



Editorial

From H1N1 to 2019-nCoV, what do we learn?

A B S T R A C T

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The COVID-19 pandemic is still raging across the world. Everyday thousands of infected people lost their lives. What is worse, there is no specific medicine and we do not know when the end of the pandemic will come. The nearest global pandemic is the 1918 influenza, which caused about 50 million deaths and partly terminate the World War I. We believe that no matter the virus H1N1 for the 1918 influenza or 2019-nCoV for COVID-19, they are essentially the same and the final cause of death is sepsis. The definition and diagnostic/management criteria of sepsis have been modified several times but the mortality rate has not been improved until date. Over decades, researchers focus either on the immunosuppression or on the excessive inflammatory response following trauma or body exposure to harmful stimuli. But the immune response is very complex with various regulating factors involved in, such as neurotransmitter, endocrine hormone, etc. Sepsis is not a kind of disease, instead a misbalance of the body following infection, trauma or other harmful stimulation. Therefore we should re-think sepsis comprehensively with the concept of systemic biology, i.e. inflammationomics.

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The 1918 influenza pandemic and COVID-19

The 1918 influenza pandemic was a human disaster that claimed approximately 50 million lives, much higher than the total number of military and civilian deaths in World War I (about 10 million). The infected cases were estimated to be about 500 million, more specifically around one-third (33%) of the world's population at that time.^{1,2} The average age of the influenza death in the US and Canada was 28 years. Globally, those between the ages of 20 and 40 were particularly susceptible.² The pathogen that caused the influenza was unclear at the war times. Until 1933 when the British scientists Wilson Smith, Christopher Andrewes and Patrick Laidlaw carried out the successful transmission of influenza to ferrets, human influenza virus was first isolated and named H1N1.³ From then on, great work has been done and people know more about influenza and H1N1.

A hundred years later, 2019-nCoV attacked the world and caused the disease COVID-19. This is a new virus and much remains to be known. On January 20, 2020, WHO reported COVID-19 as a Public Health Emergency of International Concern and ranked the risk level as “middle”. A few days later the risk was adjusted as “high”. After a month on February 28, the risk was promoted to be “very high” but the word “pandemic” was still refused. On March 11, about 4 month from the primary reported infections, COVID-19 was finally defined as “pandemic”. Till the date of June 15 2020, there were 216 countries involved with 7,823,289 confirmed cases and 431,541 deaths reported all over the world.⁴ The frequent

international exchange quickens the transmission of infectious diseases and complexes their control and prevention.

What has taught us after a century of vicissitudes? Unfortunately, the answer is no breakthrough. When facing the centennial plague outbreak, extirpating pathogens, isolating the source of infection, cutting the transmission route and enhancing the herd immunity are still the most effective measures to fight against the pandemic. Moreover, to date, no existing medicine has been found to be effective or specific to 2019-nCoV. As for the development of vaccines that can be of immunoprotective effects, there is still a long way to go. The only choice we have at present is repeated screening and isolation of infection sources to cut off the transmission route, which means endless cancel and shutdown of any social gathering, or even city lockdown.

Septic reaction

A virus is a non-cellular nucleic acid, essentially single-stranded RNA or double-stranded DNA. Viruses must parasitize host cells, which thereby may cause destruction to host cells and result in infectious diseases.

When pathogenic microorganisms invade the body, colonize & proliferate in the body, and cause local or systemic toxic reactions, it is called infection. If the infection aggravates and further induces organ dysfunction, it is called sepsis.

No matter H1N1 or 2019-nCoV, they are essentially pathogenic microorganism; and thus the first targeted organ is the lung. The main cause of death for either the 1918 influenza pandemic a hundred years ago (lethal pneumonia) or COVID-19 (respiratory failure) is believed by the managing editor Lei Li to be the same

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in essence – sepsis, although the pathological mechanism may be somewhat different.

Evolution of sepsis definition

Sepsis was first mentioned by scriptures in ancient Greece. The word “sepsis” came from the Greek word “sepo”, which means “make rotten”, and was first used in medical context in Homer’s poems. The Austria scientist Ignaz Semmelweis first introduced “sepsis” in modern medicine as the result of an infection. He found that the occurrence of “puerperal fever” can be greatly reduced by hand disinfection in obstetrical clinics, and thus believed that sepsis is an infection caused by poor hygiene.⁵ Thereafter, the study by Joseph Lister, Louis Pasteur and Robert Koch further enriched our understanding of microbiology and infectious disease. Whether H1N1 or 2019-nCoV, they can trigger abnormal immune responses, causing endothelial damage, alternation of microvascular permeability, tissue edema and coagulation disorders, which eventually result in shock and organ dysfunction.

The concept of modern sepsis, especially the understanding of its pathological mechanisms, has experienced some twists and turns. As early as 1992, sepsis was defined as systemic inflammatory response syndrome. Sepsis can be diagnosed with signs of infection and any two of the following symptoms: (1) tachycardia or tachypnea (>20 breaths/min), (2) fever (temperature>38°C) or hypothermia (temperature<36°C), (3) leukopenia (<4000/ μ L), leukocytosis (>10000/ μ L), or immature neutrophil >10%, and (4) heart rate>90 beats/min. This is the first diagnostic standard for sepsis, namely sepsis definition version 1, or sepsis-1. Because the criteria are too broad with a high sensitivity but low specificity, application of it to diagnose sepsis is very difficult, even for experienced clinicians, therefore sepsis-1 was criticized and unwelcome in clinical practice.

In 2002, the European Society of Intensive Care Medicine officially spearheaded the Surviving Sepsis Campaign in Barcelona, Spain, known as the Barcelona Declaration. At this conference, sepsis definition version 2 (sepsis-2) was proposed. The new concept version, based on sepsis-1, added some pathobiological indicators, such as organ function, morphology, cell biology, biochemistry, immunology, and circulation. The Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock was issued thereafter,⁶ which was revised and updated continuously in 2008, 2012, and 2016.⁷⁻¹⁰ However, though the indicators mentioned in the guidelines to a certain extent can accurately describe the pathophysiological process of sepsis development, the evaluation of patient status and therapeutic effects was quite troublesome and inconvenient in clinical practice. Therefore, the third international consensus definition for sepsis and septic shock (sepsis-3) was re-proposed in 2016.

The core improvement for sepsis-3 lay in that sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by a >10% in-hospital mortality with an increase in the sequential (sepsis-related) organ failure assessment (SOFA) score ≥ 2 points. Septic shock was defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure ≥ 65 mm Hg and serum lactate level >2 mmol/L (>180 mg/L) in the absence of hypovolemia. This combination is associated with a hospital mortality rate >40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor

outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed qSOFA: respiratory rate ≥ 22 /min, altered mentation, or systolic blood pressure ≤ 100 mm Hg.¹¹

Actually we believe that sepsis is essentially a kind of excessive inflammatory response against pathogenic microbes. Under the condition of trauma, some other harmful stimuli such as necrotic tissue and/or cell debris may aggravate the inflammatory insults and become an important factor to deteriorate the condition of sepsis patients.

Trauma and sepsis

Immunosuppression or excessive inflammatory response?

Although the concept of sepsis and the international guidelines for its management have been constantly updating, the mortality rate caused by sepsis has not been significantly reduced. For severe trauma patients, the major cause of death in late stage is still sepsis-related multiple organ failure. Traumatic infection and sepsis remain the biggest challenge for trauma surgeons. The inter-correlation between trauma, immune, infection and inflammation is very complex. As early as the 1960s, post-traumatic immunosuppression has been noted, including decreased lymphocyte transformation, reduced complement components and immunoglobulin following blood loss, etc. With time going on, till the 1980s, a relatively mature theory has been constructed, i.e. immunosuppressive cells, immunosuppressive factors and disordered immune-neuroendocrine network was believed as the main causes of post-traumatic immunosuppression, which induces infection and ultimately death following trauma.

However, with the proposed concept of systemic inflammatory response syndrome in the 1990s, the excessive inflammatory response and sequent damages after trauma obtained wider attention. The latter won an overwhelming position and immunosuppression is seldom mentioned. Nonetheless the treatment strategy of blindly anti-inflammation and inflammation damage control failed to yield beneficial results for trauma patients.

In recent years, autopsy of trauma sepsis death revealed numerous necrotic and apoptotic immune cells in the patient’s spleen and lymph nodes, which gradually guide the understanding of trauma sepsis back to rationality, i.e. the body response following severe trauma include not only excessive inflammation but also obviously suppressed immune defense function.

Inflammationomics

Excessive inflammatory response and suppressed immune function, this is a dilemma during the management of trauma patients at the middle and late stages. To enhance the immune function may further aggravate inflammatory damage, whereas to depress the inflammatory response may accelerate the already existing immunosuppression state. Many factors can trigger sepsis, such as various pathogenic microorganisms. Some broken tissue cells and metabolites can also aggravate septic reaction, and even induce inflammatory damage like sepsis to a certain extent.

During the onset and progress of sepsis, the participating cells are not limited to immune inflammatory cells; others like endothelial cells, liver cells, kidney cells, etc. are also involved. Regarding the signaling pathways to regulate inflammatory response receptors, it has been found that both intracellular receptors (membrane receptors, cytoplasmic receptors, nucleus receptors) and extracellular receptors (soluble receptors) are jointly involved. In addition,

endocrine factors and neurotransmitters also participate in the regulation of host response. Unfortunately, over the years, we have focused too much on the signaling pathways of some receptors. We hope to find a golden predictive/warning indicator for sepsis via simple monitoring of several proteins or improve the sepsis outcome via regulating some poorly-understood protein signaling pathways. Thousands of research studies have been conducted but few are what the clinic needs.

Now is the time to be more rational. The basic pathophysiological responses should not be ignored. We need to shift the attention, at least partly, to the systemic biology. When trauma occurs, the immuno-inflammatory response is triggered immediately: no inflammation, no wound healing; while no immunity, infection will be out of control. From another side, the immunosuppression following trauma also has a protective effect on the body. A certain degree of immunosuppression can effectively control the intensity of inflammatory response. Following trauma, the inflammatory response and immunosuppression was initiated at the same time; this is a stress/protective reaction of the body to such harmful stimuli. In recent years, the coagulation-fibrinolysis system was also found to play an important role in the series of pathophysiological reactions after the body is subjected to harmful external stimuli, such as trauma-induced coagulopathy and pulmonary microthrombosis in COVID-19, which should be paid more attention and further exploration. Regardless of the inflammatory response, immune response, or coagulation-fibrinolysis system response, it is a spontaneous defense response of the body and thus excessive human intervention would be disadvantageous for its recovery. What puzzles us at the moment is when and how much should we involve in; there is no reliable basis up to date. When the body is exposed to external harmful stimuli or injuries, the neural system stress response immediately initiated is the start point and primary cause of pathophysiological response after severe trauma. Unfortunately, we know little regarding the mechanism and regulatory factors of neuroendocrine stress response.

We should focus not only on inflammation and immunity, but also on coagulation reaction and neuroendocrine stress response, particularly the pathophysiological response under the concept of post-traumatic systemic biology. As a result, we must establish a new idea and thinking for corresponding exploration of sepsis following severe trauma. Since we have proteomics, genomics, and metabolomics, and so on, why cannot we create an inflammationomics?¹² The so-called inflammationomics is an emerging discipline that studies the onset and progress of inflammation and its outcome with the concept of systems biology, specifically inflammationomics comprehensively analyze the heat map of activated whole genome expression (genomic heat maps), the spectrum expression pattern of total protein, and the predictive value on the prognosis of inflammation via the technologies of genomics,

proteomics, and metabolomics. Based on big data, inflammationomics is supposed to provide a dynamic all-sided analysis and research on the pathophysiological process of body inflammatory response, which may set the theoretical foundation for revealing the mechanism of inflammation outcome and exploring strategies for inflammation prevention and control.

References

- Centers for Disease Control and Prevention. 1918 Pandemic (H1N1 Virus). <https://www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html>. Accessed June 16, 2020.
- World Health Organization. Test Your Knowledge of the 1918 Influenza Pandemic, Commonly Known as Spanish Flu. <https://www.who.int/influenza/gip-anniversary/quiz/en/>. Accessed June 16, 2020.
- Smith W, Andrewes CH, Laidlaw PP. A virus obtained from influenza patients. *Lancet*. 1933;2:66–68 (Barberis I, Myles P, Ault SK, et al. History and Evolution of Influenza Control Through Vaccination: From the First Monovalent Vaccine to Universal Vaccines. *J Prev Med Hyg*. 2016 Sep;57(3):E115–E120.).
- World Health Organization. Coronavirus Disease (COVID-19) Pandemic. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. Accessed June 16, 2020.
- Noakes TD, Borresen J, Hew-Butler T, et al. Semmelweis and the aetiology of puerperal sepsis 160 years on: an historical review. *Epidemiol Infect*. 2008;136:1–9. <https://doi.org/10.1017/S0950268807008746>.
- Slade E, Tamber PS, Vincent JL. The Surviving Sepsis Campaign: raising awareness to reduce mortality. *Crit Care*. 2003;7:1–2. <https://doi.org/10.1186/cc1876>.
- Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med*. 2004;30:536–555. <https://doi.org/10.1007/s00134-004-2210-z>.
- Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008. *Crit Care Med*. 2008;36:296–327. <https://doi.org/10.1097/01.CCM.0000298158.12101.41>.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. *Intensive Care Med*. 2013;39:165–228. <https://doi.org/10.1007/s00134-012-2769-8>.
- Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017;43:304–377. <https://doi.org/10.1007/s00134-017-4683-6>.
- Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:801–810. <https://doi.org/10.1001/jama.2016.0287>.
- Liu GE, Ouyang Q, Li L. Inflammationomics—A new concept to explore the new sepsis. *Chin J Traumatol*. 2015;18:251–253. <https://doi.org/10.1016/j.cjtee.2015.11.007>.

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