling and firm adhesion of PMN on the endothelium surface) and later transcapillar migration of PMN into the affected tissue. Concurrently, capillary permeability increases and fluid rich in albumin and nutrients leaks into the interstitium (8).
3) *precapillar vasoconstriction, postcapillar activation of coagulation and inhibition of fibriolysis.* These changes are one of the most important mechanisms enabling to frame the inflammatory response to the site of injury only (7, 9–11),
4) *adaptation of structural tissue* cells to ongoing defensive (inflammatory) processes.

Precapillar vasoconstriction, postcapillar hypercoagulation and compression of capillaries by oedematous fluid may threaten structural cells with hypoxia. However, these cells lower their energetic needs, which enables them to survive "unfavourable conditions" (so called *hibernation*). This process is clinically manifested as the temporary loss of function of the inflamed organ or tissue. Historically it is known as "function laesa" – the fifth sign of inflammation, added by Galen to the four legendary signs of Celsus (12–14).

Systemic level of the response to infection is in a supreme position in relation to local mechanisms and has an inhibitory character (15–18). Among the triggers of this response are the stimulation of afferent fibres of the vagus nerve, pain, and "tissue corticotrophine-releasing factor" – a substance consisting of a small amount of pro-inflammatory cytokines (tumour necrosis factor-α, interleukin-1β and especially interleukin-6), which are released from the site of inflammation into the systemic circulation. As a result, we observe an increased tonus of locally specific afferent fibres of the vagus nerve, overall activation of the neuro-endocrine system (increased tonus of the sympathetic nervous system, activation of the hypothalamus-hypophysis-adrenal glands axis), increase of body temperature and increase in the count of leucocytes. The purpose of these mechanisms is the inhibition of an excessive production of pro-inflammatory cytokines by macrophages at the site of microbial invasion. Unfortunately, only the pathway mediated by the vagus nerve has an effect in real time and is locally specific (so called *inflammatory reflex*) (19). The other mechanisms are slower, moreover locally unspecific, which means that they may influence, apart from macrophages at the site of microbial invasion, also the macrophages in healthy tissues, with the risk of their complete deactivation (so called *immunoparalysis*) (20, 21).

Patophysiology of the organism's response to infection and severe sepsis

Dysregulation of the above-described mechanisms plays an important role in the pathogenesis of severe sepsis.

An excessive local production of pro-inflammatory cytokines may result in their massive release into the systemic circulation (so called *de-compartmentalization*), where they act in *the same sequence* as in the place of microbial invasion, however with malignant effects (22). A systemic correlate of local vasodilatation is an arterial hypotension, or – in most severe cases – septic shock. Organs distant from the place of infection are at this stage threatened with a reduction of blood flow caused by the drop in perfusion pressure. As a result, we may observe a dramatically developing multi-organ failure, the reason of which is a tissue hypoxia caused by alteration of systemic supply of oxygen. Apart from generalised vasodilatation, also a depression of myocardium induced by pro-inflammatory cytokines and, in later stages, absolute hypovolemia resulting from the interstitial fluid sequestration contributes (23).

In cases when the patient survives this first – *macrocirculatory* – stage of systemic pro-inflammatory state without any organ infliction, he is endangered with later alteration of microcirculation. This is manifested by a decreased density of perfused capillaries caused by precapillar vasoconstriction, postcapillar microthrombotization and compression of capillaries with interstitial oedema (24). Blood flows through these areas via open arteriovenous shunts without the oxygen desaturation and the affected tissues are again in the risk of hypoxic damage with a possible result of hypoxic organ failure. The reasons for this are the above-described changes of microcirculation connected with alteration of regional oxygen supply and from this point of view this stage could be described as *microcirculatory.*

In case the patient survives also this stage of systemic pro-inflammatory state with no organ damage, we may observe an interesting condition. The developing organ failure may not be a manifestation of tissue damage, but the already mentioned hibernation (25, 26). The exact mechanism of hibernation is still not fully understood. It may be a result of a specific cell adaptation reaction, which is induced by "targeted switching off mitochondria" (reversible blockage of mitochondrial breathing chain by inflammatory mediators, with dramatic drop in production of adenosine-phosphate – ATP) which consequently leads to expression of foetal genetic material responsible for the conversion from normal energetic status into the state of hibernation (the need for ATP is also lowered). In nomenclature we may describe this stage of systemic pro-inflammatory state as *mitochondrial.*

The exact role of a *dysregulation of systemic level of response to infection* in the pathogenesis of severe sepsis has not been fully understood (27). The failure of systemic control of local inflammation for the reason of exhaustion of regulatory mechanisms (caused for example by repeated insults) may lead not only to systemic propagation of inflammatory cytokines, but also to amplification of their effect. Relative adrenocortical insufficiency, as a possible manifestation of exhaustion of regulatory mechanisms, is quite commonly observed in septic patients (10–40 %) and is connected with an increased mortality (28). The decreasing tone of vagus nerve may also play a significant role, which can explain why the incidence of severe sepsis grows along with the age of patients (29). It is also not clear, to what extent does the antipyretic therapy impairs the systemic level of control of local inflammation. The rise in the body temperature is an inte-

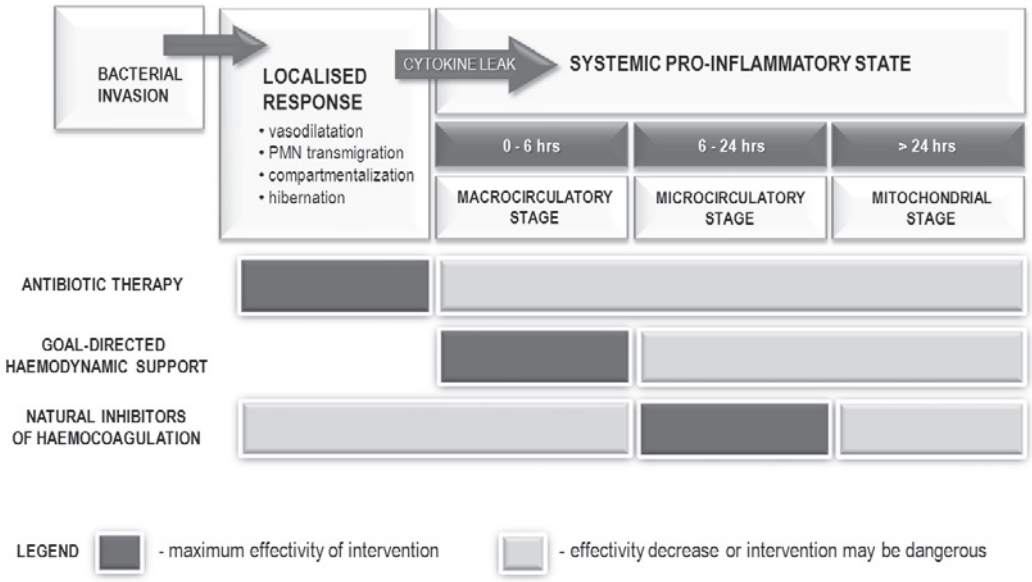

Fig. 1. The stages of systemic pro-inflammatory state and the effectiveness of therapeutic interventions.

Excessive local pro-inflammatory response as well as the failure of local and/or systemic control of inflammation at a site of infection may result in massive release pro-inflammatory cytokines into the systemic circulation. There they act in the same sequence as in the place of microbial invasion, however with malignant effects.

1. Systemic hypotension (i.e. macrocirculatory stage of systemic pro-inflammatory state) is an equivalent to initial vasodilatation at the site of infection. At this stage the distant organs may be endangers by reduction of blood flow related to decrease of perfusion pressure. However, the tissues are still capable to increase oxygen extraction, which indicate well functioning microcirculation. Causal treatment procedure presents targeted haemodynamic resuscitation resulting in increase of either systemic blood pressure and the velocity of blood flow at the microcirculation level and by these minimizing the risk of developing a subsequent microcirculatory alteration (see further…). Therapeutic potency of antibiotics declines, because these substances are not able to directly influence a consequence of systemic hypotension. Administration of natural inhibitors of coagulation (i.e. rhAPC or antithrombine) is associated with the risk of significant bleeding. This is caused by the absence of systemic hypercoagulation, which can basically develop as far as the next stage of systemic pro-inflammatory state is reached – i.e. at the microcirculatory level. Moreover, the use of anticoagulants during the macrocirculatory stage of systemic pro-inflammatory state, or even at the stage of localized response to the infection can promote de-compartmentization (i.e. a release pro-inflammatory cytokines from the site of infection into the systemic circulation) by impairment defensive hypercoagulation at the local level.

2. Systemic alteration of microcirculation (i.e. microcirculatory stage of systemic pro-inflammatory state) is an equivalent to the mechanisms of compartmentalization of inflammatory response at the site of infection. The hallmark is a decrease in density of perfused capillaries caused mainly by precapillary vasoconstriction and subsequently by postcapillary microthrombotization. Blood flows through these areas via open arteriovenous shunts without the oxygen desaturation and the affected tissues are again in the risk of hypoxic damage. In this stage the causal therapeutic procedure is administration of vasodilatators and natural inhibitors of coagulation. The efficiency of targeted hemodynamic resuscitation decrease by the reason of already developed microcirculatory alteration. Antibiotics treatment also has no opportunity to directly interfere with the processes running at this stage.

3. Reversible loss of distant organs function is an equivalent to the mechanisms of local adaptation of structural tissue cells to the "ongoing duel" between immune system and microorganisms. It could happen at the interval of more than 24 hours from the beginning of the disease, if the first two stages did not cause irreversible hypoxic tissue damage. As far as it is the case, also protective metabolic inhibition of structural cells is started as a natural component of the cytokine-induced changes on the level of microcirculation. This process begins as an inhibition of mitochondrial functions (i.e. mitochondrial stage of systemic pro-inflammatory state) and ends to a hibernation of structural tissue cells. From the phylogenetic point of view it is quite purposeful process because it protects structural tissue cells against hypoxia caused by the inflammation-induced microcirculatory alteration. In such way the cells are capable to survive unfavourable conditions, nevertheless temporarily do not carry on their function. This phenomenon is historically known as "function laesa". As causal treatment could be considered a re-activation of mitochondria (i.e. biogenesis) at this stage, but only on condition that systemic pro-inflammatory state has passed away. Redundant oxygen supply to the "adaptation-affected" tissues (i.e. haemodynamic support) can be harmful on behalf of the risk of increased generation of reactive oxygen species. Finally, the same risks also bring along aforementioned treatment procedures aimed at microcirculatory resuscitation, i.e. use of vasodilatators and natural inhibitors of haemocoagulation. Similarly to the preceding stages, antibiotics are also not able to influence these processes.

gral part of systemic anti-inflammatory response and its therapeutic lowering results in a higher mortality of the septic animals in the experiment (17, 30).

On contrary, an excessive systemic anti-inflammatory response may be a manifestation of vigorous attempt to prevent an outflow of inflammatory cytokines from the area of excessive inflammation into the systemic circulation (*compartmentalization effect*). At the same time, however, it may lead to deactivation of macrophages in healthy tissues with an uncontrolled growth of bacteria (*immunosuppressive effect*), especially when

organ systems with iatrogenic disruption of antimicrobial barrier are involved, e.g. when artificial lung ventilation with tracheal intubation is required, insertion of urine catheter or venous line, etc. This may explain why nosocomial infections at the intensive-care units are in more that in 80 % caused by infections of the respiratory tract, urinary system and bloodstream (31). The double role of systemic anti-inflammatory response may also explain the clinically observed recurrence of septic episodes, when resolution of infection in one site is later replaced with an outbreak of sepsis from another site.

Clinical consequences

If we accept the idea of time-dependent stages of systemic pro-inflammatory state, we could possibly explain the observed differences in the effectiveness of identical therapeutic interventions in patients with severe sepsis. For example, the effectiveness of an adequate antibiotic therapy dramatically drops with the time elapsed from the onset of the disease. The literary sources indicate that during the first 6 hours the chance of survival decreases by 7 % with every hour of delay (32). Moreover, to start the treatment within 24 hours after the onset of the disease may be considered almost pathetic – the death rate in these patients exceeds 80 % (33). It becomes apparent, that antibiotics are most effective if given in the stage of localised response to infection and their effectiveness (in the terms of the final mortality) significantly decreases in the stage of macrocirculatory alteration. We can also conclude that application of antibiotics in the stage of microcirculatory alteration or mitochondrial dysfunction can hardly reverse the progression of the disease. From the antibiotic's point of view, this limitation is quite understandable because these substances are indeed capable to destroy microorganisms, but they are of course unable to reverse the consequences of systemic hypotension, decreased capillary density or mitochondrial dysfunction.

Similarly to antibiotics, also the targeted haemodynamic resuscitation (further as GDT – *goal-directed therapy*) presents with certain limits within the first 24 hours of the duration of the disease. It is clearly proved by the results of the three most-cited clinical trials (34–36). In the first trial mentioned, Rivers and colleagues showed that GDT is significantly capable of decreasing the mortality of patients, in cases when it is started in the early stage of systemic pro-inflammatory state, and the haemodynamic stability is achieved *during the first 6 hours* after the admission to the hospital (10). It is necessary to point out that the patients in both arms of Rivers' study were hypotensive at the time of enrolment, and their initial value of central venous haemoglobin saturation was lower than 50 %. This clearly indicates that GDT was initiated before sepsis induced microcirculatory dysfunction – i.e. in the *macrocirculatory* stage of the systemic pro-inflammatory state.

In the earlier study, Gattinoni and colleagues used almost identical goals of the haemodynamic resuscitation as Rivers, however they did not reach a significant difference in the mortality of the protocol and control groups of patients. However, the difference was in the GDT being started later, most probably in a stage of developing microcirculatory dysfunction, as the initial value of venous haemoglobin saturation was significantly higher in both groups of patients compared to the Rivers' study.

From the point of view of the chronology, Hayes and colleagues were testing the effectiveness of GDT in critically ill patients with the onset of the intervention even later than in the Gattinoni's study and they obtained findings, which were very surprising at that time – the mortality in GTD-group was even higher than in the control group. In other words, it seems that an excessive oxygen supply to tissues can be deleterious in later stages of systemic pro-inflammatory state. This phenomenon is probably related to the already discussed metabolic adaptation – a conversion of structural tissue cells into the state of hibernation. In this way, they are able to survive local hypoxia resulting from the initial alteration of microcirculation. But after the conversion into the state of hibernation it is not possible to suspend the idea that the above-described alteration of microcirculation, i.e. *low density of perfused capillaries,* is sustained purposefully and through different mechanisms. Thus, it would present a potential defence targeted at reducing the local supply of redundant oxygen and subsequently the risk of an excessive formation of reactive oxygen species. If this assumption is correct, then we should consider microcirculatory changes after 24 hours from the onset of the disease as adaptive and desired. Moreover, it is quite logical that the augmentation of the oxygen supply may be detrimental at this stage of systemic pro-inflammatory state (37).

The last example of the time-limited effectiveness of today's widely accepted therapeutic interventions may be presented by the outcomes of a clinical trial using the natural inhibitors of coagulation, mainly the recombinant human activated protein C (rhAPC). In the ADDRESS study focused on early administration of rhAPC in patients with severe sepsis and low risk of death (APACHE II score <25 or single organ failure, *mostly hypotension*), no influence on the reduction of mortality was observed (38). According to our concept of consecutive stages of systemic pro-inflammatory state (Fig. 1), it was likely that most of the patients were in the *macrocirculatory* stage of the disease and the process of systemic inflammation had not yet "reached" the level of microcirculation, when it may induce the systemic hypercoagulation, and when the rhAPC – as the inhibitor of coagulation – becomes effective.

The time limitation of the effectiveness of rhAPC was also pointed out by the processing of data acquired in the ENHANCE study (39). The authors reported a higher mortality rate when rhAPC was administered after 24 hours from the first signs of severe sepsis. The decline in rhAPC-effectiveness in this period may be deduced from the fact that rhAPC was given only a little chance to intervene into the sepsis-induced processes on the mitochondrial level. Thus, the effectiveness of rhAPC and other inhibitors of coagulation are probably limited to the interval 24 hours from the first signs of severe sepsis. And even during this interval we need to identify a specific time-window, in which inflammation-induced hypercoagulation occurs and the intervention with inhibitors of coagulation could be beneficial. For ex-

ample, a high level of D-dimer may indicate a systemic hypercoagulation and its decrease also the effectiveness of therapeutic intervention. After all, the results of the famous PROWESS study support this theory as well (40).

Conclusion

Excessive forms of the response of organism to infection play an important role in the pathogenesis of severe sepsis. They may consist of either local pro-inflammatory response with a massive release of cytokines into the systemic circulation, or may be presented as an excessive systemic anti-inflammatory response. In the first case, the result is a systemic pro-inflammatory state, characterised by natural stages of the inflammatory response, in which dysfunction of macrocirculation is followed by microcirculation derangement and mitochondrial alteration at the end. These mechanisms are responsible for the development of a remote organs failure. A number of therapeutic interventions aimed at the management of causes and consequences of systemic pro-inflammatory state were clinically tested (e.g. antibiotics, goal-directed hemodynamic support and inhibitors of coagulation), with a surprisingly different effectiveness. The cause of this difference may lie, apart from the frequently discussed inhomogeneity of the studied patient population, also in the incorrect timing of the therapeutic interventions, which does not respect natural stages of the inflammatory response. Therefore, an identification of these stages is extremely important in clinical practice. This is valid twice in a situation when it is evident that the interval of a successful use of nowadays respected therapeutic procedures is present just within the initial 24 hours from the beginning of the disease. And even during this interval we need to identify specific time-window when will be either of another specific intervention effective.

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