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REVIEW ARTICLE

Approaches Towards the Detection of Sepsis: A Review

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Abstract

Our understanding of sepsis and its mechanisms have never been more important than they are today. In recent years we have seen sepsis manifest from bacterial infection to a broader range of pathogens, each with its unique responses from the body. This increased interest has only been further intensified by the Covid-19 pandemic and the renewed global attention towards viral-based infections and their interactions with sepsis. From Systemic inflammatory response syndrome (SIRS) to sequential organ failure assessment score (SOFA), studies have shown that early diagnosis is key, as well as finding the root of the infection to prevent further damage caused to the patient. Prompt treatment has contributed to the overall improvement of sepsis outcomes. This review summarizes the development of the cause, diagnosis, and treatments available to date.

Key Words: *Sepsis; Covid-19; Viral-based infections; Early diagnosis; Bacterial infection*

Introduction

Sepsis has often been difficult to characterize, with the definition changing multiple times throughout history [1,2]. As of 2016 sepsis has been defined as an unregulated response to infection or when an infectious agent actively multiples in the bloodstream [3,4]. If the localized infection is left untreated it can spread throughout the body creating a cascade of events which ultimately end in organ failure and death [5]. This has become one of the principal reasons for patients being admitted to intensive care units (ICU) and often becomes the major cause of health deterioration during a prolonged stay [6,7]. It is estimated that around 11.5% of ICU patients are admitted due to sepsis, with mortality within ICU being as high as 28%, depending on the method of diagnosis [8,7]. Although the number of cases of sepsis has risen dramatically since the ’90s, the mortality rate has dropped by almost 52.8% globally (1990- 2017) [7].

Cause

Sepsis can develop from any type of infection and if left untreated can be fatal [9]. Initially, sepsis was considered to be only related to gram-negative bacteria (64%) [10] due to the release of endotoxins into the bloodstream which initiates an inflammatory response. However, more recently gram-positive bacteria [11] (47%), fungus (19%) and viruses (~1%) [12] have also been shown to lead to sepsis [10]. Of these, it has been shown that fungal has the most severe outcome, with a mortality rate of 43% in comparison to gram-positive and negative bacteria (25% and 29%, respectively) [13]. These pathogens can manifest in an array of places including the lungs (64%), abdomen (20%) [14], bloodstream (15%) [15] and renal tract (14%) [10,16].

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Pneumonia

Pneumonia is the most common cause of sepsis, particularly in the elderly who are more susceptible to it [17]. Pneumonia occurs when the infection manifests itself within the lungs, causing the air sacs to become inflamed in either one or both lungs [18]. The lungs then fill up with fluid or pus, which can lead to a range of different responses, including a cough, fever, chills, and difficulty breathing [19]. More recently, 2020 has seen the long-lasting effects of COVID-19 on the body and has become a key cause of pneumonia, [20] increasing patient's risk to sepsis [21]. Often patients were diagnosed with pneumonia according to the guidelines for the treatment of hospitalized-acquired pneumonia [22]. According to Thomas-Rüddel et al. [23] sepsis was the most frequent complication of patients with COVID-19, alongside Acute Respiratory Distress Syndrome (ARDS), heart failure and septic shock [24]. COVID-19 has also been shown to damage more than just the lungs, with patients experiencing liver damage and a depressed immune response which can aid in the development of sepsis [25]. Studies have shown that patients admitted into ICU with COVID-19 experience such severe septic shock that almost 70% required drugs to support the heart and circulatory system, [26] with sepsis being the biggest cause of death in COVID-19 cases [23]. Alongside this, the long-term effects of sepsis can often leave people more at risk of contracting more severe forms of COVID-19 and therefore be at a higher risk of death [27].

Abdomen

Infection in the abdomen is the second highest cause of sepsis. This is created from the growth of pathogenic microorganisms and their by-products [28]. This inflammatory process can either be localized *via* an abscess or can diffuse into the rest of the body [14]. The abdomen is considered as one unit regarding sepsis consisting of intra-abdominal organs found in the foregut, midgut, and hindgut [29]. Often the search for the exact cause of abdominal sepsis is difficult to determine, however, it has been repeatedly linked to an inflammatory response to bacterial or yeast peritonitis, in which a thin layer of tissue lines the inside of the abdomen and causes inflammation [30]. Unlike infection within the lungs or cardiovascular system, which is easier to diagnose and treat, surgical intervention is typically the best solution to treating abdominal sepsis and the severity of this is ultimately determined by which organs are infected [31].

Bloodstream

Often the terms sepsis and bloodstream infections are used interchangeably, however, not all bloodstream infections lead to sepsis [32]. Bloodstream infections are typically defined by a pathogenic organism found in the bloodstream that causes a disease [15]. In the case of bacterial infection, this is called bacteremia [33]. If left untreated this can result in a dysregulated immune response and can lead to sepsis as the body becomes overloaded [13] If the infection is treated early, it ultimately does not have to result in sepsis [32]. Common causes of bloodstream infections stem from untreated urinary tract infections and indwelling catheters, hence if infections spread throughout the body, they become known as bloodstream infections [32-34].

Sepsis takes place when an isolated infection spreads throughout the body. Pathogens that enter the bloodstream are detected by innate parts of the immune system found there, which initiate a response by binding to pathogens present, destroying them [35]. If the infection is too strong or the immune system too weak then this binding event can cause a cascade of events to take place in a range of systems resulting in sepsis [36].

Renal Tract

Although urinary tract infections (UTI's) account for a small percentage of sepsis cases, within infections contracted in hospitals UTI's account for around 40% of cases, [37] with mortality rates being high within certain demographics of patients [38]. Complicated UTI's usually occur when urine flow is abnormal and in patients with pre-existing conditions such as diabetes and azotaemia [39]. This can often lead to disappointing responses to therapy and a progression into urosepsis [39]. It is, therefore, key to identify the infection early and prevent it from manifesting into sepsis [39].

The Heart

The events taking place often affect a wide array of human functions [13]. Once the infection has spread throughout the body, the cardiovascular system is the first to respond, experiencing high cardiac output and low systematic vascular resistance [40]. This is caused by increased lactate levels by vasodilation which can lead to hyper-perfusion and hypoxia. Around 13% of sepsis patients experience cardiac event, increasing the risk of death by 30% [41]. Cardiac events include acute heart failure, life-threatening arrhythmia, myocardial infarction and non-ischaemic myocardial injury [42-44]. Within the microcirculatory system, there is an increase in capillary permeability which causes the vascular volume to be compromised. Obstructions of the micro-vessel lumens by plugs of white and red blood cells can also cause impaired function [45]. This, along with widespread tissue factor expression, fibrin deposition, impaired anticoagulant mechanisms lead to disseminated intravascular coagulation (DIC) in which small blood clots start to develop throughout the bloodstream, blocking small blood vessels and causing an excess of bleeding which can be associated with organ failure and death [46].

Circulatory System

In severe cases of sepsis, changes in the endothelium can lead to altered function of other organs. Lungs experience ARDS [47]. in which they become more permeable, allowing for the accumulation of protein-rich fluid to flood the alveoli and reduce lung competence [48]. Oedema and alveolar damage increase the physiological dead space within the lungs which in turn impairs gas exchange, causing hypoxemia and hypercapnia [49]. Consequently, those who experience ARDS have a 35% higher risk of dying from sepsis-related infection [50]. This combined dysfunction in both the endothelial and epithelial barriers can be seen as the initiation to widespread organ dysfunction, spreading further than just the lungs [51].

The Renal System

The renal system is also a common target in sepsis, with many patients experiencing acute kidney injury (AKI) [52]. AKI is defined by 3 tests: if the serum creatinine levels are ≥ 0.3 mg/dL if there is a 50% increase in the baseline in 7 days and if the urine output is <0.5 ml/kg/h for more than 6 h [53]. Renal hyperfusion leads to tubular necrosis, causing ischaemia-reperfusion injury, oxidative stress, and tubular apoptosis [54]. A volume overload of the central venous pressure can cause subsequent organ oedema and increase intracapsular pressure and decreased glomerular filtration [55].

The liver is one of the most important organs in the immune system response [35]. It is a regulator of inflammatory responses and a target for host response [56]. A response to proinflammatory cytokines, hepatocytes can release acute phase proteins with widespread inflammatory and anti-inflammatory effects, [56] having a pivotal role in balancing the immune response to infection, clearing out bacteria and toxins whilst ultimately causing excessive inflammatory and immunosuppression [57].

The Nervous System

A wide range of mechanisms can disrupt the nervous system during sepsis [33]. Systematic haemodynamic instability causes ischemic lesions in the brain, overcoming the central nervous systems perfusion regulations [58]. The blood-brain barrier is disrupted as inflammatory responses contribute to microcirculatory failure, allowing inflammatory mediators and neurotoxins into the brain tissue [59]. In addition, increased nitric oxide diffusion into the brain then causes oxidative stress which leads to neuronal dysfunction and apoptosis [60]. These disruptions on the brain cause a wide range of responses including impaired concentration, seizures, and comas [59].

Cellular and Molecular Level

On a cellular level, a series of events eventually leads to something known as a ‘cytokine storm’ [61]. Initially, citizen cells, which are innate immune cells, can activate trooper cells such as neutrophils, dendritic cells, and platelets [61]. These cells have pathogen recognition receptors that respond to Pathogen-Associated Molecular Patterns (PAMPS) on bacterial cell walls and Damage-Associated

Molecular Patterns (DAMPS) produced from the presence of bacterial cells which leads to the expression of genes involved in adaptive immunity and inflammation [62]. These events eventually lead to a 'cytokine storm' [63]. As well as this, Migration Inhibitory Factor (MIF) production is stimulated by the production of chemicals released by bacteria [64]. Once activated, they, in turn, activate macrophages and T cells, initiating the production of pro-inflammatory cytokines [61]. A cytokine storm is when multiple inflammatory cytokines are released, creating a severe and persistent inflammatory response [65]. These cytokines can assemble into molecular complexes termed inflammasomes which in turn can trigger the production of potent cytokines such as IL-1B and IL-18 which can cause pyroptosis, in which cells swell and their membranes become porous, releasing pro-inflammatory cytokines into the extracellular space [61,66]. Pattern recognition receptors in particular Toll-Like Receptors (TLR) can induce both pro and anti-inflammatory responses [67]. For example, CD14 receptors recognize TLR-4 on the surface of bacterial cells, creating a pro-inflammatory response [68]. This pro-inflammatory response has been shown to affect both the body's immune system and coagulation system as well as the autonomic nervous system [69]. When the inflammatory cytokines exceed a certain threshold, this can cause systematic injury, in which Reactive Oxygen Species (ROS) such as hydroxyl radicals and nitric oxide cause damage to cellular proteins, lipids and DNA [70]. This in turn can also cause the death of mitochondrial cells, causing a reduction of energy expenditure as ATP cells go into hibernation, which is consistent with retained oxygen levels in sepsis [38]. This reduced performance in mitochondria and retained oxygen level can exacerbate organ failure due to reduction of cell performance [59].

Demographics of Sepsis

With the definition of sepsis becoming more established the number of cases has risen dramatically from the 1990s [71]. In 2015 alone the number of identified cases increased by around 41%, with the year 2016-2017 rising a further to 38% [62]. Although shocking, this increase may well be simply because there is a greater understanding/awareness of sepsis [71]. Although the number of cases of sepsis has increased dramatically, the mortality rate in-hospitals has decreased from 20% to 15% in the UK [62]. Studies conducted determined that low-income countries are likely to experience severe sepsis due to illnesses like malaria and dengue fever as they are more prevalent [72,73]. With an underdeveloped immune system, neonates are at a much higher risk of developing sepsis then older children, with those that are premature and those from low-income countries being at a higher risk [74]. Around 61% of neonatal sepsis is caused by respiratory infections, followed by meningitis and bacterial infections [75]. In young children, the most common causes of sepsis are typically due to the bloodstream and respiratory infections; 67.8 and 57.5% respectively [13].

As well as the very young, there is a sharp increase in older patients experiencing sepsis when exceeding 65 years of age [76]. Common causes of sepsis in older patients include respiratory tract infections (48%) and UTIs (24%) [76]. Older patients are typically more likely to get sepsis due to pre-existing chronic conditions rather than age itself, such as obesity, diabetes and cancer which are more crucial in patients of advanced years [76]. A common symptom in elderly patients is delirium, which can often be missed in emergency departments leading to a decline in cognitive function and untreated infection [77]. Due to the long-term effects of sepsis, older patients are more likely to see lasting effects of an infection, with around 43% of >65-year-old patients dying after at least two years of experiencing a case of sepsis [78].

Immunocompromised is when a patient has an impaired immune system which can often cause it to become suppressed [79]. Individuals with immunosuppression have been linked to an increase in the number of sepsis cases over the years which often makes it harder to treat [80]. Examples of immunosuppression include chronic conditions such as HIV/AIDS, [81] cirrhosis, [82] asplenia [18] and autoimmune diseases [83]. Patients experiencing a compromised immune system are sometimes unable to defend against infection which allows it to spread, which, if left untreated can cause the body to go into shock and ultimately death [79]. A study done by Tolsma et al. showed that of patients admitted to ICU with sepsis, 31% had underlying immunocompromised issues, with a mortality rate higher than that of similar patients [84].

One major example of high-risk immunosuppressed patients are those undergoing cancer therapies [85]. This is typically caused by both a combination of cancer itself and the treatments for it [85]. Cancer patients who experience sepsis have a 52% higher mortality rate and are likely to stay in hospital for three times longer than the patient who is not experiencing cancer [86]. Solid tumours accounted for the highest mortality in cancer patients experiencing sepsis (95%), compared to those who did not [87]. The main reasons for cancer patients being at a higher risk of sepsis are due to several factors. Firstly, frequent hospital visits for a patient with cancer is far higher than non-cancer patients, meaning the chance of contracting a hospital-acquired infection is higher [88]. In addition, depending on the type of cancer experienced the likelihood of frequent surgeries, punctured skin and catheters can lead to an increased risk of an infection leading to sepsis [89]. Cancer therapies such as chemotherapy cause a depressed immune system and thus leave it exposed to a host of opportunistic infections [86,55]. The effect of sepsis on the body is diverse, and can cause long lasting consequences, as seen in (Figure 1) [13].

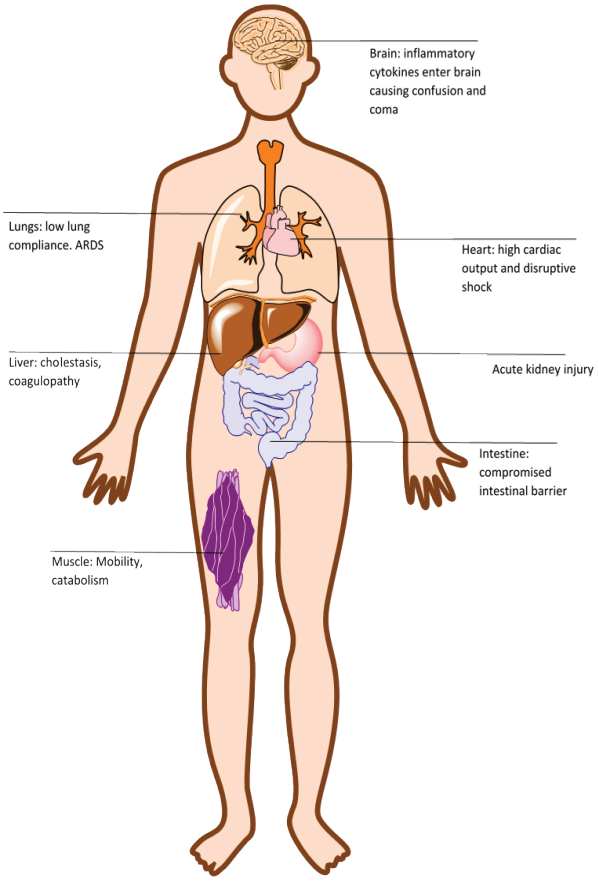

Figure 1) *Diagram of the body and subsequent responses to infection leading to sepsis. Adapted from Gotts et al. [13].*

Diagnosis

Typically, patient's experience fever, coughing, phlegm, shortness of breath, sweating, shaking chills, headaches, muscle pain, fatigue and chest pain whilst breathing [90]. All these symptoms are also present in other illnesses, hence why sepsis is difficult to initially detect [71]. Multiple methods have been used to detect sepsis, including systematic inflammatory response syndrome (SIRS) [71] and sequential organ failure assessment (SOFA) [91] however, both methods lacked accuracy [71]. In the early 1990's the detection method known as (SIRS) was developed [92]. This was a point-based system where if patients met two or more of the criteria this would then fulfil the definition of SIRS. However, in 2001 SIRS was reviewed and additional criteria added [93]. Although SIRS gave clinicians a way of defining sepsis, it also made diagnosis less specific and overly sensitive [2]. In 2006, the UK sepsis trust developed the Sepsis Six, a tool to aid health care professionals in easy diagnosis of patients. These techniques saw a 50% reduction in mortality related to sepsis in the UK and aided in a better understanding of sepsis worldwide [94]. In 2016 the Society of Critical Care Medicine and the European Society of Intensive Care (SCCM/ESICM, respectively) evaluated SIRS and compared it with more up-to-date methods and eventually replaced SIRS with SOFA, which was shown to have more superior criteria than that of SIRS and was much easier to calculate [71]. The scoring system for SOFA can be seen in (Table 1) and (Figure 2).

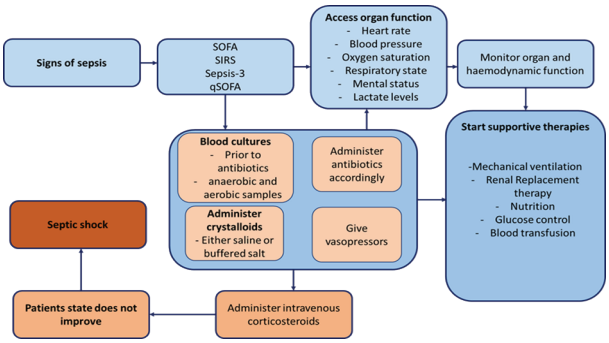

Figure 2) *Identification and treatment of sepsis. If treatment is unsuccessful or if the infection is not identified quickly enough, then patients can go into septic shock. Adapted from Thompson et al. [136].*

Although the SOFA is more accurate than SIRS in identification, it is much more complex and is often difficult to use in low-income countries were

TABLE 1

SOFA scoring system [13].

Organ system	0	1	2	3	4
Respiratory, PO_2/FiO_2, mmHg (kPa)	≥ 400	<400	<300	<200	<100
Nervous (Glasgow coma scale)	15	13-14	10-12	6-9	<6
Cardiovascular	MAP ≥ 70 mm/Hg	MAP<70 mm/Hg	Dopamine ≤ 5 µg/kg/min	Dopamine>5 µg/kg/min	Dopamine>15 µg/kg/min
Liver (Bilirubin mg/dL [µmol/L])	<1.2 [<20]	1.2-1.9 [20-32]	2.0-5.9 [33-101]	6.0-11.9 [102-204]	12.0 [204]
Coagulation (platelets x 10^3/µl)	≥ 150	<150	<100	<50	<20
Kidneys (creatinine mg/dL) [µmol/L])	<1.2 [<110]	1.2-1.9 [110-170]	2.0-3.4 [171-299]	3.5-4.9 [300-440]	>5.0 [>440]

acquiring the equipment necessary for these tests is expensive [95]. Because of this and the potential for excessive time to diagnose SCCM/ESICM created a simpler method of diagnosis, called quick SOFA (qSOFA) [91]. This is a modified version of SOFA, only having three criteria, with one point rather than a grading system for each test [91]. This means that a qSOFA score of ≥ 2 indicates the presence of sepsis [96]. Although an improvement from SIRS, both SOFA and qSOFA require organ dysfunction to take place, to get an accurate result [71]. At this point, however, it is often too late for patients and permanent damage can take place [97]. As well as this, some key signals of the presence of sepsis are ignored [91]. These include things such as lactate levels, which are a common identification of the presence of sepsis [91]. When comparing SOFA and qSOFA it is clear how simplistic qSOFA is, as seen in (Table 2).

TABLE 2

Table of qSOFA score.

Assessment	qSOFA Score
Low blood pressure (SBP ≤ 100 mmHg)	1
High respiratory rate (≥ 22 breaths/min)	1
Altered mentation (GCS ≤ 14)	1

Once either SOFA or qSOFA has been performed the experiments can be done to move forward and fully evaluate what is the cause of sepsis occurring [97]. Blood cultures are the gold standard for determining if a pathogen is present within the body [9]. However, blood cultures can take several days to determine what pathogen is present within the body, at which point the patient's chance of mortality will increase, with the death rate increasing to 32% after 3 days [98]. Other methods that diagnosticians have found useful include the use of biomarkers such as procalcitonin (PTC). This biomarker, unlike others such as C-reactive protein (CRP), have been elevated in patients experiencing bacterial sepsis, showing a higher accuracy then CRP, a better sensitivity, and more specificity [99]. Although this is the case, both CRP and PTC have been shown in higher levels in patients experiencing sepsis and septic shock when compared to patients experiencing SIRS. These have therefore been a crucial aid in diagnostics, with several tests for PTC and CRP being available in both Europe and US for several years- with the National Institute for Health and Care Excellence

(NICE) updating its guidelines in 2017 to help with early assessment, including early diagnosis with Biomarkers such as PCT and CRP [100].

Gram-Negative Sepsis

Gram-negative bacteria account for over half of sepsis cases, globally. Gram-negative bacteria are defined by their thinner layer of peptidoglycan and outer membranes made of lipopolysaccharide, preventing them from staining as readily as gram-positive bacteria [101,102], Although this staining method is used to identify differences between gram-negative and gram-positive bacteria, not all bacteria stain, accordingly, hence making this method of identification far from comprehensive [101].

Gram-negative bacteria have a much more complicated cell structure, containing multiple membrane layers, lipopolysaccharides and porin, amongst other proteins [103]. The outer membrane can hold the cell structure and maintain cell shape due to the reduced amount of peptidoglycan found in the cell wall [103]. Differences in the structure of these pathogens cell membranes can be seen in (Figure 3).

preventing unwanted organelles from entering [105]. This thick peptidoglycan layer is what retains crystal violet dye during staining methods and helps prevents damage to the cell [102].

Fungal Sepsis

Fungal infections have become an increasing risk to critically ill patients which can often lead to sepsis and consequently higher risks of mortality [106]. With fungal sepsis equating to around 19% of all sepsis cases, increasing the study of these pathogens is also important [107]. The link between fungal sepsis and mortality is much higher (40-60%) [108,109] than bacterial sepsis (30%) [110] and thus can increase extensive health care costs [111]. Often the reason for high mortality in sepsis-related fungal infections is due to how these infections present within the body, which is often disregarded during sepsis detection [112,113]. Diagnosis can also be difficult, with low yielding blood cultures, slow susceptibility testing, and sometimes the need for deep tissue sampling [114]. For this reason, early diagnosis is key, to help reduce the risk of the spread of the infection as well as reduce the number of deaths [34]. Although similar, fungal sepsis

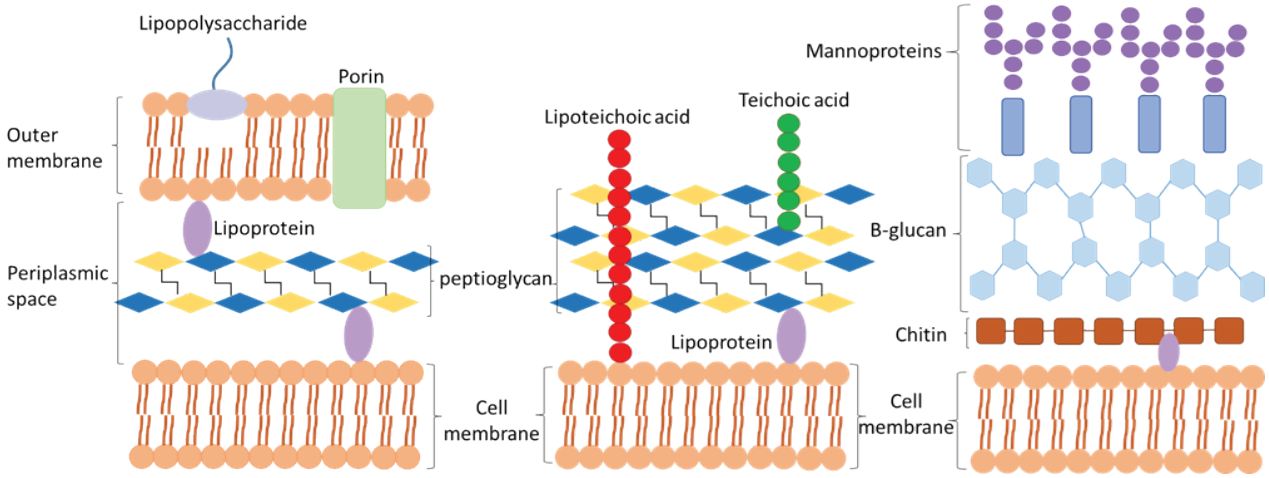

Figure 3) *Components of (a) gram-negative bacteria, (b) gram-positive bacteria and (c) fungal cells.*

Gram-Positive Bacteria and Sepsis

Gram-positive bacteria are becoming an increasing cause of sepsis and often result in a higher rate of mortality in the UK and US [104]. These cells contrast gram-negative bacteria by having a much simpler structure, containing a thick peptidoglycan layer to maintain the structure of the cells, and

follows different mechanisms then that of bacterial or viral, following different transduction pathways [69]. As well as this, fungi present carbohydrates on their surface instead of bacterial or viral cell-surface markers, causing a more diverse range of cell-surface receptors and ultimately leading to a different cytokine profile to that of bacteria and viruses [69]. Fungi affect approximately 12% of

health-care-associated infections, with the most common culprits being Candida (70-90%) and Aspergillus (10-20%) [114]. Candida is the most common fungal infection accounts for around 8-10% of bloodstream infections in the US and 2-3% in Europe [115]. When Septic shock is accompanied by Candidaemia this can cause the mortality rates to be as much as >60% [116]. These types of infection typically arise from either gut colonization or transmigration of pathogens through the mucosal barrier with other methods of entering the body including contaminated foreign materials, via the use of intravenous catheter bags, [117] which account for up to 40% of cases of Candidaemia cases [118]. Other entrances for foreign bodies include patients experiencing organ transplants and the use of invasive monitoring devices [114]. Blood cultures reveal that Candida accounts for 12.6% of colonies either by itself or in presence of other bacterial infections [119]. Often invasive Candida can frequently occur due to a compromised immune system already lead by a bacterial infection [120]. Although evidence has shown that fungal infections can cause sepsis and have high mortality rates, classical diagnostic methods fail to reach the criteria required to prevent sepsis [112]. Often blood cultures, the gold standard for determining which pathogens are present in a sample are insensitive to fungal samples and can often take longer than 72 h to obtain a result [121].

Viral Sepsis

Although fungal and bacterial sepsis are the most predominant causes of sepsis, viral infections can also lead to sepsis [13]. Patients with evidence of sepsis, but no link to fungal or bacteria present should be reviewed with viral sepsis in mind [122]. Although viruses only contribute to a small number of sepsis cases, it is argued that this is an underestimate of the viral sepsis cases [122]. As described by the Southeast Asia Infectious Disease Clinical Research Network, viral sepsis cases accounted for 76% and 33% of cases in paediatric and adults, respectively [123]. When using the sepsis-2 [71] definition in tropical middle-income countries, it showed that other methods of diagnosis can often underdiagnose viral sepsis [123]. Viral infections that commonly cause sepsis included the Herpes Simplex Virus (HSV), [124] Influenza Virus [125] and Dengue Virus [123] the prevalence of these infections is dependent on the demographic [122]. These viral infections are often present alongside other pathogens that cause sepsis and can complicate the diagnosis [126]. Something notable in the development of viral sepsis is that after the initial inflammatory response from the host, there is an extended period in which the immune system is suppressed [127]. This can be characterized by both the innate and adaptive immunity having decreased function, which often leads to the increased infection from secondary pathogens [126].

To add to the difficulties, viral cells contrast other pathogens dramatically [128]. These are the smallest of all microbes and are made up of DNA/RNA surrounded by a protective coat called a capsid that is formed from proteins. These can additionally be surrounded by a secondary structure known as an envelope, which is made from a mixture of the host's cell membrane and viral glycoproteins [129]. These glycoproteins can bind onto receptors on the hosts' cell membrane and allow it to be incorporated [128] into the cell, using the cells binding mechanisms to create more of itself, eventually causing the cell to rupture and release new viral cells [128].

Causes

The most common isolated microorganisms that can trigger sepsis are Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa and Candida spp related organisms [130,106,131]. Of these, ram-negative accounts for around 62% of cases, with gram-positive bacteria causing around 47 % of cases [10]. Initially, sepsis was believed to be a response to gram-negative bacteria [40] due to the release of endotoxins found on their surface [108,132,104,133]. However as more research was conducted it was shown that a much larger range of pathogens could cause sepsis, including gram-positive bacteria, [132,104] fungus (19%) some viruses and an increase in multi-resistant bacteria. Although gram-negative bacteria and gram-positive bacteria are the largest causes of sepsis cases in the world, fungal sepsis has a much higher mortality rate (43% mortality, compared to

the 25- 29% in gram-negative and gram-positive infections) [119].

Treatments

Sepsis can be difficult to treat due to many factors [132]. All over the world, there are various ways of treating sepsis in the early stages; in the UK alone clinicians use the method known as National Early Warning Score, which analyses the degree of illness a patient is experiencing and how far clinicians should intervene [134]. In 2018, the '1-h bundle' was developed [135]. This was a list of treatments to be conducted on patients within one hour of diagnosis that had been shown to reduce the risk of mortality which included the use of intravenous fluids, measuring lactate levels, vasopressors, blood cultures ad broad-spectrum antibiotics [135,35]. Once these had been completed, it was critical to find the source of the infection and treat it [97]. Sources like abscesses, [89] ischaemic bowels, [136] gastrointestinal perforation [137] infections of the binary or urinary system, [117] and or infected implanted devices must be treated immediately [138]. The need for intravenous fluids is due to hypovolaemia, [136] in which there is a decrease in intravascular volume because of increased vascular permeability [28]. Crystalloids or colloids are often given before vasopressors, typically within 3 h of identifying that there may be sepsis present, with adult patients being treated with 2-3 L of the latter [139]. To help with vasodilation of both the venous capillary vessels and arterial resistance vasopressors are often used [26]. The mortality rate is vastly reduced if crystalloids and vasopressors are used within the first 6 h of detection [140]. If patients are experiencing a severe case of refractory circulatory failure, then they can be treated with low doses of corticosteroids to modulate both the immune and cardiovascular systems [141]. Anything above 200 mg a day has been shown to increase mortality, due to the development of superinfections [141,142]. When corticosteroids, such as hydrocortisone, are used there has been a link to the reduced need for ventilation systems, reduced frequency of blood transfusions and an earlier discharge from intensive care [143]. Although shown to have a link between the use of corticosteroids and reduced time in intensive care, they are used with caution in lower concentrations with the addition of other treatments due to the risk of superinfection [136]. Acute injury accounts for over half of septic shock patients, with those experiencing it in ICU having a higher chance of mortality [136]. Common indicators of acute kidney injury include uraemia, fluid overload and hyperkalaemia [144]. Renal replacement therapy has become one solution for this, preventing the need for early use of vasopressors and modulating patient's temperature [144]. The use of renal replacement can also limit organ damage and fluid overload, allowing for the removal of inflammatory mediators that are responsible for onset sepsis [144]. This has been used to help reduce the need for vasopressors and lower the temperature of patients, as well as help limit organ injury [144]. Finally, the use of ventilation system >16 h with a tidal volume of 6 mL/kg has also been shown to reduce the effects of acute ARDS and reduce mortality [145].

Sepsis can lead to permanent damage to the body, and so reliable and early diagnosis of sepsis is key [136]. With SOFA leading to around 30% of patients being misdiagnosed, [146] the administration of futile antibiotics leading to extra costs on hospitals and a survival rate that decreased by the day, a quick and affordable method of detecting sepsis is required [147].

Conclusion

Rapid diagnosis and treatment are key to the survival rate of patients experiencing sepsis. The Covid-19 pandemic has highlighted the importance of development and innovation in the diagnostic field. As such, due to the close relationship between Covid-19 and sepsis, it is important that the scientific sector continues to develop its understanding of sepsis, especially as a bi-product of these infections. Although the definition has changed dramatically over the past three decades, from SIRS to more recently SOFA, diagnosis can still lead to sepsis cases being misdiagnosed [71]. This is commonly seen in viral sepsis cases that do not present in the same way as bacterial or fungal sepsis cases. However, treatment for all types of sepsis is similar: antibiotics, intravenous fluids, vasopressors and controlling the source of infection. As medicines become more advanced, so does our understanding

of sepsis and how it affects patients in both the long and short term, new and interesting detection methods are surely upon the horizon. The need for better detection in the form of a user-friendly point of care device is of paramount importance.

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Conflicts of Interest

The authors declare no conflict of interest.

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