

Research on Risk Factors Affecting Sepsis Outcomes

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Abstract: Sepsis is one of the diseases with a highest mortality rates in the world. The Sepsis 3.0 consensus places more emphasis on host response to infection, and the concept of "heterogeneity" has been introduced in recent years in understanding sepsis. Therefore, more and more scholars began to pay more attention to the patients themselves, trying to find risk factors for adverse sepsis outcomes, so as to optimize clinical treatment plans and improve patient outcomes. This coincides with the concept of Traditional Chinese Medicine, which is an indispensable part of world medicine, and if the risk factors affecting sepsis outcomes are discussed from the perspective of integrated Traditional Chinese and Western medicine, it will be conducive to a better understanding of sepsis, thereby helping to optimize the individualized treatment of sepsis.

1. Introduction

Sepsis is a critical infectious disease with acute onset, rapid progression, high risk and poor prognosis, which imposes a great public health and financial burden on many countries and regions^[1-4]. How to effectively prevent or delay the occurrence of adverse outcomes after infection is the direction that medical workers have been working hard. In 2016 the third international consensus defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection^[2]. That is to say, different infections faced by different hosts may have different degrees of inflammatory reactions and organ damage. At the same time, more and more attention is paid to the individualized treatment of patients with septic. Individualized treatment is the characteristic of the Traditional Chinese Medicine (TCM) system. The theory of TCM attaches great importance to individual differences. When the same disease appears in different individuals, it is not a process-based treatment method, but the best treatment plan is applied to patients through careful dialectics, and the treatment effect under the guidance of this theory is often better.

Scholars have been trying to better understand the disease from the "heterogeneous response" of different patients with sepsis^[5-6]. The so-called "heterogeneity" coincides with the concept of TCM that "treatment based on syndrome differentiation" and "treating the same disease with different therapies". Analyzing various factors that may affect disease outcome from the perspective of integrated Chinese and Western medicine can better carry out targeted interventions and maximize the value of integrated medicine in the treatment of sepsis.

2. Basic information

2.1 Age

In a survey of the effect of age over 24 years on sepsis outcomes in the United States, the mean age increased from 64.1 years in 1979 to 68.2 years in 2002 among approximately 10.4 million sepsis cases, and that older patients over 65 years accounted for 64.9% of sepsis cases^[7]. Older patients are not only more likely to have persistent immunosuppression, but also have multiple organ failure and higher mortality than non-elderly patients^[8]. Li. et al. found through data analysis that age is an independent risk factor for death in elderly patients with sepsis. In addition, retrospective studies have shown that sepsis rates were the first highest in infants and young children and the second highest in older adults from 1990 to 2017^[9]. The proportion of neonatal deaths from sepsis, particularly in preterm infants, is also increasing^[10-11].

Modern medicine believes that immune function declines with age. The theory of TCM holds that "... Today, the five collections are all declining, the muscles and bones are degenerate, and the heavens are exhausted", "... However, men past the age of sixty-four and women past forty-nine have normally lost this ability that the capacity to procreative". The functions of the elderly body began to decay, the five organs are weakened, the transportation and transformation is weak, and the circulation of qi and blood is limited, which increases the risk of serious diseases in the elderly group. Increasing age reduces the body's immune response to infection through a variety of ways. Immunosenescence results in populating immune tissues with less functional T cells, and perhaps B cells dendritic cells, that do not function well^[12]. In addition to changes in the immune system, aging also deteriorates the integrity of the skin and increases the risk of skin and soft tissue infections^[13]. At this time, once the body with asthenia of healthy qi feels poisoned, it is powerless to resist pathogenic factors.

Newborns are often infected due to immature immune systems or iatrogenic problems. Newborns come from an absolutely sterile environment to a bacteriological environment, and any bacteria can become a pathogen^[14]. In addition, various diseases inherited from the mother are also a major factor in the development of infection in newborns. Because infants and young children are "delicate and delicate, the qi is not filled", the form and function of various organs are immature. Especially premature infants and infants with maternal pathogenic factors are congenital deficiencies, when infected with poison, healthy qi is not enough to resist the disease, and a poor outcome soon occurs.

2.2 Weight

Animal experiments have found that mice that die in the cecal ligation and puncture model (CLP) show significant weight gain during the acute phase of infection (5 days after CLP modeling is complete), while mice that survive the acute infection phase lose significant weight^[15-16]. At the same time, mice experienced significant weight loss in the 3 days before death during the slow progression of CLP-induced sepsis (days 6-28)^[15]. Early in sepsis, rapid weight loss is associated with a high probability of survival. However, in advanced sepsis, it becomes a sign of impending death^[16]. It has been suggested that weight loss during the acute infectious phase is the result of metabolic stress exerted on animals by bacterial infection after surgery. In a retrospective analysis, patients with a higher Body Mass Index (BMI) had better 30-day and one-year survival outcomes than normal-weight patients. Regardless of age, the 28-day case fatality rate was higher in the low-weight group than in the non-low-weight group.

Suwen · On the principle of Yin and Yang said "refined food, form taste, metabolic essence, qi born shape", body muscles are transformed by essence qi, when the essence is full, the muscles and

bones are full. *Lingshu ·Shou Yao Gang Rou Chapter* said "Skin and flesh are fruitful, if they do not bear each other, they will die, blood and qi meridians will win the shape and life, and if they are not victorious, they will die", the skin and muscles are tightly wrapped with each other, and the qi and blood meridians are full of life, otherwise they will die. The enrichment of body muscles can reflect the strength of the human body's qi, blood and liquid, and when the qi and blood are strong, it is often strong to resist evil. In the process of long-term confrontation between good and evil, once the good does not defeat evil factors, the body will quickly lose its flesh, often indicating a bad ending. Some attention should be given when the patient has significant weight changes or extreme values of body weight.

2.3 Body temperature

Sepsis patients with hypothermia have been found to be older, have a lower BMI, have a higher probability of septic shock than other thermogenic patients^[17], and have the highest proportion of deaths^[18]. And the lowest mortality rate at temperatures between 37.4 - 38.5°C^[19]. Other studies have shown that a temperature <36°C is statistically significant for increased mortality in non-elderly patients with sepsis (age <75 years), whereas a temperature > 38.3°C tends to reduce the risk of death^[20].

Patients with sepsis often cause pathogenic evil qi, such as blood stasis, Qi stagnation, and turbid phlegm. When these turbid evil block the body and affect the normal flow of qi and blood, they will consume qi to hurt yin and burn saliva, thus causing fever. Fever is a manifestation of the resistance between human body's qi and evil qi. The increase in body temperature to a certain extent indicates that righteousness and anti-evil are powerful. Modern medicine believes that after the body is infected with pathogenic bacteria, macrophages in the liver and lungs begin to release lipid mediators, of which prostaglandin (PG) E₂ plays a key role, and PGE₂ in the blood will enter the brain to cause fever^[21]. In addition, Interleukin-6 (IL-6) is also another important factor in fever. The same degree of fever has a protective effect on the body, but if the patient has a continuous low temperature, it means that the body is weak and unable to resist, and the outcome is often poor. Therefore, monitoring vital signs in patients with sepsis should be noted for hypothermia.

3. Underlying diseases/comorbidities

3.1 Lung and intestinal diseases

An epidemiological survey showed that the most common underlying causes of sepsis was diarrhoea, and the second is lower respiratory tract infections. Lower respiratory tract infections are most associated with sepsis mortality, followed by diarrhoea, with COPD ranking sixth^[9]. It can be seen that lung and intestinal infections are causing adverse sepsis. In animal experiments, in CLP-induced sepsis mouse models, the lower respiratory tract rapidly accumulates gastrointestinal bacteria, including bacteroides, enterococci and *Lazheimerium* bacteria, and can maintain this state for 5 days^[22], which shows the close relationship between lungs and intestinal infections. Many clinical studies have also shown that in patients with sepsis, the lungs are the most common site of infection, followed by intraperitoneal infection^[23-24].

The theory of "lungs and large intestine" plays a very important role in the theory of sepsis in TCM. *Suwen ·Cough Theory* said "The long-term cough of the five organs is transferred to the six internal organs. If the lungs cough endlessly, the large intestine will suffer from it", the lungs and the large intestine, one yin and one yang, the surface is opposite. Professor Wang Jinda also successfully developed animal models of enterogenic endotoxin in the 80s of last century and induced acute respiratory distress syndrome (ARDS), which confirmed the objectivity of traditional

Chinese medicine "lung and large intestine". Modern medicine believes that during septic *acute lung injury (ALI)/(ARDS)*, with the aggravation of ischemia and hypoxia, increased cytokine levels will lead to damage to the intestinal barrier and increase intestinal permeability, causing intestinal microorganisms, bacteria, endotoxins or their products to cross the mucosal barrier and transfer to systemic circulation through mesenteric lymphatic vessels, exacerbating the host inflammatory response, inducing acute pulmonary edema, and further aggravating the intestinal inflammatory response through positive feedback^[25-27]. *Suwen · Five Organs Generation* mentions that "all qi belong to the lungs", the lung is the main pipe of the qi, lung qi decay will inevitably affect other organs. When the lungs are degraded, the function of the water channel is limited, the whole body fluid infusion disorder, gathering into various pathological products, affecting the development of sepsis outcome^[28]. Therefore, when patients have lung or intestinal diseases, they should be paid attention to in time.

3.2 Renal failure

Studies have found that sepsis is the most common cause of acute kidney injury (*AKI*) and acute renal failure (*ARF*) in critically ill patients^[28-29], and mortality within one year in patients with septic *AKI* is 40%^[30]. In a retrospective study in Korea, a reduction in 30-day survival in patients with sepsis was significantly associated with the severity of *AKI*, which was associated with increased mortality^[31]. Clinical observations suggest that patients with sepsis with *AKI* have higher in-hospital mortality and 90-day mortality than patients with sepsis without *AKI* ^{[29][32]}.

In the *Suwen · Six Verses of Tibetan Elephant Theory*, "The kidney, the main sting, the foundation of sealing", the kidney is the foundation of the acquired, fixing essence, and preventing the loss of qi, blood and fluid. *Jingyue Quanshu* describes the kidney like "The yin qi of the five organs cannot be nourished unless it is here, and the yang qi of the five organs cannot be sent out unless it is here", and the physiological function of the kidney is related to the whole process of human growth and development. When evil poison attacks and turbid evil congestion will lead to unfavorable gasification of the kidneys, and the healthy qi will gradually weaken, endangering the fundamentals. Although the rate of *AKI* in patients with sepsis is very high, modern studies are not fully aware of the pathogenesis. Insufficient renal perfusion caused by acute tubular necrosis caused by infection has always been the focus of research, but there is also evidence that the role of local microcirculation and inflammatory signals is more important^[33]. The use of nephrotoxic drugs and massive fluid resuscitation in treatment can also increase renal vascular pressure, leading to intracrenal edema and intracystic pressure. Elevated and decreased glomerular filtration rate^[34]. Moreover, whether most kidney diseases can be reversed depends on the outcome of the struggle between good and evil and whether the treatment is timely. Therefore, sepsis treatment should prevent kidney failure or kidney damage.

3.3 Liver disease

In the ranking that affects the mortality rate of sepsis, cirrhosis ranks fifth^[13]. Studies have found that up to 46% of patients with sepsis were accompanied by liver dysfunction, and cirrhosis/chronic liver insufficiency was closely related to the mortality rate of sepsis ^[35-36].

The liver is the main drainage, the main hides blood, and the joy is up and depressed. The liver is damaged, the leakage is derelict in its duties, a series of evil poisons and other pathological products accumulate in the body, the whole body qi machine is not smooth, blood stasis blocks the veins, and the condition is further aggravated. When sepsis occurs, a large number of bacteria in the intestine that help the body obtain nutrients are transferred from the damaged intestinal barrier into the bloodstream and through the portal vein into the liver. When the liver is damaged, the function that

would otherwise eliminate bacteria is disrupted, and the risk of bacterial infection is greatly increased. The liver is essential for removing bacteria and related toxins from the blood, such as Kupffer cells that effectively recognize and eliminate circulating bacteria, but severe systemic inflammatory responses can also lead to cell damage^[37-38]. TCM mostly starts from "asthenia of healthy qi and sthenia of pathogenic factors" when treating liver injury with sepsis. The treatment methods are also mainly to activate blood circulation and remove stasis, and support the right and drive away evil spirits.

3.4 Heart failure

Mortality is increasing in patients with cardiac insufficiency and sepsis^[39]. Approximately half of patients with sepsis are accompanied by cardiac diastolic dysfunction and are associated with mortality^[40]. And hypersensitivity troponin I (hs-cTnI) concentrations were associated with increased mortality in the first 14 days in patients with sepsis in an observational analysis of myocardial injury and outcomes in patients with sepsis^[41].

The heart is the official of the monarch, the sun in the yang, and heart damage often indicates that the disease has entered a more critical stage. When good and evil struggle to reach the heart, insufficient heart qi will cause palpitations, aggravate blood circulation, blood stasis and obstruction. If the pericardium is hot, there will be coma, delirium and other mental changes. After a large amount of rehydration and vascular pressurization drugs, the venous reflux increased and the heart entered a high dynamic state. However, this state is often accompanied by decreased myocardial function. Pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and IL-6 inhibit cardiomyocyte contractility and induce the expression of vascular cell adhesion molecule-1 (VCAM-1) in the coronary endothelium, mediating neutrophil infiltration into the myocardium. At the same time, nitric oxide (NO) can exacerbate mitochondrial dysfunction, reduce myocardial oxygen utilization, perpetuate the release of pro-inflammatory cytokines, and downregulate β adrenergic receptors^[42], further aggravating heart damage and continuing to aggravate the condition. When patients have cardiac primary disease or indicators of myocardial damage, pay attention to it in time and pay attention to the use of vasopressors.

3.5 Stroke

Stroke ranks fourth among patients with sepsis in the number of patients with sepsis^[13]. Infection can lead to stroke, which can also induce immunosuppression and increase the risk of infection^[43]. Sepsis exacerbates inflammation and thrombosis. In a cross-analysis of stroke cases in California, USA^[44], sepsis was significantly associated with an increased chance of internal ischaemic or hemorrhagic stroke at 15 days. Similarly, the most likely to cause stroke are urinary tract infections and lung infections^[45].

TCM understands that stroke is often considered to be qi and blood rebellion, organs qi machine disorders. Patients will be accompanied by or not accompanied by limb paralysis symptoms. At this time qi and blood flow is worse, cannot nourish the surrounding limbs, blood stasis is further aggravated, and even affect the mental condition, irritability, delirium, etc. The evil poison to the body to bring continuous harm, so for sepsis patients to monitor blood flow, cautious use of vasopressors, to prevent the occurrence of stroke.

Risk factors affecting outcomes in patients with sepsis include studies of male and female hormone levels^[46-48], and other laboratory indicators. This article mainly explores the effects of different host populations on outcomes, so the indicative results will not be repeated here.

Individualized treatment is the most advanced treatment plan in the world today, and exploring the individual differences of sepsis patients from the perspective of integrated traditional Chinese

and Western medicine can help clinicians evaluate the possibility of certain serious complications in certain types of patients, so as to prevent, delay or avoid the occurrence of adverse outcomes of patients with sepsis.

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