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Review article

Sepsis in the era of data-driven medicine: personalizing risks, diagnoses, treatments and prognoses

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Abstract

Sepsis is a series of clinical syndromes caused by the immunological response to infection. The clinical evidence for sepsis could typically attribute to bacterial infection or bacterial endotoxins, but infections due to viruses, fungi or parasites could also lead to sepsis. Regardless of the etiology, rapid clinical deterioration, prolonged stay in intensive care units and high risk for mortality correlate with the incidence of sepsis. Despite its prevalence and morbidity, improvement in sepsis outcomes has remained limited. In this comprehensive review, we summarize the current landscape of risk estimation, diagnosis, treatment and prognosis strategies in the setting of sepsis and discuss future challenges. We argue that the advent of modern technologies such as in-depth molecular profiling, biomedical big data and machine intelligence methods will augment the treatment and prevention of sepsis. The volume, variety, veracity and velocity of heterogeneous data generated as part of healthcare delivery and recent advances in biotechnology-driven therapeutics and companion diagnostics may provide a new wave of approaches to identify the most at-risk sepsis patients and reduce the symptom burden in patients within shorter turnaround times. Developing novel therapies by leveraging modern drug discovery strategies including computational drug repositioning, cell and gene-therapy, clustered regularly interspaced short palindromic repeats -based genetic editing systems, immunotherapy, microbiome restoration, nanomaterial-based therapy and phage therapy may help to develop treatments to target sepsis. We also provide empirical evidence for potential new sepsis targets including FER and STARD3NL. Implementing data-driven methods that use real-time collection and analysis of clinical variables to trace, track and treat sepsis-related adverse outcomes will be key. Understanding the root and route of sepsis and its comorbid conditions that complicate treatment outcomes and lead to organ dysfunction may help to facilitate identification of most at-risk patients and prevent further deterioration. To conclude, leveraging the advances in precision medicine, biomedical data science and translational bioinformatics approaches may help to develop better strategies to diagnose and treat sepsis in the next decade.

Key words: sepsis; translational bioinformatics; computational medicine; precision medicine; genome informatics

Background

Sepsis is a persistently growing health concern in America, especially in light of the aging population demographics. More than 1.5 million people are affected by sepsis in the USA each year, leading to 250 000 deaths [1]. This results in an estimated mortality rate of 17%, which is staggering for such a prevalent disease. Sepsis is also a burden to the healthcare system financial state, accounting for $23.7 billion in 2013 alone (6.2% of all hospitalization costs) [2]. It is the primary cause of death of intensive care unit (ICU) patients, even as sepsis patients occupy only 10% of ICU beds [3]. Mortality rates attributed to sepsis remain disappointingly high at 15–20%, necessitating novel diagnostic and treatment strategies for earlier prevention and management to improve clinical outcomes [3, 4]. Traditional approaches, which assay single biomarkers, largely fail to identify most of the patients at risk for sepsis and instead are better suited to predict severity and mortality [5]. Hence, we need a systems medicine approach to diagnose, treat and estimate the prognoses of sepsis. With the introduction of longitudinal electronic health records (EHR) [6, 7], low-cost genomics and other molecular profiling technologies [8], novel machine intelligence algorithms [9, 10], modern drug discovery and companion diagnostics development strategies [11], we now are equipped with a plethora of powerful tools not previously available [10, 12]. In this review, we address some of the current challenges, and forecast how various aspects of precision medicine, biomedical data science and translational bioinformatics approaches will collaboratively help us to combat sepsis.

Defining sepsis

Difficulties in treating sepsis is partly due to challenges in understanding the mechanisms underlying the syndrome given its wide pathophysiological and clinical variability. Even a strict definition of sepsis has been elusive. In 1992, an international consensus panel first defined sepsis as a systemic inflammatory response syndrome (SIRS) [13]. In addition to establishing the SIRS criteria, the panel also defined sepsis, severe sepsis, septic shock, sepsis-induced hypotension and multiple organ dysfunction syndrome [14]. Severe sepsis includes acute organ dysfunction whereas septic shock results from significant reduction of tissue perfusion due to hypotension that is refractory to fluid resuscitation and with hyperlactatemia [14]. Sepsis was recently reevaluated by the task force of the European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) in their guidelines in 2014, in order to redefine sepsis and the criteria for diagnosis. In the Sepsis-3 paper, sepsis was re-defined as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection' [15]. This definition was clinically supported by a source of infection with two or more quick sequential organ failure assessment (qSOFA) criteria. Sepsis-3 removed the severe sepsis classification entirely as no objective definition for end-organ dysfunction currently exists. It was also recognized by ESICM/SCCM guidelines that sepsis remains a poorly understood process. Therefore, no gold standard could yet be established to unequivocally identify a septic patient.

The wide variability in the clinical manifestations of sepsis contributes to the challenges in its definition. As a syndrome, the constellation of septic signs and symptoms is largely dependent on the site of infection, the causative pathogen, the pattern of end-organ dysfunction and the underlying healthy physiological profile of the patient [16]. Although the etiology of sepsis is unknown in one-half of cases, the majority of cases are caused by hospital or community acquired gram positive cocci *Staphylococcus aureus*, pathogenic *Streptococcus spp.* and gram negative bacilli such as *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella* [17]. In addition, fungi species such as *Candida albicans, Histoplasma* and (especially in the case of

patients with AIDS) *Pneumocystis jirovecii* are known to cause sepsis in immunocompromised patients [18, 19]. Symptoms in severe sepsis and septic shock that indicate organ dysfunction include altered mental status, dyspnea, oliguria, jaundice and dysglycemia [16, 20]. Unfortunately, many of these symptoms are not highly specific to sepsis. Furthermore, the body's physiologic response to increase systemic vascular resistance by endogenous catecholamines during the early stages of septic shock may offset the initial drop in blood pressure due to decreased effective intravascular volume from diffuse capillary leakage [21]. However, later stages of sepsis are characterized inability to effectively compensate and resulting systemic tissue hypoxia leading to acidosis and vasodilation [22]. A better understanding of the complex host response elicited during sepsis further suggests that the SIRS criteria of 1992 needed to be redefined in order to more accurately diagnose patients at risk for clinical deterioration. As the Sepsis-3 criteria has described, 'sepsis is a multifaceted host response to an infecting pathogen that may be significantly amplified by endogenous factors' [15]. Rather than a solely host pro-inflammatory response to infection, sepsis is now recognized as a complex interplay between both pro- and anti-inflammatory responses [23]. Inflammatory stimuli from the pathogens trigger host immune cells to release proinflammatory mediators such as TNF-a, IL-1, IFN-y, IL-12 and IL-18. These proinflammatory mediators interaction with prostaglandins, platelet activating factors, adhesion molecules and stress hormones results in vasodilation, increased vascular permeability and reduced perfusion. In addition, pro-inflammatory molecules activate opposing anti-inflammatory molecules, such as IL-10, that lead to periods of immunosuppression. These periods of immunosuppression can contribute to increased risk of nosocomial infections and reactivation of latent viruses [24]. This multifaceted host immune response with major nonimmunologic factors (cardiovascular, neuronal, autonomic, hormonal, metabolic and coagulation) may contribute to diminished oxygenation of the end-organs, leading to acute organ dysfunction.

Risk stratification and diagnoses

Sepsis is a syndromic condition that increases mortality in both pediatric and adult populations. Early identification may help set the course of treatment strategies and maximize therapeutic efficacy. The need to develop earlier preemptive identification and prophylactic treatment will benefit all ages but will clearly require personalized approaches based on different sub-populations (immunocompromised or non-immunocompromised; geriatric versus pediatric etc.). Development of new risk stratification algorithms, multianalyte diagnostics and biomarker panels are emerging to proactively identify patients at risk for sepsis. In this section, we propose the development of integrative approaches and multi-analyte-based diagnostic aids coupled with machine learning to enable better outcomes. We also discuss the possibilities of designing a polygenic risk score for sepsis and associated outcomes.

An integrative approach for the accelerated diagnoses and personalized treatment

Much work has focused upon improving early diagnosis, treatment and prognosis of sepsis with diagnosis criteria, biomarkers of sepsis and host genomics. Identifying biomarkers associated with sepsis offers multiple clinical benefits. By expanding clinical biomarkers of sepsis, such as serum lactate and procalcitonin [25], with pro-inflammatory and anti-inflammatory cytokines, chemokines and acute phase proteins, we will be able to measure and create unique biochemical profiles for sepsis. Profiling of, for instance, 16 s ribosomal RNA via PCR can help identify a causative bacterial agent even when blood cultures are negative [26]. Current approaches for diagnosis and treatment include antimicrobial stewardship via microarray analysis [27] and point of care detection of bacterial DNA from whole blood [28], but combining new sequencing technologies with machine intelligence could improve the yield of these approaches. In addition, changes in biomarkers over the clinical course of sepsis can be used to monitor improvement or deterioration during management. Also, intensive biochemical profiling could help identify sepsis patients at higher risk for poorer outcomes such as with multiple organ dysfunction [25, 26]. Finally, the use of biomarkers in conjunction with a patient's unique genetic susceptibility to infection will allow us to generate individualized prevention strategies and medical therapies for patients at risk with sepsis [29]. As a result, the clinical approach to sepsis will evolve to require a systems view with analysis of patient vitals, unique biomarker profile, metabolites, host genomic profile and his or her microbiome [30, 31]. Diagnostics aids can also be built by combining different omics modalities and multi-analyte technology platforms. For example, proteogenomics is a hybrid biotechnology approach that combines genomic sequencing or transcriptomic sequencing with proteomics profiling to provide a static-to-dynamic view of biological systems. A proteogenomics platform was recently developed to develop a liquid biopsy to detect multiple types of cancers [32]. By similarly using biomarker signatures from different analytes and combining predictive models using proteogenomics, metabo-proteomics and other hybrid-omics technologies can be built for diagnoses and prognoses (Figure 1) [31, 33, 34]. Furthermore, responders and non-responders can be identified using multi-modal diagnostic platforms. The refinement of these methods could be used to develop personalized, comorbidity-based drug discovery strategies.

Predictive algorithms for accelerated diagnoses of sepsis

Designing predictive models may help stratify patients who may benefit with the end result of improved resource allocation and outcomes [35–41]. A variety of algorithms are already used to predict stages of clinical acuity in the setting of hospital admissions (See Table 1) [42]. Several risk stratification tools have also been reported that may potentially give an early indication of sepsis. Variants of algorithms like the modified early warning system, such as TREWScore [43] were recently proposed to help predict patients at risk. TREWScore is a targeted real-time early warning score that predicts which patients are most susceptible to septic shock within few hours. This prediction is achieved using a Cox proportional hazards model with L1 regularization as a supervised model with time until the onset of septic shock as the dependent variable. The model assumes that the onset of shock and the sepsis severity levels are critical. The baseline hazard function was fit using a multiple imputation method and estimated from a subset of 400 000 time-to-event and feature pairs from the development set. This has been used to repeatedly sample the event time for each interval-censored sample and generate 100 complete copies of the development dataset. A separate model was trained from each of the N copies of the development dataset. To predict on data from a new subject,

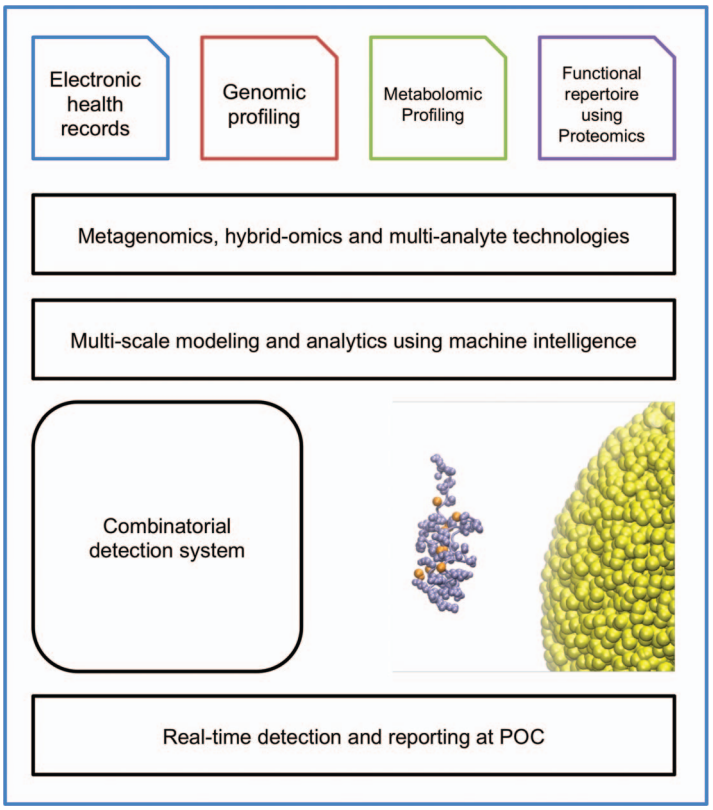

Figure 1. Translational bioinformatics framework for developing multi-analyte, heterogeneous, data-driven diagnostic aid for sepsis.

Table 1. Representative list of algorithms for predicting patient outcomes in the setting of sepsis

Sepsis risk algorithms	Abbreviation	Benefits
BOMBARD	BOMBARD	BOMBARD was more accurate than SIRS and qSOFA at predicting severe sepsis/septic shock and sepsis mortality.
Hamilton early warnings system	HEWS	Good discriminative ability for predicting the occurrence of a critical event among septic patients.
Modified early warning system	MEWS	Provides great predictive value and accuracy for early clinical deterioration.
National early warning score	NEWS	NEWS has better performance than qSOFA and SIRS.
Quick version of sequential organ failure assessment	qSOFA	Ability to predict mortality based on organ dysfunction severity and easier to score clinically than SOFA.
Reasons for geographic and racial differences in stroke-severe sepsis risk score	REGARDS-SSRS	Effective for predicting community-dwelling adults at high risk of sepsis.
Systemic inflammatory response syndrome	SIRS	Higher sensitivity to detect sepsis-related mortality than qSOFA
Sepsis 'sniffer' algorithm	SSA	SSA reduced the risk of incorrectly categorizing patients at low risk for sepsis, detected sepsis high risk in half the time, and reduced redundant NST screens.
Targeted real-time early warning score	TREWScore	Ability to detect at risk patients early using a learned algorithm model that takes into account many more factors.

predicted risk values were obtained from each of the N models; these values were combined using Rubin's equations that compute the final risk value as the average of risk values outputted from each of the *N* models. The area under the curve obtained for the TREWScore was 0.83 (95% CI, 0.81–0.85). At a specificity of 0.67 [false-positive rate of 0.33], TREWScore achieved a sensitivity of 0.85. Patients were identified at a median of 28.2 h before shock onset.

A polygenic risk score for sepsis and adverse outcomes

Risk stratification using panel of genetic variants to identify patients at risk for complex diseases like myocardial infarction, stroke and neuropsychiatric disorders is an emerging theme of precision medicine [44–46]. Emerging results from genome-wide association studies (GWAS) reveal several plausible risk alleles associated with sepsis and related clinical outcomes

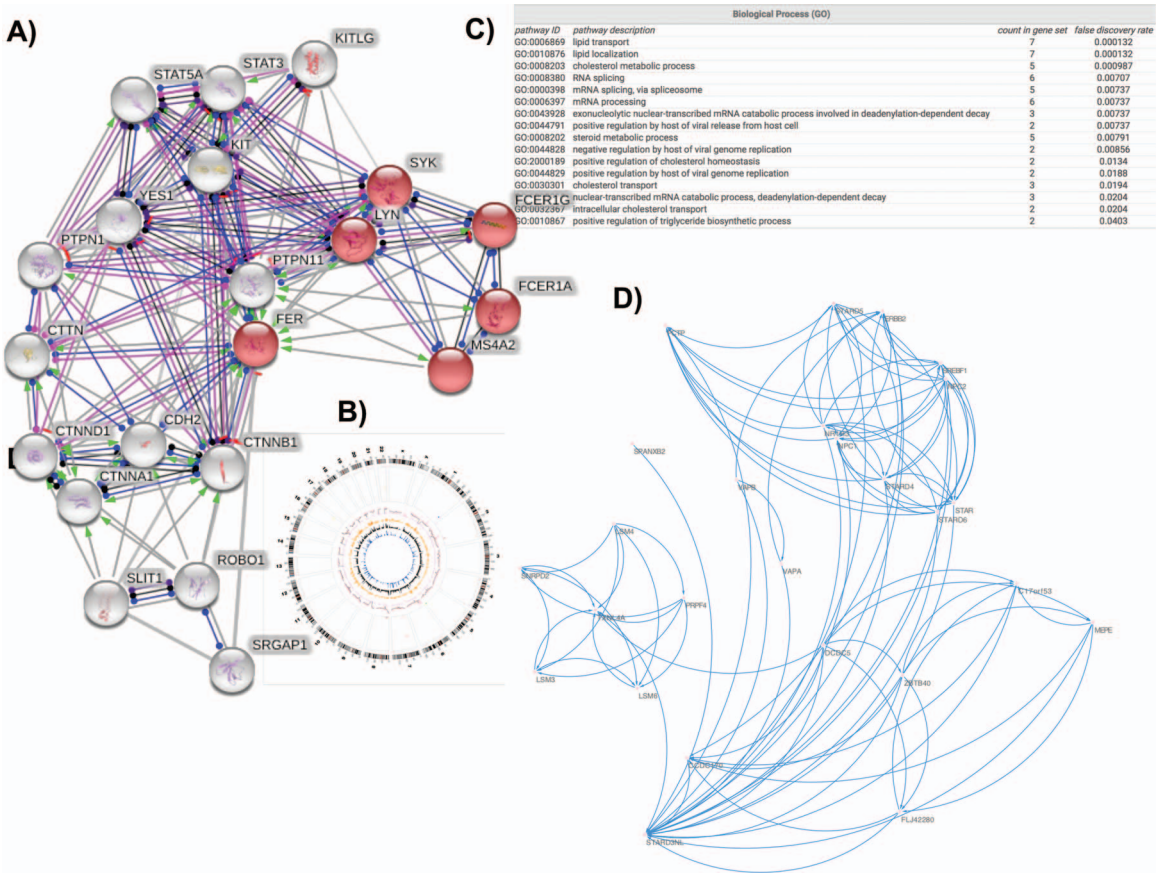

Figure 2. Emerging targets, pathways from genome-wide association studies of sepsis phenotypes. (**A**) Molecular neighborhood of FER protein; red nodes are proteins implicated in regulation of mast cell degranulation. (**B**) Genome-wide associations of variants implicated in response to sepsis therapy. (**C**) Biological processes mediated by the molecular neighborhood of STARD3NL. (**D**) First-degree interactome of STARD3NL.

[47, 48]. A study that combines GWAS with deep sequencing identified association of several interesting genes with clinical outcomes like 28-day mortality after sepsis (*VPS13A*) and procalcitonin level in sepsis patients (*CRISPLD2*). Another GWAS investigation surveyed the genetic landscape to find the potential variants indicating survival from sepsis due to pneumonia. While such investigations address a critical knowledge gap, it remains elusive whether any common genomic markers could be predictive of the incidence of sepsis. In the absence of such direct genomic evidence for predictive sepsis risk, developing a genetic risk score for various detrimental outcomes associated with sepsis (heart failure, respiratory arrest, etc.) may help to find patients that need accelerated care in the context of an infection (Figure 2). While the health economic utility of whole-genome sequencing is still being debated, sequencing the genome and providing such information to compute risk scores may help to identify and accelerate treatments using genomic information [49].

Limitations of using singular biomarkers highlights the need for combinatorial markers of syndromic stages in sepsis

More than 100 biomarkers are listed in sepsis-related review articles and meta-analyses showing varying degree of clinical utilities for diagnoses. Many of these biomarkers are only effective after the infection reaches a stage where treatment is less effective or the beginning of major complications arise. Emerging advances in liquid biopsies [32, 50] and other molecular signature-based screening of diseases could help in designing a better diagnostic aid for various stages of sepsis. One such strategy could involve searching for a combination of existing biomarkers that could inform the preeminent stages of information. Leveraging data from EHR and using laboratory-based data points across different analytes and building predictive models may help in building such models preemptive diagnostic panels. Recently, we build a companion diagnostic aid to predict response of statin, a drug that reduces blood cholesterol, using a combination of data from gene expression profiling, biochemical assays and imaging data integrated using machine intelligence methods [51]. Similarly, models can be built by data from patients with sepsis using data already aggregated in EHR by integrating multi-analytes (genetic variation, protein level, metabolite signature, gene expression signature etc.) with machine learning for effective monitoring of sepsis [39, 52].

Recently, Sweeney *et al.* [53] have developed a diagnostic aid to classify the underlying infection as viral or bacterial using gene expression signatures. With a lower negative likelihood ratio than that of procalcitonin, their integrated antibiotics decision model (IADM) can be useful to rule out bacterial infections [36]. IADM has a lower negative likelihood ratio than procalcitonin. Thus, IADM may be more useful to rule out bacterial infections that require antibiotics compared to viral infections.

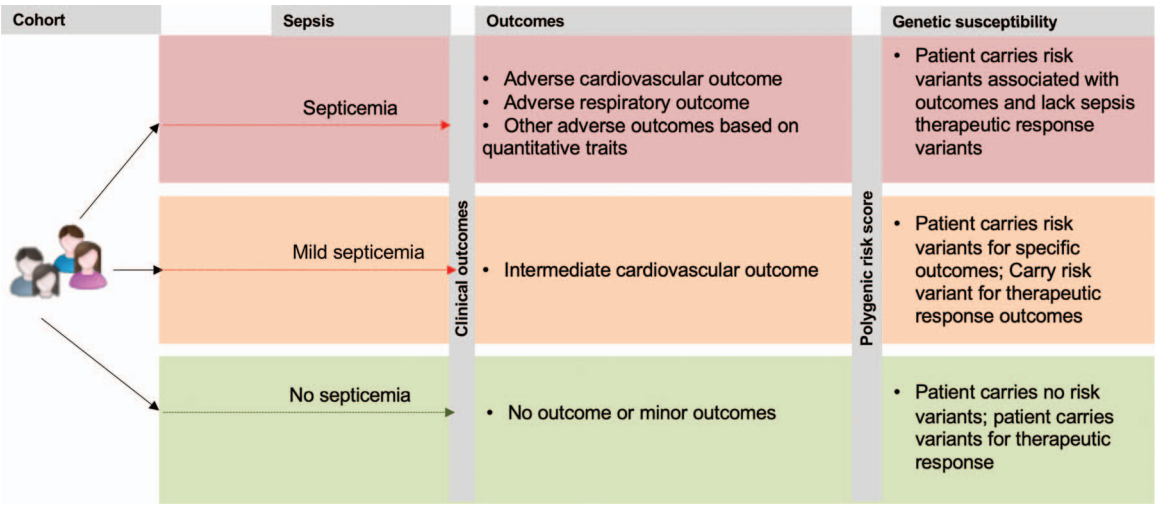

Figure 3. A personalized genomic framework for developing a polygenic risk for sepsis and associated outcomes.

While several statistical and machine learning algorithms are making progress in healthcare as decision aids, it should be noted that such methods have higher degree of false positive rates and the assessment of the patient's post prediction—whether the patients flagged were eventually survived remains open. Hence, modeling the accelerated identification with progression of patients through various clinical pathways is critical. Modeling the end-to-end patient life cycle of the infection from probability, identification, treatment and recovery from sepsis using reinforcement learning or Bayesian deep learning methods may help to improve such models in the future [34, 36, 54].

Treatments and Prognosis

Emerging drug discovery strategies for developing treatments for sepsis

Current clinical pathways to target patients with sepsis include rapid response to septic patients and immediate initiation of antibiotic therapy. Depending on the clinical profile of the patient and time of sepsis detection, *bona fide* sepsis diagnosis can have a mortality rate as high as 30%. Furthermore, the evolution of drug-resistant forms of sepsis is also a major concern. Hence, leveraging modern drug discovery approaches may yield new therapies for sepsis. Here we briefly discuss some of the emerging themes (computational drug repositioning, cell and gene-therapy, clustered regularly interspaced short palindromic repeats (CRISPR)-based genetic editing systems, immunotherapy, microbiome restoration and nanomaterial-based therapy and phage therapy) in drug discovery in the context of sepsis.

New evidence from genomic and phenomic studies—druggable targets, mechanisms and therapeutic response in sepsis

As more research focuses on the host immunologic responses to infection, it has become increasingly clear that genomics may help broaden our understanding of sepsis' pathogenesis. A landmark study in 1988 provided strong evidence for genetic susceptibility to infection. It demonstrated a 5.8-fold increase in mortality in adopted children who had at least one biological parent die from infection [55, 56]. This set off a gold rush in genomic research to identify the basis for genetic susceptibility to infection. The prime targets are genes involved in inflammatory pathways. Initial focus was directed primarily on single nucleotide polymorphisms (SNPs) in those genes [57]. Advances in sequencing technology and expression analysis led to the identification of candidate genes, genomic regions, structural variants, genetic variants and new molecular mechanisms implicated in sepsis susceptibility [48, 58–66].

A number of polymorphisms in genes for antigen recognition and inflammatory pathways have been implicated [23]. Recently, a GWAS has identified a single gene strongly associated with sepsis survival. Those who are homozygous for the C allele of the Tyrosine-protein kinase Fer (*FER; P = 6.00e-6;* dbSNP identifier: rs4723738) gene were shown to have a 44% reduction in sepsis mortality [47]. Given the high frequency of this allele, there could be a substantial population benefiting from this protective effect. The variant is encoded in chromosome 7 and has a compound role in mediating multiple autoimmune diseases including type 1 diabetes, rheumatoid arthritis, juvenile idiopathic arthritis, multiple sclerosis and Crohn's disease. The precise role of FER or its interacting partners in sepsis response remains elusive and requires further biochemical discovery and translational research. Empirical protein structure results suggest that this gene encodes FCH, SH2, and tyrosine kinase domains. These different domains can be modeled using structural templates with sequence identity ranging from 40–100%. Thus, this could be a potential druggable target to modulate therapeutic responses in sepsis patients (Figure 3). We explored the molecular neighborhood of FER to assess its potential as a target and identified that within a network of 20 interactors, the protein–protein interaction network is highly enriched for relevant biological interactions. The interactors collectively mediate biological processes like regulation of mast cell degranulation, leukocyte activation and innate immune response. Molecular functions include IgE receptor activity, and signaling pathways mediated by tyrosine kinases, whereas cellular localization were enriched for various membrane locations. Proteins were also enriched across KEGG pathways including adherens junction, Fc epsilon RI pathway, cancer, asthma and leukocyte transendothelial migration (Figures 3 and 4).

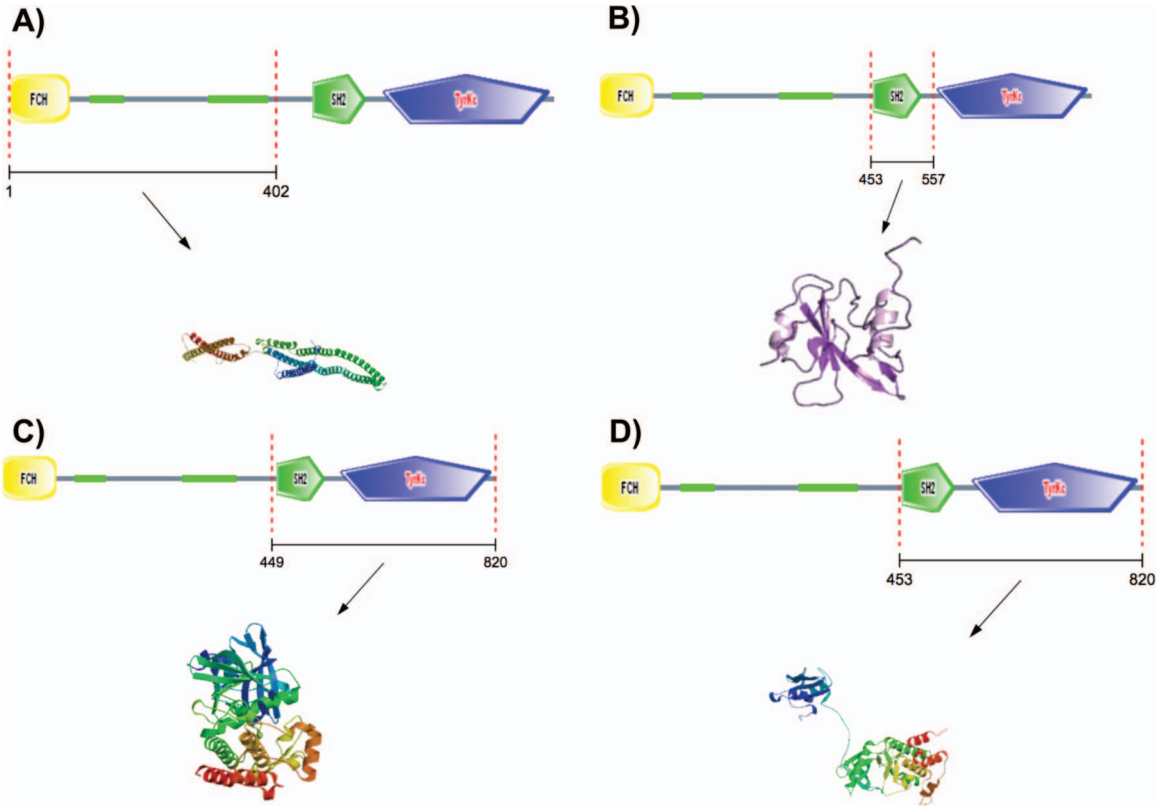

Figure 4. Homology modeling of FER protein, a putative target for therapeutic response in sepsis.

Phenome-wide association studies (PheWAS) enables the simultaneous identification of risk or protection for multiple phenotypes that are associated with genetic variants [67, 68]. We performed an empirical analysis of the data from PheWAS catalog (https://phewascatalog.org/phewas) for phenotype 'Treatment response for severe sepsis'. We found that variants associated with sepsis response could mediate protective effects for 203 conditions including migraine, chondrocalcinosis and pelvic inflammatory disease among others (mapped genes includes *KRT18P32, MKL1, TTC4P1, STARD3NL, NKX2-6;* all observations $P \leq 0.05$; OR ≤ 1.00). We further noted that conditions such as congenital anomalies of head and neck, congenital anomalies of intensive, hypertensive complications, jaundice, postinflammatory pulmonary fibrosis etc. were associated with mapped genes such as *MKL1, NKX2-6, STARD3NL, KRT18P32, TTC4P1* (all observations $P \leq 0.05$; OR ≤ 1.00) (Figures 3 and 4). Collectively these phenotypes are indicative of one or more complications in the setting of sepsis, and could be indicative of shared pathways driving common pathobiology. Hence, exploring the genomic and phenomic bases of these co-morbidity cascades may yield new druggable targets.

We explored the molecular neighborhood of one of these genes, *STARD3NL,* using predicted and experimental protein–protein interaction data from human proteome. The exact functional role of *STARD3NL* is yet to be elucidated beyond an indication as a component of cholesterol transport pathways, functional enrichment analyses of the molecular neighborhood ($n = 20$ genes) indicates that the protein could play a critical role in viral genome replication and positive regulation by host of viral release from host cell (Figure 4).

We also analyzed the current druggability status of the four emerging genes using the Illuminating Druggable Genome—PHAROS database ([69], see: https://pharos.nih.gov/idg): *FER, STARD3NL*, and *VPS13A*. Briefly, IDG-Pharos provides a four-level framework for simplifying the target development/druggability status. *Tclin* indicates the target have approved drugs with known mechanism of action; *Tchem* refers to the evidence targets with some level of chemical activity evidence; *Tbio* level suggests the availability of biological evidence and finally, *Tdark* applies to targets without any clinical, chemical or biological information. Interestingly, *FER* has nine compounds that could target the protein and have a *Tchem* level. Whereas both *STARD3NL* and *VPS13A* have a status of *Tbio* status that indicates the availability of biological knowledge about the target. However, both of these proteins are classified as 'non-IDG' candidates that illustrate the difficulty to target these using current approaches.

Computational drug repositioning

Developing a new molecule or combination therapy to target a disease requires extensive funding, years of fundamental research to understand the mechanism, even before any clinical trials are initiated. However, computational drug positioning using Food and Drug Administration (FDA) approved compounds for new indications may reduce upfront costs and decrease time-to-market [41, 70]. Computational drug repositioning is a growing area of translational research with evidence for more than 200 compounds indicated across thousands of disease indications (See: RepurposeDB—Reference Database of Drug Repositioning Investigations, http://repurposedb.dudleylab.org/) [71]. Recently, Ghosh *et al.* [72] performed a randomized control trial to assess the efficacy of 650 compounds in Septic patients/C57Bl/6 mice and human endothelial cells. They identified compounds in the family of

3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor drug class (statins) as lead candidates. Mechanistically, they propose that −3-methyl-glutaryl-CoA reductase inhibitors may operate through a novel Foxo1-angiopoietin-2 mechanism to suppress *de novo* production of angiopoietin-2 to inhibit sepsis. Multiple studies have shown that inflammation plays an integral role in chronic cardiovascular diseases like coronary artery disease; see results from CANTOS (https://clinicaltrials.gov/ct2/show/NCT01327846) and Jupiter trials (https://clinicaltrials.gov/ct2/show/NCT00239681). Interestingly, it has been demonstrated that intensive statin therapy is most effective in those with high baseline levels of inflammation. This may be particularly relevant as patients die of cardiogenic shock in the setting of sepsis. Delineating the etiological routs of cardiogenic shock from bacterial toxins and life-style or genetic attributable cardiovascular disease is a challenge. Sepsis and cardiovascular diseases are potentially comorbid, given the role of chronic inflammation from endothelial dysfunction [73]. Identification of statins as a putative anti-sepsis agent is an interesting finding that needs further study. In another study, Kim *et al*. [74] used drug repositioning for identifying potential candidates for SIRS. Computational drug repositioning can also be used to identify combination of therapies and therapeutic opportunities especially for comorbid diseases [75–77]. For example, we recently reported a method to target molecular sub-network of genes shared by two diseases as plausible signature driving pathways associated with both diseases [78]. Such pathways could be targeted specifically using repurposed compounds for better outcomes.

Cell and gene therapy for sepsis

Cell therapy is typically defined as the administration of living whole cells to the patient for treatment of diseases. The use of mesenchymal stem cells as a potential therapy is being considered given the cells' immunomodulatory properties on cytokine and chemokine synthesis in sepsis. MNCs are able to reduce tissue inflammation and produce antibacterial peptides that target offending pathogens, thereby reducing morbidity and mortality. However, there are effective dose uncertainties, high costs, production challenges and regulatory landscape that must be considered [79]. Gene therapy is a set of strategies that modify the expression of an individual's genes or repair abnormal genes. This involves administering specific DNA or RNA molecules using viral or non-viral vectors (see https://www.asgct.org/education/gene-and-cell-therapy-defined and https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/default.htm). With the advent of single-cell RNA sequencing and other technologies, disease level cell profiles can help find population of cells increased or depleted in the setting of sepsis and its phenotypes. Kymriah (tisagenlecleucel) is a cell-based gene therapy chimeric antigen receptor-T cell that specifically induces an immune response against cancer cells for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia. Similarly, developing cell-specific immune response to sepsis-associated cells may help to improve prognoses [80, 81].

Immunotherapy for sepsis

Application of immune therapy is an idea that is more than three decades old [82–85]. However, the availability of modern immunotherapy strategies combined with next-generation sequencing technologies [86–89] can be applicable to a variety of conditions including cancers, infectious diseases [90], respiratory diseases, [90] and cardiovascular diseases [91]. Several therapeutics that combine the concept of immunotherapy with cell and gene therapies are in the advanced stages of clinical trials for various cancers. Immunotherapies are currently being evaluated as a candidate for various infectious diseases including viral, bacterial and fungal infections [92–98]. Some of the most promising immunotherapies currently being studied for use in sepsis attempt to reduce T cell exhaustion and apoptosis or augment immune cell proliferation and activation. Recombinant interleukin-7 blocks apoptosis while enhances lymphocytic activation and proliferation (Figure 5). Programmed cell death 1 (PD1) or PDL1-specific antibodies inhibit PD1-PDL1 interaction to reduce apoptosis and augment T cell activation by macrophages as well. Recombinant interferon-γ; (IFN$-\gamma$) and recombinant granulocyte/macrophage colony-stimulating factor (GM-CSF) primarily act on monocytes/macrophages to enhance activation of innate immunity. Both IFN$-\gamma$ and GM-CSF help increase expression of HLA-DR, enhancing antigen presenting capacity, and pro-inflammatory cytokine production.

Phage therapy to target sepsis

Phage therapy is an emerging therapeutic approach to leverage lytic bacteriophages to combat specific bacterial strains associated from infection. Phage therapy is currently being explored as a therapeutic strategy for sepsis [99–101]. An area of growing concern in the prevention of sepsis is the emergence of antimicrobial-resistant bacteria (AMR) [102]. AMR is defined as having either having a multi-drug resistance (MDR) or extensive drug resistance, formerly well-managed bacterial strains like *Mycobacterium tuberculosis* have emerged now as potentially lethal threats in cases where the bacterial load cannot be managed by traditional therapy. With the prolific use and misuse of antibiotics there is concern among the healthcare community that proper antibiotic stewardship may not be enough to prevent the increase of drug resistant bacteria involved in many sepsis cases [103]. Bacteria that have adapted to be resistant to modern forms of bacteriostatic medications are increasing in number and are beginning to present more often, so new approaches like bacteriophage therapy are emerging as a potential responses to bacteria-induced sepsis. Bacteriophages are viral bodies that have evolved to be highly specific in targeting specific bacterial strains for reproduction while typically ignoring human cells. Already MDR strains like *P. aeruginosa* have drastically low survival rates if they proliferate into extraintestinal spaces, but there is promising results that a combination of *P. aeruginosa* bacteriophage treatment and antibiotics can turn back the inflammatory response and control bacteria load to the point of recovery [104]. It should be noted that the optimal use of antibiotics is critical to ensuring the safety, efficacy and outcomes for such treatments.

Microbiome restoration using probiotics and synbiotics

Emerging evidence also suggests that gut microbiome may also play a critical role in sepsis and its acuity in the clinical setting [105–113]. For example, Bifidobacteria spp. were upregulated in controls compared to late onset sepsis samples and Escherichia spp. were upregulated in necrotizing enterocolitis and sepsis [106, 114]. Similarly, evidence for the role of microbial dysbiosis in the microbiome, pathobiome as well as microbiome restoration are emerging in sepsis. For example, a randomized symbiotic trial has shown that sepsis in rural areas of countries could be

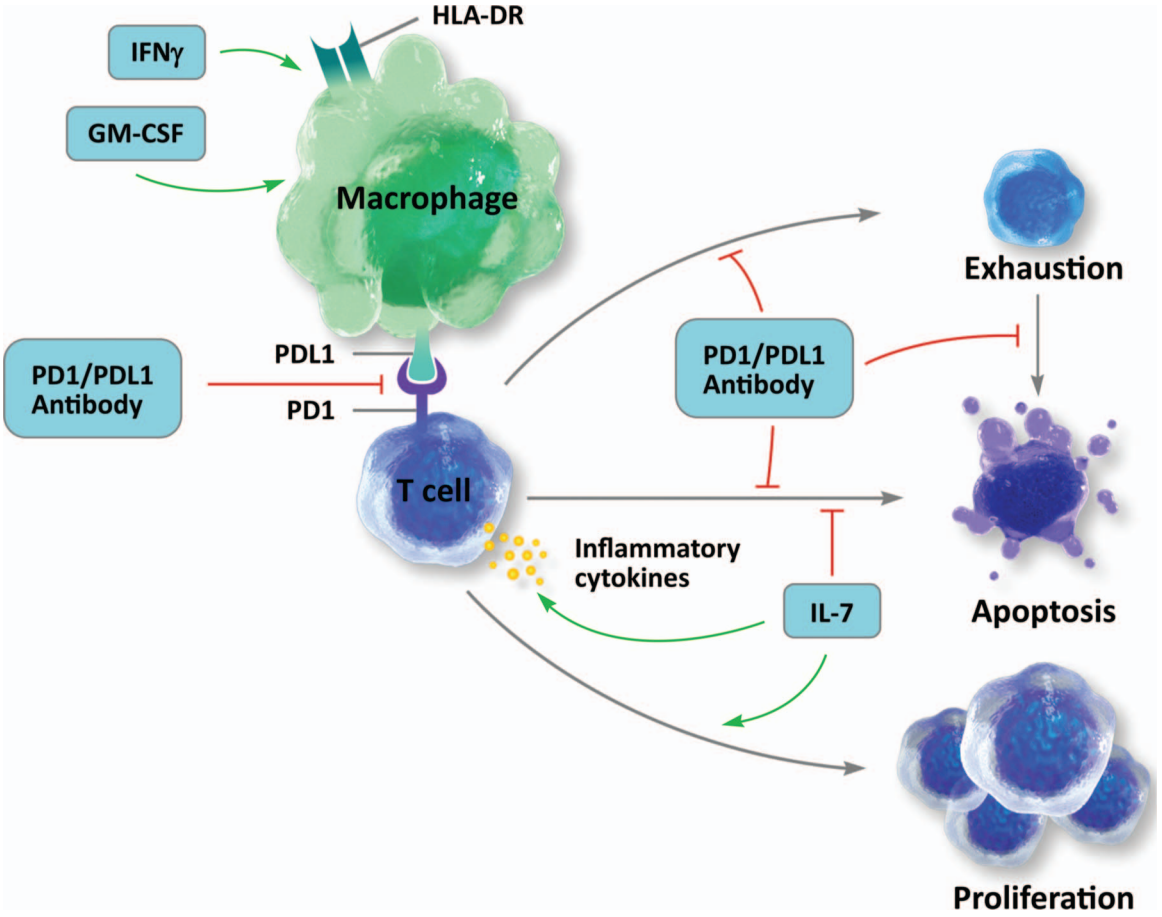

Figure 5. Emerging immunotherapy opportunities in the setting of sepsis.

prevented using a symbiotic diet (mix of probiotic and prebiotic strains [115]) containing *L. plantarum* ATCC-202195 [116]. Further studies would need to understand whether such synbiotic treatment would be beneficial for adults and patients with multiple comorbidities.

Nanobiotechnology-based theranostic approaches for sepsis

Nanotechnology and its recent advances in the medicine offers a new class of treatment, diagnostic and theranostic opportunities for sepsis [117]. For example, sialic-acid decorated nanoparticles [118] biological microelectromechanical systems [119], nanoparticles (cerium oxide [120], antioxidant nanoparticles [121], biomimetic nanoparticles [122], sialic acid-coated nanoparticles [118]) are being explored as materials for developing diagnostic and therapeutic approaches to target sepsis.

Genetic editing to target sepsis

Genetic editing is a modern approach for precise genetic engineering to edit (insert, delete or modify) genomic regions [123–125]. New methods including CRISPR and CRISPR-associated genes based systems are particularly precise in their ability to edit genomic regions with varying degree off-target effects [126, 127]. While the use of genetic editing is an active area of research, genetic editing could be used to diagnose or target the infectious agents in the context sepsis [128–132].

Prognosis of sepsis therapies

Compared to risk stratification diagnoses and treatment, sepsis prognoses may be the least studied research theme in the context of the disease. Long-term prognoses of sepsis patients are poor. Patients with no organ damage have 15–30% mortality rates, whereas patients with severe sepsis or septic shock have a mortality rate of 40–60% [133–136]. While there are several studies reporting advances in the early detection of sepsis, factors that drive successful, long-term prognoses remain elusive. As a range that involves ~20% differences, precisely subtyping sepsis and modeling care pathways may help to improve prognoses. Care pathway modeling is an emerging theme in biomedical and healthcare data science [137–139]. Briefly, care pathway modeling estimates the disease or syndromic trajectory for a given patient and how perturbations via medications or other clinical interventions could help to lead to a positive outcomes and better prognostic outlooks [132, 140, 141]. Modeling various care pathways for different age groups and patient subtypes may lead to the development of intelligent clinical decision systems. Combing various biomedical and healthcare data sources and building a national and international case repository with extensive clinical history and patient reported information may help to tackle this challenging problem [38].

Discussion

Sepsis is a complex infectious disease with diverse clinical manifestations. Viral, bacterial and fungal agents as well as

metagenomic interactions are implicated in sepsis and differential phenotypes. Although not well understood, there is an association between pneumococcal pneumonia and septic shock. In a recent study, 114 of 1041 patients with pneumonia had a septic shock upon admission [142]. However, independent risk factors could be involved such as tobacco smoking and chronic corticosteroid treatment. As well as pneumonia, bloodstream infection has a higher correlation to triggering sepsis. Septicemia, a bloodstream infection, which involves dangerous bacteria and toxins transporting through the human body, that can eventually lead to sepsis if left untreated since after all sepsis is a severe complication of septicemia. Analyzing single-modality data would only lead to the limited understanding of the pathobiology. However, leveraging the combination of biomarkers, data from EHR and combining with in-depth molecular profiling and modeling using multi-scale modeling may yield new insights. Sepsis is a syndrome with a high risk of mortality, ICU visits and hospital readmissions. Sepsis is evolving as a significant clinical, scientific and operational encounter that influences healthcare outcomes. Precise diagnoses with ample time for clinical interventions, treatment with higher response rates and progressive outcomes in sepsis remain as significant challenges. In this article, we provided an overview of emerging technologies including the role of computational medicine, novel therapeutic opportunities and application of machine intelligence methods that may help improve them. As a primary cause for mortality rates associated with hospitalization, developing informatics solutions, predictive models and personalizing risk estimates would have significant implications in quality of healthcare delivery and influence patient outcomes. However, mere data-driven methods or informatics approaches may not provide results without constant feedback from clinical pathways and patient trajectories.

Emerging role of translational bioinformatics approaches in sepsis

Translational bioinformatics approaches are collectively accelerating the discovery of therapeutic strategies for rare and common diseases. Recent progress in cardiology, oncology, immuno-oncology and autoimmune diseases was the net result of growth in computing, artificial intelligence, biomedical technologies and translational bioinformatics. However, the impact of translational bioinformatics approaches in the area of sepsis is very limited. For example, PubMed search retrieves around 700 papers for a query with '*sepsis* + *bioinformatics*' compared to 10× times publications that discuss bioinformatics approaches in the setting of cancer and cardiovascular diseases. The apparent lack of translational bioinformatics research could be attributed to various reasons; one reason could be the lack of centralized informatics resources that compile a variety of biomedical and clinical data in the setting of sepsis. Organizing the biomedical data and combining clinical data including patient trajectories, clinical history and therapeutic responses may help to build a community that could ask broad research questions to understand various molecular etiologies of sepsis and target them using individualized approaches.

Future prospects

Despite the availability of care guidelines that reliably improve outcomes, overall sepsis mortality has increased in the past decade. Most healthcare organizations are struggling with mortality rates between 19–30% for *bona fide* sepsis patients. This high morbidity and mortality adversely influence quality of healthcare delivery, revenue-cycle, and reduce patient recovery rates. The clinical implications from different sepsis cases must be considered for data analysis. Understanding root and route of sepsis incidents from heterogeneous biomedical and health care would help to find identify drivers that prevent infection. Designing translational bioinformatics resource that aid in developing predictive models, multianalyte diagnostic aids, targeted drug discovery and repositioning strategies would help to stratify and treat patients at risk and improve prognoses.

Competing Interests

KS has received consulting fees or honoraria from McKinsey & Company, Alphabet, LEK Consulting, Parthenon-EY, Philips Healthcare, OccamzRazor and Kencore Health. JTD has received consulting fees or honoraria from Janssen Pharmaceuticals, GlaxoSmithKline, AstraZeneca, and Hoffman-La Roche; is a scientific advisor to LAM Therapeutics, NuMedii, and Ayasdi; and holds equity in NuMedii, Ayasdi, and Ontomics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Key Points

- Sepsis is a life-threatening condition that affects more than 30 million people worldwide every year with high mortality rates (15–20%).
- Irrespective of advances in translational bioinformatics, sepsis remains to be an understudied theme compared to cancer and cardiovascular diseases.
- Understanding the clinical trajectory that leads to sepsis incidents from real-world data streams would help to develop diagnostics and therapeutic approaches to target sepsis and reduce its global disease burden.
- Developing predictive models using molecular data combined with clinical data would help to stratify patients at risk for improved care and design healthcare strategies that improve outcome and reduce mortality.
- Combining biomedical big data with translational bioinformatics approaches and machine intelligence could help to develop novel strategies to combat sepsis.

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