PERSPECTIVE

Sepsis: An Evolutionary Perspective (Sepsis through the Eyes of a Microbe vs Clinical Sepsis through the Eyes of an Intensivist)

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Abstract

"Change of gene frequency in population" is the most fundamental concept of evolutionary biology. Human sepsis is a quantitative biological war between microbial genes and human genes, fought through their respective phenotypes. The prize of this war is an increase of gene frequency. Stating that sepsis is caused by a dysregulated host response is missing one half of the septic syndrome. Clinicians may gain a different perspective into the many intricacies of sepsis by conceptualizing it as an adaptive evolutionary process, rather than an abnormal physiological state. Clinicians may also get a deeper perspective by seeing it as a genotypic evolutionary process of natural selection rather than a phenotypic pathophysiological event.

Keywords: Intensive care, Microorganisms, Sepsis.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23670

Sepsis in the Time of a Pandemic

We are in the midst of a global pandemic. In simplistic clinical terms, humans are getting infected by and spreading the novel coronavirus (SARS-CoV-2). We are also becoming critically ill in large numbers with coronavirus disease-2019 (COVID-19). A small strand of RNA has fundamentally challenged the millennia of human physiology and also fundamentally changed human behavior. We in the intensive care essentially see this as a form of severe pneumonia, multi-organ failure, and we treat it following our usual principles and practices. These practices are based on us applying our medical education to our critically ill patients. Our medical education is built on a foundation of physiology, pathology, pharmacology, internal medicine, anesthesia, and finally intensive care medicine. Unfortunately, we were not taught evolution (natural selection or survival of the fittest) at any point in our medical curriculum.

We can look at this pandemic in basic biological terms. From an evolutionary perspective, this is a competition between the RNA of the SARS-CoV-2 genome and the DNA of the human genome. Both are "trying" to maintain or increase their share in the overall biological population, through their phenotypic responses. It is in the virus' "interest" to multiply in the host and then spread to other hosts. It does this by inducing coughing and then spreading via droplets and aerosols to other susceptible humans. But it is not in the virus' "interest" to lose its source of growth by causing too high a human mortality. It would be the equivalent of killing the goose that laid the golden eggs. It is in the humans' interest to kill or contain the virus. Humans do this with all the innate and adaptive immune responses selected over evolutionary time. Humans also use other physiological compensation mechanisms to tide over this crisis with a hypermetabolic response and with other compensatory stress responses. Our behavior also gets modified in terms of wearing masks, hand hygiene, and maintaining a physical distance. And in some cases, refusing to do so. Finally, we treat the symptomatic and severely ill with our medical knowledge. All these responses are essentially extended phenotypic responses, programd by our genes. As clinicians, we view success in phenotypic terms of a patient clearing the virus and recovering to a pre-illness physiological status.

In evolutionary terms, it is not enough to look at a phenotypic outcome alone, we need to look at genotypic success. Genotypic success is simply increasing the number of genes in the overall biological population. From January 1, 2020, to date, the RNA of the SARS-CoV-2 has increased its gene frequency far more effectively than the human DNA numbers. The virus has therefore had more evolutionary success. Hopefully, this trend will reverse. Presumably, in a few years, the number of human genes will remain steady and the number of viral genes will either become stable or decrease. This would lead to a new steady-state in quantitative terms of human vs SARS-CoV-2 genes.

Understanding Evolutionary Biology

Nothing in biology makes sense, except in the light of evolution.
—Theodosius Dobzhansky

Evolution is not a branch of biology. It is the fundamental principle upon which all other branches of biology are built on. This is equally true for medicine and critical care. "*Change of gene frequency in population*" is the most fundamental concept of evolution.[1,2] Darwin[3] and Wallace showed that evolution by natural selection best explains the vast diversity in biology, resulting in the survival

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How to cite this article: Kapadia FN. Sepsis: An Evolutionary Perspective (Sepsis through the Eyes of a Microbe vs Clinical Sepsis through the Eyes of an Intensivist). Indian J Crit Care Med 2020;24(12):1165–1168.

Source of support: Nil

Conflict of interest: None

of the fittest. The unit of natural selection is the Mendelian gene.[4] Watson and Crick,[5] along with Wilkins and Franklin, elucidated the structural nature of the gene in the DNA molecule. These genes code for amino acids and proteins, which in turn create structure and subsequently generate function. The individual organism survives by using the information in the genetic code. The information allows it to capture the nutrients and energy needed to resist entropy and maintain its phenotypic complexity. That complexity allows the organism to respond to environmental threats. The organism that can survive environmental threats and reproduce successfully transmits its genes to the next generation. Their genes are naturally selected and increase their frequency in the overall biological gene pool. Those organisms that cannot survive environmental threats obviously cannot transmit their genes to the next generation. Their gene frequency decreases in the overall biological gene pool. If one accepts this view, then human sepsis is essentially a quantitative war between microbial genes and human genes, fought through their respective phenotypes. The prize of this war is a subsequent increase in gene frequency. When the influenza pandemic of 1918 resulted in high human mortality, the percentage of influenza genes increased in the overall biological population and the percentage of human genes decreased. When the smallpox vaccine was used extensively, the percentage of Variola genes decreased while those of humans increased in the overall biological population. Symbiotic relationship favors shared genes survival regardless of survival of humans or bacterial individuals. The human bowel flora, the viral bacteriophages of the bowel mucosa, and the mitochondrial genes are examples of a symbiotic relationship between microbial and human genes.

A rarely appreciated fact is that every cell of every living organism has continuously been alive for the last 2.5 to 3.5 billion years. In this vast period of evolutionary time, each cell has accumulated survival mechanisms that have overcome all adverse environmental factors to survive to the present time. This equally applies to microbes and humans. Three billion years of prokaryotic evolution have made microbes ruthlessly efficient at surviving all environmental and biological threats. Two billion years of eukaryotic evolution and 600 million years of large animal evolutionary selection have resulted in complex but poorly understood physiologic adaptations that are ruthlessly efficient in ensuring human healing and survival. Sepsis occurs when these two surviving mechanisms clash and compete with each other.

The human immune system is a very advanced evolutionary system. The most fundamental biological defense consists of phenotypic "locks", like cell membranes and walls, and phenotypic "keys" that can penetrate these defensive locks. This is the basic strategy across all biology. The septic syndrome is the clinical manifestation of the bacterial keys penetrating the human cellular locks and the human keys doing the same to the bacterial locks.

Sepsis Through the Eyes of a Microbe

Microbes have been around for 3–3.5 billion years, while *Homo sapiens* only evolved 200 to 250,000 years ago. Microbes are therefore better adapted to living with large animals including humans, than the other way around.[6] Each human, animal, or plant is a whole ecosystem of microbes. Making an animal sterile and microbe-free in an experimental setting invariably worsens the health of that animal. There is a ubiquitous interaction between prokaryotic microbes and eukaryotic organisms throughout all of biology. These are mostly mutually beneficial or symbiotic, and much less frequently they are adversarial. Sepsis is one such adversarial event.

Metaphorically, how would a microbe view human sepsis? The microbe would note that it is hard to extract energy from the inanimate environment. It would therefore evolve a strategy to cultivate an alternate store of energy. Cyanobacteria precursors of chloroplasts evolved to capture solar energy via oxy-photosynthesis and store it in glucose. Alphaproteobacteria precursors of mitochondria evolved to capture the energy in glucose and store it in NADH and ATP. These cyanobacteria and alphaproteobacteria fused with other microbes,[7] probably archaea, to first become eukaryotic cells, then larger multicellular organisms, and finally a food chain from plants to herbivores to carnivores to scavengers. The microbes, for the propagation of their genes, could at any time reclaim the captured solar energy from the whole food chain. Recent estimates suggested that an individual human has 23,000 genes in 30 trillion human cells and each human carries 3 million microbial genes in 39 trillion microbes,[8] and that 7% of the human genome is viral DNA. The mitochondrial genes too are descendants of bacteria and are nearly identical to the genome sequence of *Rickettsia prowazekii*.[9] These numbers favor the perspective that the microbes are cultivating humans and other multicellular organisms as an ongoing source of nutrients.

Sepsis Through the Eyes of an Evolutionary Intensivist

Evolution is Cleverer Than You Are

—Second Rule of Leslie Orgel.

Evolution by natural selection is now unquestioningly accepted as the foundation of all biology, but it appears to have bypassed clinical and academic medicine. Concepts in medicine and sepsis are still rooted in the phenotypic features of anatomy, physiology, pathogenicity, and immunology.

All three versions of the surviving sepsis campaign[10] start with the statement that "sepsis is *caused* by a dysregulated host response". This concept assumes association is the same as causation. It also assumes that abnormal values of the host mediators are manifestations of deleterious dysregulation rather than a protective adaptive regulation. It is one-sided, as it ignores the ongoing role of the microbial invasion. It is superficially rooted in the phenotypic features of physiology and immunology but ignores the naturally selected genetic code that programs these responses. In certain specific situations, the dysregulated host response may be deleterious, as in allergic or autoimmune diseases. It may be rapidly lethal in anaphylaxis or after the injection of endotoxin. Unlike the above two, the host response in sepsis has a more prolonged and sequential series of pro- and anti-inflammatory components, followed by a state of immune exhaustion or anergy.[11] Unlike anaphylaxis, immune modulation in sepsis, with few exceptions, has not been associated with improved survival.[12] This failure of immune modulation to improve outcomes may be explained by viewing any abnormality of the host response as a protective adaptive one, rather than a deleterious dysregulated one. Looking at the underlying genotypic war between microbe and host allows a deeper understanding of sepsis. Human sepsis occurs when pathogens first breach the physical defense barriers and then compete with the various additional defense mechanisms of the innate and the adaptive humoral and cellular immunity. Sepsis syndrome is *caused* by competition between the two genomes.

The absence of the host response, dysregulated or not, would simply hasten death.

Evolutionary Adaptive Response vs Abnormal Physiological Response

Clinical care and outcomes may improve by focusing on evolutionary concepts rather than physiological ones. This can be explored by evaluating our approach to a physiological abnormality. It may make physiological sense to try to control tachycardia with a beta-blocking drug or ivabradine. An evolutionary approach will first ask if this tachycardia is a useful adaptive trait or an exhausted physiological one. Simply asking the question makes a clinician evaluate it differently. "Abnormal" responses like tachycardia or raised IL-6 need not be normalized. They may be adaptive and enhance survival. They may be maladaptive and worsen outcomes. *The only way to know if a physiological response is adaptive or not is to evaluate clinical outcomes in RCTs.* The last two decades of trials in critical care have repeatedly demonstrated that improvement in physiological parameters is not enough to improve clinical outcomes.[13] The focus now is clearly on mortality and other clinical outcomes. One could state that we have finally switched from physiological to evolutionary outcomes. Unfortunately, it requires much more effort to follow clinical outcomes. These can only be evaluated in clinical trials, and one needs to wait for 1–3 months of data to evaluate the efficiency of the intervention. It is much easier to track physiological outcomes as they happen in real-time in the ICU. Clinicians need to shift their focus from the readily available bedside physiological data to patient-oriented outcomes reported in clinical trials. Clinicians need to constantly remind themselves that every host response they see in their septic patients has been selected and preserved over millions or billion years. Clinicians need to remember that evolution is cleverer than they are, and ask themselves *why* this response exists. It is plausible that tachycardia is needed to maintain high cardiac output. It is plausible that the hypertensive response to an intracranial hemorrhage is needed to maintain cerebral perfusion. It is plausible that an exaggerated cytokine response is needed to clear residual microbes. It is plausible that a fall in left ventricular ejection fraction is an attempt at conserving myocardial energy. It is plausible that decreased nutritional intake is a strategy to divert energy reserves from digestive and absorption functions to increased immune and metabolic demands. Reversing each of these "abnormalities" could either be beneficial or harmful, and *only* outcome studies can clarify if our interventions are beneficial or not. This approach may cause the clinician to pause and think, before simply attempting to reverse an "abnormal" physiologic response. It could also explain why a "less is more" approach is associated with good outcomes,[14] proving that evolution is smarter than we are. The approach of being restrictive with interventions allows the naturally selected survival mechanisms to function. These evolutionary selected traits overcome the adverse pathophysiological state triggered by the disease.

Evolutionary Genotype vs Physiological Phenotype

Putting the "gene frequency in population", rather than the organism at the center of biology requires clinicians to think counter-intuitively. Sepsis could be viewed as the final step of an evolutionary strategy by microbes to maximize their survival by cultivating nutritional sources in the form of larger organisms. This is similar to humans cultivating crops, poultry, and cattle for their nutrition. Humans gained in terms of numbers after the agricultural revolution 10,000 years ago. From a gene frequency perspective, the strategy of feeding humans has increased the survival of these crops, cattle, and poultry. They have been naturally selected over those plants and animals that do not serve as human food. Counter-intuitive as it may sound, they recruited humans to ensure their survival and won the evolutionary prize of increased gene frequency in their overall biological populations.

What is the relevance of this to clinical sepsis? The word sepsis comes from putrefaction that denotes that, after death, the bacteria are reaping the harvest they sowed. Sepsis could be viewed as the breakdown of a stable symbiosis when the more aggressive pathogenic bacteria or a weakened host result in putrefaction before death. The microbes have evolved phenotypic features that can invade larger animals and plants to serve as a shelter and nutrient source. If these microbial features threaten the host, the host develops countermeasures to contain or eliminate the microbe. An "arms race" race evolves, with either microbe or host gaining an advantage and the other subsequently evolving a counter-strategy. The phenotype of the microbe that favors it includes the ability to invade a cell, to multiply quickly to release endotoxins or exotoxins, etc. The phenotype of the host includes physical barriers, an innate, and an adaptive system. Humans also developed a cognitive response that allowed our principles and practices of medicine to contain the invading microbes. Each of these phenotype features in the microbe or host is a manifestation of an underlying genotype. These genes randomly mutate and, if the mutation is beneficial, it gets selected and increases its frequency or numbers. This is the mechanism by which microbes develop resistance to antibiotics.

Summary

Simply stating that sepsis is caused by a dysregulated host response is missing one half of the sepsis syndrome. Clinicians may gain a different perspective into the many intricacies of sepsis by conceptualizing it as a genotypic evolutionary process of natural selection rather than a phenotypic pathophysiological event. To some extent, this has already happened as trials in critical care have shifted their focus from pathophysiological-based surrogate targets to clinically relevant survival and fitness-based outcomes. These clinically meaningful outcomes of decreased mortality, decreased severity, and enhanced recovery are themselves surrogates for the evolutionary goals of natural selection of the underlying genes.

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