Research Article

A Conceptual Model of Sepsis as a Dysregulated Host Response: Depicting Directionality of Immunologic and Metabolic Dysregulation: The OO(H)NO! Model

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ABSTRACT

Background: Mortality from sepsis continues to remain high in hospitalized patients worldwide. Previously, the conceptual model of sepsis was based on the systemic inflammatory immune response syndrome, an *adaptive* model. In 2016, a new definition of sepsis was proposed as a *dysregulated* host response to infection. However, until now, no model has been proposed to elucidate what immunologic and metabolic mechanisms are dysregulated.

Aim: We sought to propose a new directional model of sepsis, from adaptive to dysregulated. This will help to elucidate evidence-based immunologic and metabolic mechanisms that are dysregulated in sepsis.

Methods: The literature was reviewed for themes comparing and contrasting sepsis before and after the 2016 consensus definition of sepsis. Themes from research published after 2016 were described, connecting immunologic and metabolic mechanisms in sepsis. This information further informs the results of earlier research published by the primary author.

Results: In recent years, evidence of dysregulation in innate immune signaling and cellular respiration has been uncovered. The authors constructed a new conceptual model of sepsis to elucidate the current definition of sepsis as a dysregulated host response. Themes uncovered in sepsis research post-2016 were used to guide the construction of the model.

Conclusion: The model proposed here supports clinicians in applying the current definition of sepsis to a physiological model. This can benefit clinicians by offering new ways of recognizing sepsis and researchers by recommending a physiologic model to advance sepsis research.

Keywords: Sepsis, model, immunologic dysregulation, metabolic dysregulation

INTRODUCTION

Historical Timeline -Previous Understandings of Sepsis

According to the Oxford English Dictionary (OED, 2023), sepsis is an infection of part of the body in which pus is produced. Many clinicians and non-clinicians

have misunderstandings about the meaning of sepsis, often confusing the condition with bacteremia or urosepsis. This dates to the early twentieth century, when sepsis was previously defined as a pathogen in the bloodstream (Gyawali et al., 2019). The term sepsis has been used in medical literature since the classical era. however, until 1991, there was no consensus definition of sepsis (Gyawali et al., 2019). Sepsis was first defined in 1991 by the Society for Critical Care Medicine (SCCM) as the Systemic Inflammatory Response Syndrome (SIRS), a symphony of adaptive immunological responses in the presence of infection (Bone et al., 1992). For the first time, an acceptable consensus definition of the condition of sepsis enabled clinicians and scientists to start to collect data on clinical observations, which finally led to an emerging body of evidence in the literature to guide practice (Gyawali et al., 2019). In 2001, Rivers et al. published "Early Goal-Directed Therapy" (EGDT) based on a single-center investigation using a central venous catheter to guide resuscitation based on measurements of mean arterial pressure (MAP) and central venous saturation of carbon dioxide (ScvO2) (Rivers et al. 2001). These guidelines established by Rivers were widely adopted by the Society for Critical Care Medicine (SCCM) and led to the inception of the Surviving Sepsis Campaign (SSC) (Zhang et al., 2017). Early goal-directed therapy became regarded as the best practice for sepsis care, eventually serving as the underpinning of the Centers for Medicare and Medicaid Services (CMS) mandated bundle of intervention for sepsis management for entities under their pay-for-performance programs (Alexander et al., 2022). Given the weight of CMS reimbursement to hospital operations, tremendous resources were and continue to be allocated to meeting CMS's bundle (Alexander et al., 2022).

Early goal-directed therapy remained the accepted standard of care until it was challenged in 2014. Multiple studies were conducted to challenge and ultimately discredit EGDT; there were no significant differences between outcomes for patients treated with EGDT guidelines vs. provider-driven care (Nguyen et al., 2016). This disrupted everything that was known about sepsis in the scientific community. The various investigators who challenged EGDT eventually became a collaborative network to reexamine the beliefs around sepsis care, including criteria for identifying the condition and its clinical management (Nguyen et al., 2016).

In 2016, a new consensus-based definition of sepsis was proposed: a dysregulated host response to infection resulting in organ failure (Singer et al., 2016). The international panel of experts recommending this new definition also recognized what many clinicians long thought that SIRS

could no longer be used for accuracy in sepsis recognition (Singer et al., 2016). To this day, SIRS remains accepted by many organizations as the framework to base sepsis recognition (Prasad et al., 2020). However, SIRS is an *adaptive response*. It is not only an adaptive response to infection but to many other stressors like trauma and anxiety (Graham & Stacy, 2020). The authors of this article suggest that as an adaptive response, SIRS, cannot be supported as a conceptual model of a dysregulated host response to infection (Graham & Stacy, 2020).

The panel suggested that the sequential organ failure assessment, better known now as the sepsis-related organ failure assessment, or SOFA, should be considered as it has specific measures to recognize organ failure in sepsis (Singer et al., 2016). Despite SOFA's greatly improved specificity for sepsis over SIRS (approximately 78% vs 58%), there is still a significant margin of error in sepsis recognition using SOFA (Marik & Taeb, 2017).

Struggling to Make Meaning of the New Definition of Sepsis.

By the time this new definition of sepsis was proposed, many years of potentially lost time in understanding the true nature of sepsis had passed, with sepsis continuing to be the number one cause of mortality (as high as 50%) of hospitalized patients (Global Sepsis Alliance, 2023). The 2016 definition of sepsis and acknowledgment of the lack of specificity for SIRS and SOFA underscored the urgency to invest in new sepsis research. And although a new definition of a dysregulated host response to infection resulting in organ failure was proposed, no explanation was offered as to which physiologic mechanisms have become dysregulated. In recent years, nurse scientists have revisited metabolic monitoring and its relationship to early sepsis recognition, as it has the potential to identify dysregulation in cellular respiration (Graham & Mayo, 2021; Graham et al., 2023). As we continue to learn more, there is an opportunity to create a conceptual model to recommend specific immunologic processes within the host that are *dysregulated* in sepsis.

METHODS

Evidence in the literature (published 2015-2023) comparing sepsis before and after the 2016 consensus definition of sepsis was reviewed for common threads (Graham & Stacy, 2020). The first author has been establishing a program of sepsis research since 2015 and has multiple peer-reviewed publications on the topic. In the earlier article, the case for dysregulated oxidative phosphorylation had already been established but needed further support. To inform the post-2016 body of evidence, the following search terms were used in the database PubMed: Sepsis definition, metabolism in

sepsis, cellular response to infection, organ dysfunction in sepsis, mitochondrial dysfunction in sepsis, metabolic dysregulation in sepsis, and dysregulated immunologic response to sepsis. Theoretical articles that had not been tested were rejected.

Of the articles describing tested results, the search yielded elements of dysregulated immunologic response involving pattern recognition mechanisms of immune cells such as toll-like receptor 4 (TLR4). The search also yielded further evidence supporting dysregulated cellular respiration (also called cellular metabolism or oxidative phosphorylation) in sepsis. From this evidence, the authors constructed a model to explain the dysregulated nature of sepsis. Elements of the prior definition of sepsis that remain (a systemic host response to infection) were kept in the model; those elements that have since been rejected (SIRS, EGDT) were removed from the model. Elements from the new 2016 definition of sepsis (dysregulated host response to infection, organ dysfunction) were added to the model. Commonalities from research published post-2016 were explored, connecting immunologic and metabolic mechanisms in sepsis to describe the nature of the dysregulated host response. This information further informs the results of earlier research published by the primary author.

RESULTS

A search of the literature yielded commonalities, which include dysregulated metabolic and immunologic responses specific to oxidative stress, oxidative phosphorylation, and immune signaling by TLR4. A new conceptual model of sepsis was developed to elucidate the current definition of sepsis as a dysregulated host response, incorporating elements uncovered in sepsis research post-2016. The elements of the model are explained here.

Dysregulated oxidative phosphorylation.

There are increasing contributions to the literature for evidence of disrupted or *dysregulated* cellular respiration in sepsis. Specifically, processes within the electron transport chain, the part of the mitochondrial structure responsible for downregulating oxygen (oxidative phosphorylation) into usable energy or ATP (Graham & Mayo, 2021, Graham et al., 2023). The result is the inability of the cell to *respond* to oxygen, in which case cells must rely on *anaerobic* respiration. Thus, lactate continues to be added to serum despite resuscitative efforts (Graham & Stacy, 2020). It is still unclear what causes this disruption to normal cellular respiration/metabolism. Some theories include mitochondrial injury on exposure to lipopolysaccharide endotoxin or dysregulation further

upstream, the pyruvate cycle, ultimately resulting in the inability to activate oxidative phosphorylation within the electron transport chain (Graham & Stacy, 2020; McCall et al., 2022). There remains, however, still no evidence to propel these hypotheses forward. Recently, disruption of TLR4 activity has shown promising evidence to explain dysregulation along the electron transport chain (Zhang et al., 2021). Dysregulated cellular respiration in sepsis is represented in our model by the "low oxygen consumption (VO2)" fuel gauge on the right panel.

Nitro Oxidative Stress, TLR4 activation, and Over-inflammation

Toll-like receptor 4 (TLR4), is a pattern recognition receptor embedded within the cell membrane of cells of the innate immune system (Kuzmich et al., 2017). Pattern recognition receptors (PRRs) are activated by damage-associated molecular patterns (DAMPs), as well as pathogen-associated molecular patterns (PAMPs)(Kuzmich et al., 2017). Well established in the literature, TLR4 is activated by pathogens, such as bacteria and fungi, triggering inflammatory responses to attack, and rid the host of the pathogen (Zhang et al., 2021). This is a normal immunological finding. Oxidative stress is a harmful immunologic state, where exposure to exaggerated or prolonged inflammation can become toxic to the host, eventually leading to cell death and organ dysfunction (Di Meo & Venditti, 2021). A recent review describes an increasing body of evidence associating the regulation of nitrooxidative stress with TLR4 activity (Zhang et al., 2021). Thus, it is suggested that TLR4 dysregulation may account for the missing link to explain the dysregulation of oxidative phosphorylation in sepsis. The middle panel of the model represents inappropriate TLR4 signaling, resulting in excessive inflammation, impacting cellular respiration represented in the VO2 fuel gauge.

Adaptive TLR4 Activation

Lipopolysaccharide (LPS) is a molecular structure of the cell wall of gram-negative bacteria. The cell surface molecule TLR4 has a particular *ligand* (binding molecule) for LPS, meaning it can recognize gram-negative bacteria in the host, and responds by activating two specific synergistic immunologic pathways; *myeloid differentiation primary response 88* (MyD88) dependent and *TIR domain-containing adaptor molecule 1* dependent (TICAM1) to contain the (Oneill & Bowie, 2007). When the pathways activated by TLR4 are intact, a normal response will contain the pathogen and close the loop of this innate immune response (Kuzmich et al., 2017). However, if either pathway is dysregulated, this loop will not close, and the cell will become overwhelmed with a never-ending loop of inflammation (Ciesielska et al., 2021). Adaptive TLR4 activation is represented in the left

panel of the model, with efficient cellular respiration demonstrated in the VO2 fuel gage.

Dysregulated TLR4 Activation

Immunologic signaling is highly complex. Although much remains unknown about what immunologic mechanisms have become dysregulated in sepsis, much of the literature describes a possible dysregulation of toll-like receptor 4 (TLR4) activity, a property of the innate immune response (Kuzmich et al., 2017). When activated by GM-endotoxin or other microbes, TLR4 will activate the cellular signaling molecules MyD88 and TICAM1, two synergistic pathways of immunologic response to attack the pathogen (Kuzmich et al., 2017). Specifically, MyD88 has been demonstrated to be protective against severe sepsis (Heipertz et al., 2017). Researchers have identified that disruption in either pathway resulted in decreased cellular metabolism, particularly in disruption of the MyD88 pathway (Lauterbach et al., 2019). Downregulation of TLR4 activation occurs when interferon regulatory factor 4 (IRF4) is activated, targeting the MyD88 section of the TLR pathway (Negishi et al., 2005).

Endocrine disruptors and Their Relationship to TLR4 Dysregulation

Per the National Institutes of Health triclosan, atrazine, bisphenol a (BPA) and phthalates, dioxins, perchlorate, per- and poly-fluoroalkyl substances (PFAS), and phytoestrogens are the most common endocrine disruptors responsible for toxic environmental exposure. Triclosan, bisphenol A (BPA), and phthalates are especially prevalent, even *ubiquitous* (Ohnishi, 2008).

Much evidence exists for the relationship of endocrine disruptors to immunologic processes; many studies have been conducted on mice. Less is known about the specific impact of exposure on TLR4 activation. Due to the ubiquity of the endocrine disruptors triclosan, BPA, and phthalates, much more is known about their specific impacts on TLR4 activation.

Triclosan and TLR4

Triclosan, a widely available antimicrobial agent, is so ubiquitous that it is found in 75% of urine samples in the U.S. (Calafat et al., 2008). Triclosan exposure has been demonstrated to increase the expression of a ligand with an affinity for TLR4. In mouse studies, exposure to Triclosan demonstrated impaired immune response after only four days of exposure. (Marshall et al., 2017)

Bisphenol A, Phthalates and TLR4

Substantial evidence exists for impacts on TLR4 activation and signaling from Bisphenol A (BPA). Exposure to BPA has been shown to be associated with TLR4 activation in multiple conditions, including exacerbation of type

2 diabetes and pulmonary disease (Ma et al., 2021, Wang et al., 2021. Additionally, in utero, exposure to BPA has also been linked to TLR4 activation in fatty liver disease (Lin et al., 2019). A search of *PubMed* yielded a plethora of articles describing BPA and its relationship to inflammation, including a review substantiating the relationship of "ubiquitous" BPA and phthalates to allergy and asthma in humans (Robinson & Miller, 2015)

Mitigation of exposure to endocrine receptors

A review by Hampl and Starka (2020) describes *dysbiosis,* or an imbalance of helpful gut flora and pathogens, occurring because of exposure to endocrine disruptors. We now know the gut's important role in regulating many endocrine, neuroendocrine, and immunologic processes; however, there remains a paucity of evidence as to which specific mechanisms are directly impacted by this relationship (Hampl & Starka, 2020; Guo et al., 2020).

Sepsis and the postindustrial era

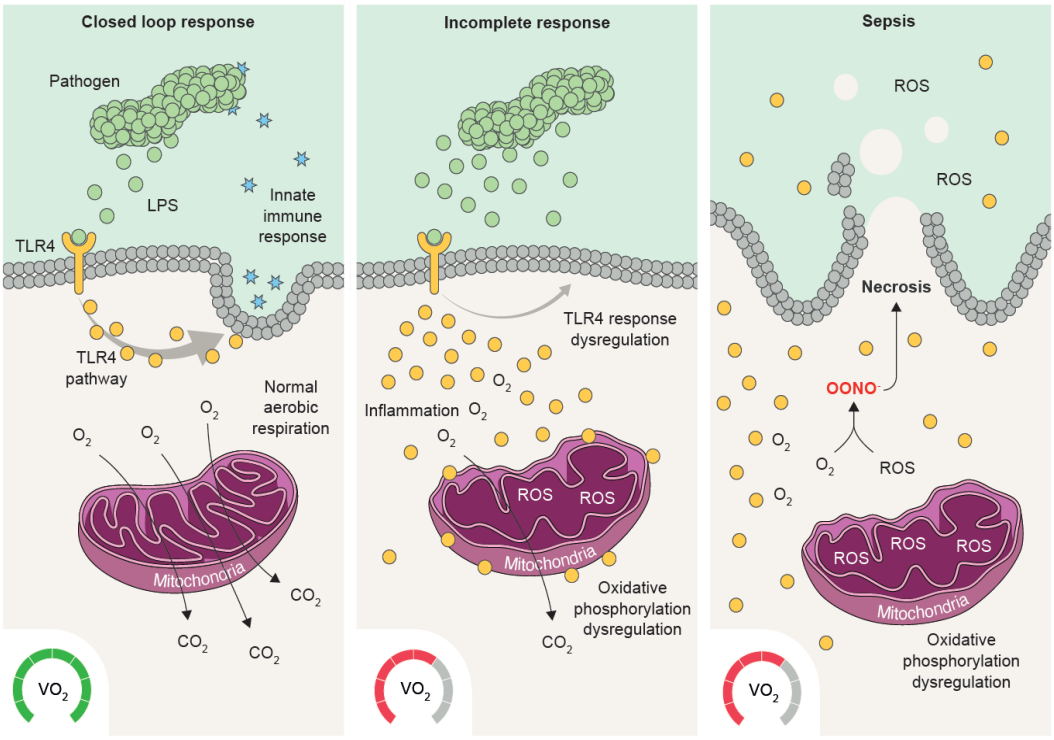
As described earlier, the definition of sepsis has changed multiple times since the early twentieth century (Kuzmich et al., 2017). This makes it difficult to track the incidence of sepsis over time. Additionally, no global reporting index is specifically designed to track sepsis (Rudd et al., 2020). The industrial era provided a miraculous new treatment for infection in the form of antibiotics (Hutchings et al., 2019). This certainly positively influenced global sepsis incidence; however, worldwide deaths from sepsis remain as high as 25-50% (Global Sepsis Alliance, 2023). There is much to understand about which mechanisms have been dysregulated in sepsis. If the ubiquitous exposure to endocrine disruptors in the industrial era is responsible for increased immunologic frailty, this could explain why sepsis remains such a global health burden as the top killer of hospitalized patients around the world despite available antibiotics (Hutchings et al., 2019).

This article proposes a new model of sepsis, depicting the directionality of the adaptive response to infection toward the dysregulated response to infection observed in sepsis. The authors suggest that exposure to ubiquitous endocrine disrupters in the post-industrial era has altered the ability of TLR4 to contain pathogens despite their recognition. In sepsis, the inflammatory cascade is activated upon recognition of the pathogen. However, activation of TICAM1 and MyD88 has become dysregulated and cannot cleave to contain the pathogen. The result is excessive inflammation due to ongoing exposure to the pathogen. This leads to excessive oxidative free radicals, ultimately Peroxynitrite (OONO-) that accumulate and eventually signal the cell to rupture, leading to cell death and organ failure

in sepsis. As sepsis is cause for alarm, and as the superoxide's molecular structure is phonetically similar, the authors chose to name the model for the expression of alarm, "Oh No!"

Figure

The OO(H)NO! Model of Metabolic and Immunologic Dysregulation in Sepsis Model



On the left, the adaptive response to infection. TLR4 on the cell wall recognizes the pathogen and activates MyD88 and TICAM1 in tandem to contain the pathogen. VO2 is normal as cellular respiration remains intact. The panel in the middle demonstrates inappropriate activation of MyD88 and TICAM1. Thus, the pathogen cannot be contained, resulting in an excessive inflammatory response due to increasing exposure to the ill-contained pathogen. Cellular respiration has become dysregulated, compromising VO2, and thus ROS accumulates. The panel on the right demonstrates the dysregulated response. VO2 is low as the cell becomes overwhelmed by ROS, oxynitrite forms, and the cell ruptures, causing cell death and, ultimately, organ failure.

Note: The OO(H)NO! Model of Metabolic and Immunologic Dysregulation in Sepsis Model was commissioned by the author with a graphic designer specializing in molecular biology, at Vividbiology.com, with funds from a grant from the American Association of Critical Care Nurses

DISCUSSION

The effect of disrupted TLR4 activation on oxidative phosphorylation

When the adaptive pathways activated by TLR4 in the presence of LPS or other pathogens are disrupted, the cell cannot close the loop on the innate immunologic response. The result is unregulated activation of TLR4, which turns deadly when persistent inflammation disrupts oxidative phosphorylation. Consequently, the cell must continue to rely on anaerobic respiration despite oxygen delivery, resulting in the persistent contribution of lactate to the host's serum (Graham & Stacy, 2020). Once oxidative phosphorylation becomes dysregulated, Reactive Oxygen Species (ROS) accumulate, overwhelming the electron transport chain's ability to utilize further incoming oxygen. As incoming oxygen reacts with ROS, Peroxynitrate (OONO-) is the resulting molecule. This molecule causes catastrophic rupture and necrosis of the cells, furthering the inflammatory cascade and resulting in cell death and organ failure (Stamler et al., 1992).

If, as described earlier, the downregulation of TLR4 signaling is dependent on MyD88's response to IRF4, disruption of the MyD88 pathway may interfere with the downregulation of TLR4 activation, resulting in persistent, toxic inflammation (Negishi et al., 2005).

Monitoring of oxygen consumption (VO2) is available to clinicians and has been demonstrated as a parameter to help distinguish critically ill patients with and without sepsis (Graham & Mayo, 2021). Metabolic monitoring currently available offers meaningful metabolic information, which is not only significant in sepsis but also increasingly important in the precise determination of energy expenditure (kcal/day), which is required for the determination of caloric requirement, which is key to care of the critically ill patient. The gold standard for metabolic monitoring is indirect calorimetry (Delsoglio et al., 2019). This technology, however meaningful, is challenging to adopt clinically, as it requires specialized equipment and skill (Graham & Mayo, 2021). Additionally, there are contraindications to its use in patients with respiratory failure (American Association for Respiratory Care, 1994).

Limitations

The growing body of research pertaining to sepsis, considering the 2016 definition of sepsis, aligns well with the proposed model. However, there is still only a paucity of evidence to support it. In addition, much of the cellular-level science has been conducted on mice, which may or may not apply to human beings.

Implications for Nursing

Clinical surveillance is a specialty specific to the discipline of Nursing. Nurses conduct clinical surveillance (monitoring) and collect patient data nonstop during their shifts. They then use this data to make rapid real-time

care decisions. Care decisions include recognizing new signs that could signal patient deterioration, including sepsis. Adding metabolic monitoring, such as oxygen consumption as a physical parameter or vital sign, could be key to improving the specificity of sepsis recognition in the clinical setting. More precise models of clinical surveillance in sepsis may result in Nurses' ability to recognize sepsis early and accurately, allowing them to initiate lifesaving therapy in a timely manner.

Implications for Future Research

This model contributes important information to elucidate which mechanisms are dysregulated in sepsis; however, much more research needs to be done to support it and further develop it. Future research should also include building a base of evidence to inform clinical surveillance as a science specific to the nursing discipline. Recognizing the distinct ability nurses have to continuously collect patient data to inform rapid decision-making differentiates nurses from other members of the care team and further establishes the science of nursing. Additionally, further research must be done to establish accepted parameters of oxygen consumption that can be adopted into Nursing Clinical Surveillance.

Other opportunities include exploring areas with high exposure to endocrine disruptors and mapping them out to understand the relationship of dose of exposure to sepsis outcomes in those areas. Once these findings are further understood, researchers may have vital information to create new therapeutic and pharmacological interventions.

CONCLUSIONS

The sepsis model proposed here may help clinicians apply the current definition of sepsis to a physiologic model. Additionally, it explains dysregulated oxidative phosphorylation, which is measurable in the clinical setting by monitoring measures of oxygen consumption. This contributes to a deeper understanding of the host immunologic and metabolic mechanisms that have become dysregulated in sepsis and serves as a springboard for future research.

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