# Increasing awareness of sepsis

**Blajic, Nikola Daniel Leo Albert**

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Nikola Blajic

# Increasing awareness of sepsis: World Sepsis Day

GRADUATION PAPER

Zagreb, 2014

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Nikola Blajic

# Increasing awareness of sepsis: World Sepsis Day

GRADUATION PAPER

Zagreb, 2014

This graduate thesis was written at the Intensive Care Unit in the Department of Medicine, Sisters of Mercy University Hospital Zagreb, mentored by Assistant Professor Vesna Degoricija, MD, PhD, and was submitted for evaluation in the academic year 2013/2014.

## List of Abbreviations

| | |
|---|---|
| RRR | relative risk reduction |
| ARR | absolute risk reduction |
| ACCP | American College Of Chest Physicians |
| SCCM | Society of Critical Care Medicine |
| ESCIM | European Society of Intensive Care Medicine |
| CDC | Centers for Disease Control |
| ICU | intensive care unit |
| MODS | multiple organ dysfunction syndrome |
| NHS | National Health Services |
| MRSA | Methicillin resistant staphylococcus aureus |
| CRP | C-reactive protein |
| VAP | ventilator associated pneumonia |
| SIRS | systemic inflammatory response syndrome |
| WHO | World health organisation |
| GBDR | Global Burden Disease Report |
| TNFα | tumour necrosis factor alfa |
| TLR | toll like receptor |
| NK | natural killer |
| PRR | pseudo response regulator |
| PMN | polymorphonuclear |
| PAMP | pathology associated microorganism |
| NOD | nucleotide-oligomerisation domain |
| NF | nuclear factor |
| ROS | reactive oxygen species |

## Table of Contents

## Summary:

Title: Increasing the awareness of sepsis
Name: Nikola Blajic

Sepsis is a potentially life-threatening systemic inflammatory response in the presence of infection, most commonly due to bacterial infection. It occurs predominantly among vulnerable patients, such as elderly, immunocompromised or patients with multiple comorbidities. Pulmonary, gastrointestinal, genitourinary, and primary bloodstream infections account for the majority of infectious sources in septic patients. The term „systemic inflammatory response" (SIRS) is used in cases of an evident systemic response in the absence of infection. Severe sepsis is sepsis with dysfunction of a least one organ, and septic shock is defined as severe sepsis with hypotension. With rising hospitalization rates sepsis clearly became a problem and has up to this time been underestimated by the global health community. A sepsis campaign was founded by the non-profit organization Global Sepsis Alliance to increase public and professional awareness of sepsis. A higher incidence is particularly due to more resistant bacteria, demographic shifting and more surgical procedures amongst others. On the 2nd October 2002 in Barcelona, intensive care professionals from around the globe joined to reduce the number of deaths from sepsis. Since then unfortunately the Global Burden of Disease Report (GBDR) and the WHO website still only list "maternal sepsis" and "sepsis in new-borns", despite the effort of the surviving sepsis campaign. This may partly explain why most non-professionals, journalists and politicians do not know the term "sepsis". Successful early diagnosis and treatment remains difficult and is one of the key features of reducing sepsis incidence. In the pathogenesis of sepsis a central mediator does not seem to exist, although TNFα has been commonly proposed for this role. Diagnosing sepsis includes two or more of these conditions: temperature > 38 ° C or < 36 °, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or PaCO2 < 32 torr (< 4.3 kPa), and WBC > 12 000 cells/mm3 or < 10% immature forms. Complications of sepsis include end-organ dysfunctions also called multiple organ dysfunction syndrome (MODS). The treatment of sepsis requires immediate intravenous antibiotics. The initial empiric anti-infective therapy should include one or two drugs against all possible pathogens, most commonly gram positive bacteria.


Keywords: sepsis, increasing awareness, infection, epidemiology, treatment

## Increasing awareness of sepsis : World Sepsis Day

Apart from the daily hospital environment, lately sepsis came to people's attention as it was reported in the news. In January 2013, a young boy from Queens died because his sepsis was detected too late. As a consequence, and being the first politician to introduce this, New York Governor Andrew Cuomo announced that hospitals in his state would be required to adopt specific guidelines.

Sepsis occurs when our body exceeds its normal response to an infection by damaging its own tissues and organs[1,2]. It can lead to shock, multiple organ failure, and death, especially if it is not recognized early and treated immediately. As early as 1972 Lewis Thomas said that our arsenals for fighting off bacteria are so powerful, and involve so many different mechanisms, that we are in more danger from them than from the invaders.

The previous failure of new treatments for severe sepsis and septic shock were related to lack accurate diagnoses. Physicians, epidemiologists and microbiologists used different definitions and terminology for this disease. To capture of valid epidemiological data, it is important to have standardized terms. In 1992 sepsis was defined in by the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM)[3] as condition in patients with infections that have at least two of four criteria of the so-called systemic inflammatory response syndrome (SIRS). If this response is related at least to one organ dysfunction it is defined as severe sepsis. The concept of septic shock is limited to patients who despite adequate treatment still present with circulatory failure. In 2001 the International Sepsis Definitions Conference adjusted the concept of SIRS and defined a broader concept of sepsis, and again in 2012 by the SCCM and ESICM. They expanded the list of signs and symptoms of sepsis with acronym PIRO. In PIRO[4], P stands for the predisposition, indicating pre-existing comorbid conditions or chronic conditions which affect the patient's prognosis. I represents insult or infection, which suggest the clinical presence of microorganisms and a high index of suspicion. R represents the response to the infectious agent, such as hypotension or hypoxemia and including the development of SIRS. The last letter O stands for organ dysfunction ranging from acute respiratory distress syndrome (ARDS) to acute kidney failure as well as the failure of the coagulation system[4]. PIRO was introduced as a tool for risk assessment and prognosis, to

increase inclusion of sepsis in clinical trials, and to improve the outcome of therapeutic interventions [3]. However, these new definitions for SIRS, sepsis, severe sepsis and septic shock differ considerably from the microbiologically oriented definitions for epidemiological purposes by the Centres for Disease Control (CDC) in the USA, Europe and the International Classification of Diseases (ICD-10).

Yet, severe sepsis accounts for 20% of all admissions to intensive care units (ICUs) and is the leading cause of death in non-cardiac ICUs [5,6]. In the US more than 500 patients die of severe sepsis daily [5]. Nevertheless sepsis is more common if the patient is very young or very old, has a compromised immune system, wounds or injuries or has invasive devices such as intravenous catheters or breathing tubes. The World Sepsis Campaign was founded to target the reduction of mortality rates of sepsis by increasing its awareness in the public and in healthcare professionals. What the campaign is trying to promote are two vital elements that predicate the evolution of this problem: first, poverty and severe restrictions on basic healthcare and survival needs and secondly endemic diseases that predicate the huge prevalence of the problems of sepsis. The campaign is advertising pocket cards for healthcare workers and laypeople which are available through their website or social media such as Facebook. They are currently being supported in 2239 hospitals / healthcare services or departments [7].

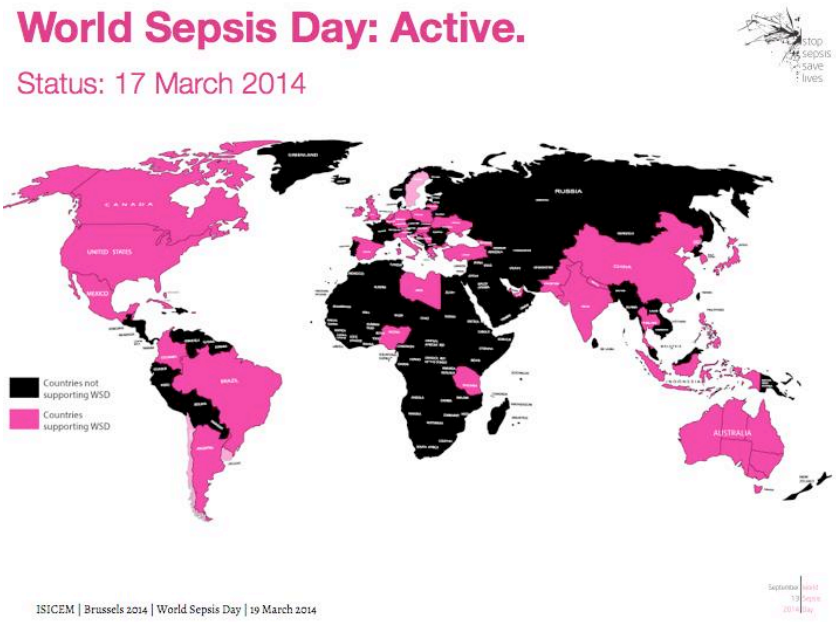



Figure 1: World Sepsis Day supporters by countries according to SSC 2014 [7]

The idea for the campaign was based on the previous success of the "Milan Declaration" made at a meeting of the European Association for the Study of Obesity, which helped raise awareness of

the problems of obesity. A similar success is hoped for Surviving Sepsis, which is a collaborative project by three major intensive/critical care organizations: the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM), and the International Sepsis Forum (ISF). As previously there weren't any guidelines for treating sepsis, the campaign revealed their initial guidelines in 2004 and an updated version was published in 2008. The revised guidelines from 2012 contain two bundles, a resuscitation bundle for the first 3 hours and a management bundle for the following 6 hours. Apart from the fact that mortality rates from sepsis increase for every hour that antibiotic treatment is delayed (see Figure 2), there is also the problem that antibiotics are losing their effectiveness because too many patients who don't need them are getting them, or are being given the wrong ones.

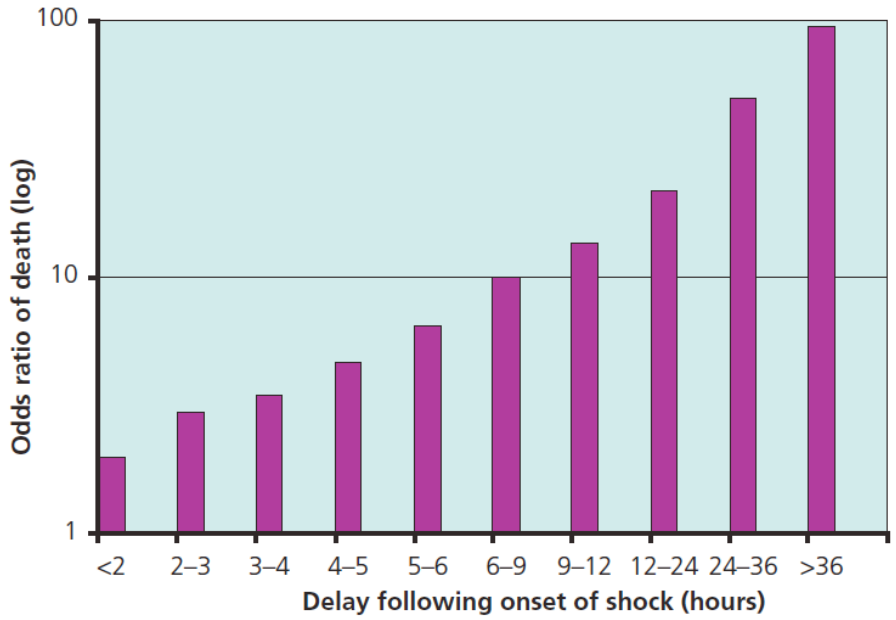



Figure 2: Mortality increases with delay in antibiotic therapy according to Kumar *et. al.* 2006 [8]

The documented incidence of sepsis worldwide is 1.8 million cases each year, but this number is confounded by a low diagnostic rate and difficulties in tracking sepsis in many countries [9]. For the inpatient care of septicaemia or sepsis in 2008, an estimated $14.6 billion was spent on hospitalizations for this condition, and from 1997 through 2008, the inflation-adjusted aggregate costs for treating patients hospitalized for this condition increased on average annually by 11.9%[10]. Although treatment costs increase, septicaemia and sepsis continue to have fatal outcomes. In addition, those who survive severe sepsis are more likely to have long-lasting organ

damage, cognitive impairment, or physical disability. The main challenge for this campaign is the difficulty in diagnosis. Because of lack of training, intensive-care physician often miss the diagnosis or diagnose it too late. This is especially problematic, given that early treatment is associated with greater success [11]. However, the incidence of sepsis is increasing due to medical progress, which is associated with an increase of invasive, diagnostic and therapeutic procedures. In addition there are more elderly patients with the need for intensive therapy. As people age, the effectiveness of their immune system begins to decrease, and it becomes much more difficult to fight off infections. Moreover, many elderly patients have chronic conditions, such as diabetes, that further impairs their immune systems.

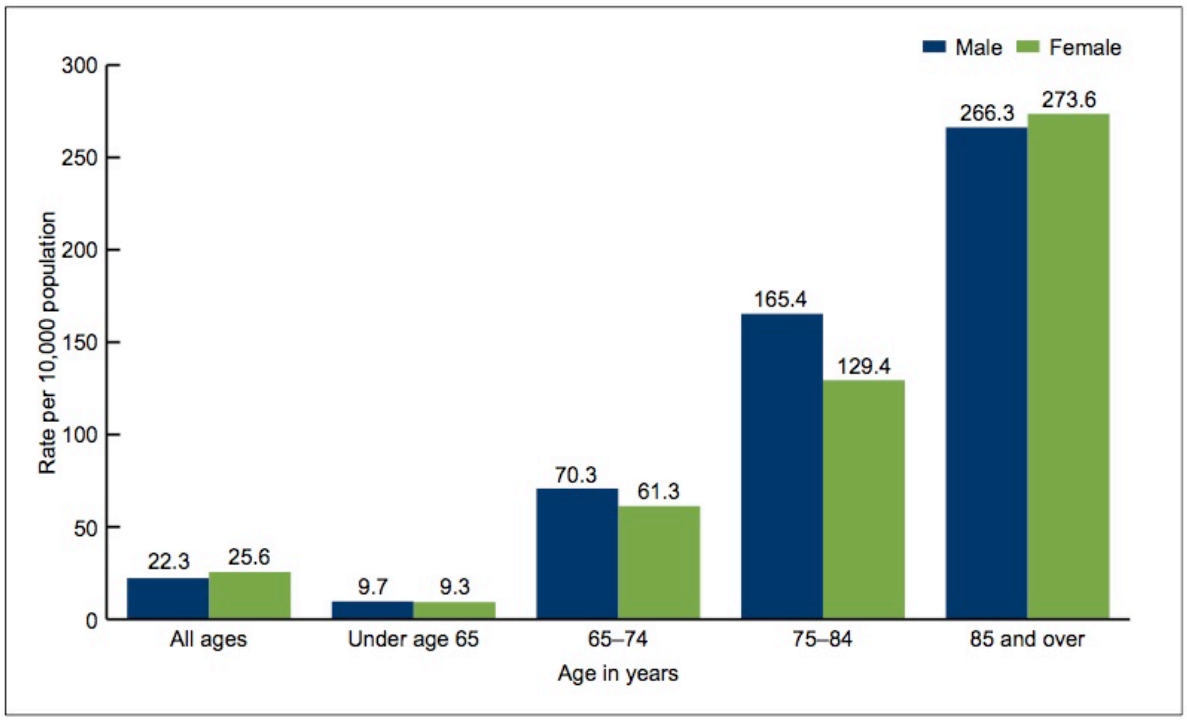



**Figure 3 : rates of hospitalization for septicaemia and sepsis, by sex and age, 2008, According to : CDC/NHCS , National Hospital Discharge survey, 2008** [7]

The study by Hall *et al*. on inpatient care for septicaemia and sepsis demonstrated that hospitalization rates for those patients aged 85 and over (271.2 per 10,000 population) were about 30 times the rate for those under age 65, and were more than four times higher than the rate of 65.7 per 10,000 for the 65–74 age group [10]. Furthermore the incidence of sepsis is high in premature babies and neonates who have underdeveloped immune systems, making it for them

problematic to fight off infections. Infants born before 37 weeks of gestation and those born with meconium staining are at high risk for developing sepsis. Mortality for septic infants is up to 50% [12]. Another risk group are obese patients, who are often less ambulatory and are bedridden so that they develop bedsores, which are perfect locations for infection development. Major trauma and burns also put patients at increased risk for infections by destroying the body's natural protective barrier. However, sepsis may occur in an otherwise healthy person and can occur very quickly.

Further reasons for the growing sepsis rates might be immunosuppressive drugs, chemotherapy, organ transplantation, and increasing microbial resistance to antibiotics. The European Antimicrobial Resistance Surveillance Network (EARS-Net) reports that MRSA remains a public health priority as the percentage is still above 25% in seven of the 30 reporting countries [13]. Particularly there are high percentages and increasing trends of antimicrobial resistance in gram-negative bacteria in Europe described in this report, which illustrates the continuous loss of effective antimicrobial therapy against these microbes and underlines the need for extensive strategies targeting all health care sectors. The CDC report from 2013 estimates that in the US more than two million people are affected every year with antibiotic-resistant infections, with at least 23,000 dying as a result. In fact, we are in an emerging crisis of antibiotic resistance for microbial pathogens throughout the world. Antibiotic resistance on epidemic scale has been described in numerous pathogens by CDC and EARS.

The initial goal of the sepsis campaign was to reduce sepsis rates by 25% within 4 years. It took them in total approximately 8 years to reduce it by 20 %. This represents 20 % of relative risk reduction [14]. According to the prospective cohort study on the outcome of the SSC in ICU by Levy, M.M., *et al.,* unadjusted hospital mortality rates decreased from 37.0% in the first quarter in the campaign to 30.8% by 2 years (P = 0.001).

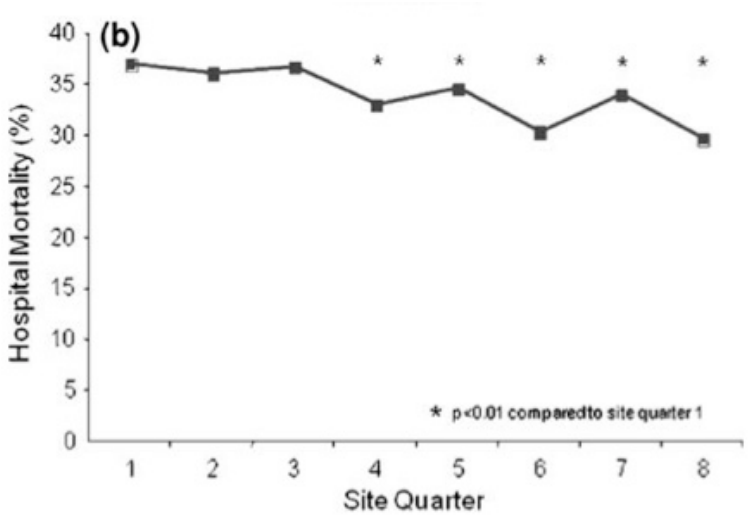



Figure 4: change in hospital mortality over time according to Levy, M.M., *et al.* [14]

On average, unadjusted mortality rates decreased by 0.91% for each quarter in the campaign [15] (see Figure 4). So for every quarter that a site or network stays in the campaign, there is about 1% reduction in hospital mortality from sepsis. In other words, the longer a site stays in the campaign, the more patients survive. High compliance sites achieved a RRR up to 36 %[15]. Remick criticises their data saying that sepsis mortality was based on 28-day survival, in contrast to most mortality studies, which are based on 5-year survival. Hence, in addition to its high lethality, sepsis also contributes to a significant number of years of life lost [16]. Improved treatment of sepsis could offer decline in global mortality.

Generally, prevention of sepsis includes increasing awareness in healthcare workers and society, reducing antibiotic resistances and better standards of hygiene worldwide, amongst others. According to Nelson the prevention from a surgical perspective requires strict adherence to aseptic surgical technique, maintaining of a supportive operating room environment, early identification and treatment of the high-risk patient, prophylactic antibiotics, and correction of any nutritional deficits prior to surgery [17]. Hence, better education in triage and treatment strategies is needed, including better implementation of the Surviving Sepsis Campaign guidelines. Moreover it is important to follow the goal of providing guidance in better antibiotic use, aiming to prevent all patient infections by appropriate infection. Kumar *et. al.* retrospectively studied the impact of delay of initiation of appropriate antimicrobial therapy and found that it was the strongest predictor in survival [8]. If an effective antibiotic was started within the first hour of documented hypotension in septic shock, the survival rate was 79.9%. Each

further hour of delay over the next 6 hours decreased average survival rates by 7.6%[8]. Noteworthy is however that only 50% of patients received appropriate treatment during the first 6 hours, which emphasizes the need for antibiotic de-escalation and better guidelines for professionals.

One of the most common places where sepsis is treated is the ICU in our hospitals. The German Sepsis Society (Deutsche Sepsis-Gesellschaft e.V. (DSG)) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv und Notfallmedizin (DIVI)) elaborated on what prevention should include:

1. Infection prevention models (for ventilator-associated pneumonias, central venous catheter- associated bacteremias and urinary catheter-associated urinary tract infections). Implementing training programs and universal safety protocols [18] [19-26]
2. Manipulation of devises
   2.1 Hygienic hand disinfection [27,28]
   2.2 Using aseptic techniques with any central intravascular catheters [29]
   2.3 Removal of catheters as soon as they are no longer indicated [30]
   2.4 The use of endotracheal tubes with the possibility of subglottal suction can be considered as it is associated with decreased risk of pneumonia [31]
3. Keeping the head of the bed elevated whenever possible in intubated patients, to prevent ventilator-associated pneumonia (VAP).[32]
4. Early oral or parenteral nutrition helps to reduce infections and the duration of inpatient stays [33] in surgical patients.
5. The perioperative or postoperative use of immunomodulating parenteral nutrition (arginine, omega-3 fatty acids, nucleotides) is recommended for use in elective surgical patients with gastrointestinal tumours or in patients with multiple trauma who are able to receive oral nutrition. This nutrition is associated with a reduction of the duration of inpatient stay as well as a reduction in the number of nosocomial infection cases.[34,35]
6. A moderate intravenous insulin therapy to lower the increased blood glucose levels (threshold value of > 150 mg/dl (> 8.3 mmol/l) may be considered in ICU patients. Tight glucose control (TGC) revealed no differences in hospital mortality between patients who were managed by a ‘tight glycaemic control (TGC)’ protocol and those who were not, i.e.

with either an IIT (target values of 80–110 mg/dl) or a moderate glycaemic control regimen (target values of <150 mg/dl). [36]

7. Selective bowel decontamination reduced the rate of nosocomial infections in ICU patients, especially pneumonia and bacteraemia cases. (For patients with longer intubation periods, > 48 h). [37,38]
8. The use of oral antiseptics reduces ventilator associated pneumonias (VAP). [39]
9. When the frequency of infections remains high despite intensive control measures it is recommended to use antiseptic-coated catheters. [40,41]
10. It is recommended to administer a pneumococcal, meningococcal and Haemophilus Influenzae B vaccine to patients with anatomical or functional asplenism, regardless of their underlying disease, prior to or during the inpatient stay after splenectomy. For immunosuppressed or chronic patients this recommendation is valid as well.[42-45]

Prognostic factors for the outcome of sepsis include the host's response to infection, the site and type of microorganism invasion, lactate levels (see Figure 5), and when therapy is commenced.

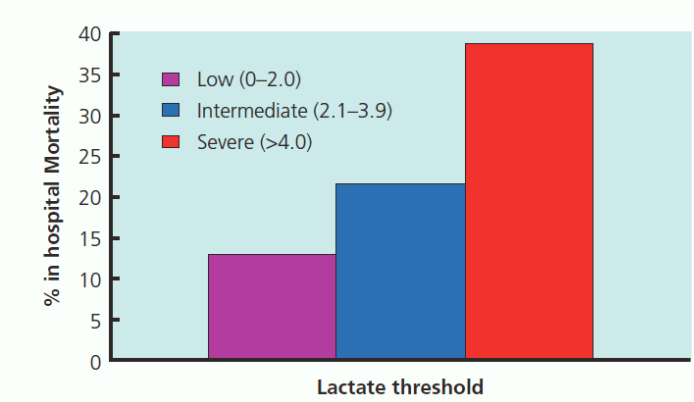



Figure 5 : Mortality compared to lactate levels according to Trzeciak *et al.* 2007 [46]

Furthermore a prospective analysis performed in 1992 by Knaus showed that patients with sepsis failing to develop fever had a worse outcome [47]. New onset atrial fibrillation [48], comorbidities such as AIDS or immunosuppression, and advanced age of the patient (above 40) [5] also have prognostic importance. Age is a risk factor due to increased comorbid conditions and a higher exposure to resistant bacteria as stated by Angus *et al.* [5]. Urosepsis showed the lowest mortality rate compared to septic shock from ischemic bowel syndrome [49] and nosocomial

infections in particular have higher mortality rates compared to community acquired infections [50,51].

## Epidemiology of sepsis:

It is estimated that on average sepsis has an incidence of 56 to 91 cases per 100,000 people, with a mortality rate of 30% [52]. Nevertheless, these estimates are accompanied by wide margins of uncertainty. Hospitalizations for septicaemia or sepsis increased from 326,000 in 2000 to 727,000 in 2008, and the rate of these hospitalizations more than doubled from 11.6 per 10,000 people in 2000, to 24 per 10,000 people in 2008 [10]. The economic burden in Europe for a typical episode of sepsis has been estimated to be approximately 25,000 Euros [7].

**Table 1: Identified studies of the incidence, prevalence and mortality of sepsis according to *Hall et. al (2011)* [52]**

| Article | Country studied | Geographic setting | Population studied | Time setting and duration | Incidence as reported (prevalence only where indicated) | Mortality as reported |
|---|---|---|---|---|---|---|
| Martin et al. [9] | United States | Nationwide | 750 million hospitalizations in the United States, identified 10319418 cases of sepsis | 22-year period | 240.4 per 100000 population | 17.9% (1995-2000) |
| Silva et al. [14] | Brazil | Five mixed ICUs in two different regions of Brazil: São Paulo State and Santa Catarina State | The total number of enrolled patients was 1383 (81.9%) out of 1688 patients admitted to the ICUs of the participating centers. | 21 May 2001 – 31 January 2002 | *Sepsis:* 61.4 per 1000 patient-days / *Severe sepsis:* 35.6 per 1000 patient-days / *Septic shock:* 30.0 per 1000 patient-days | *Sepsis:* 33.9% / *Severe sepsis:* 46.9% / *Septic shock:* 52.2% |
| Elhag et al. [15] | Kuwait | Jabriya, Kuwait City – Mubarak Al-Kabeer Teaching Hospital | 3845 patients / 19606 patients | 18 months (January 1982 – June 1983) | 10.9/1000 hospital admissions | |
| Flaatten et al. [13] | Norway | Nationwide | All patients admitted to all Norwegian hospitals during 1999 | One year | *National:* 1.49 cases/1000 inhabitants / *Under 1:* 1.1/1000 / *Over 80:* 8.7/1000 | 13.5% |
| Hoa et al. [16] | Vietnam | Ho Chi Minh City – southern Viet Nam. | All patients admitted to the hospital whose blood culture was positive | 1 June 1993 – 30 May 1994 | 20.4 episodes per 1000 admissions | 6.0% |
| Harrison et al. [17] | United Kingdom | Nationwide | 343860 admissions to 172 adult units | December 1995 – January 2005 | Severe sepsis: 66 hospital admissions per 100000 population | |
| Angus et al. [10] | USA | Florida, Maryland, Massachusetts, New Jersey, New York, Virginia and Washington. | All acute care hospitalizations with ICD-9-CM codes for both a bacterial or fungal infectious process | 1995 (12 months) | 3.0 cases per 1000 population | *Severe sepsis:* 28.6% |
| Braun et al. [18] | USA | Midwest, Northeast, Southeast, and Western United States | Enrollees in 16 IPA network plans | 1 July 1995 – 31 December 1999 | Severe sepsis: 0.91 cases of per 1000 enrollees | |
| Finfer et al. [19] | Australia and New Zealand | Twenty-three closed multi-disciplinary ICUs of 21 hospitals (16 tertiary and 5 University affiliated) in Australia and New Zealand | Results are presented for 3543 ICU admissions in 3338 patients | 1999 – 2000 | 0.77 per 1000 population | |
| Engel et al. [20] | Germany | Random sample of German hospitals in all 16 federal states of Germany and belonging to 310 hospitals | 1380 hospitals (total number of beds: 488727) | | *Sepsis prevalence:* 12.4% / *Severe sepsis prevalence:* 11.0% | |
| Salvo et al. [21] | Italy | 99 Italian ICUs, distributed throughout the country | 1101 patients who fit criteria from all the ICUs | April 1993 – March 1994 | | *Sepsis:* 36.0% / *Severe sepsis:* 52.0% / *Septic shock:* 81.8% |
| Watson et al. [22] | USA | Florida, Maryland, Massachusetts, New Jersey, New York, Virginia and Washington | 942 non-federal hospital admissions under 19 y olds. | 1995 (12 months) | *Severe sepsis:* 0.56 cases per 1000 children / *Severe sepsis, infants (<1 y):* 5.16 per 1000 / *Severe sepsis, 1–4 y:* 0.49 per 1000 / *Severe sepsis, 5–9 y:* 0.22 per 1000 / *Severe sepsis, 10-14 y:* 0.20 per 1000 / *Severe sepsis, 15–19 y:* 0.37 per 1000 | |

ICU – intensive care unit, y – year

Table 1 shows an overview of identified studies on the incidence, prevalence and mortality from sepsis. Unfortunately, there are no respective data yet from developing country. Moreover, international and national surveys indicate that 20- 40% of sepsis patients that require treatment in the intensive care unit developed their sepsis outside the hospital [53]. The rate of sepsis developing after surgery trebled from 1997 to 2006 [53].

A study on the outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe confirmed a significant difference in their unadjusted mortality. More patients in the USA than in Europe were admitted to ICUs from emergency departments and in Europe more patients were admitted from general wards [14]. In addition the median lengths of stay were slightly longer in Europe than in the USA in ICU and in hospital [14]. However, patients admitted to the ICU with severe sepsis and septic shock in Europe were more severely ill than those in the USA, as indicated by increased rates of organ failure, a greater need for mechanical ventilation, and a longer length of stay in hospital. The higher unadjusted mortality odds ratio in Europe disappeared with severity adjustment [14]. This raises the question: are patients being denied early ICU access in Europe as compared to the USA, and doing worse as a result? Or are patients being unnecessarily over-treated in the US, increasing cost and burden? Concerning this data they there is no clear answer but it is probably somewhere in the middle.

| | USA | Europe | p value* |
|---|---|---|---|
| (Continued from previous page) | | | |
| Infection site | | | |
| Pneumonia | 8589 (45·8%) | 2986 (45·2%) | 0·409 |
| Urinary tract | 5744 (30·6%) | 570 (8·6%) | <0·0001 |
| Abdominal | 3589 (19·2%) | 2105 (31·9%) | <0·0001 |
| Meningitis | 204 (1·1%) | 157 (2·4%) | <0·0001 |
| Skin | 1369 (7·3%) | 272 (4·1%) | <0·0001 |
| Bone | 302 (1·6%) | 75 (1·1%) | 0·006 |
| Wound | 1119 (6·0%) | 159 (2·4%) | <0·0001 |
| Catheter | 928 (4·9%) | 174 (2·6%) | <0·0001 |
| Endocarditis | 196 (1·0%) | 95 (1·4%) | 0·010 |
| Device | 264 (1·4%) | 60 (0·9%) | 0·002 |
| Other infection | 2850 (15·2%) | 498 (7·5%) | <0·0001 |

Data are number of patients (%) or median (IQR). ICU=intensive care unit. *p value is based on either Pearson's $\chi^2$ test for categorical variables or Wilcoxon rank-sum test for continuous variables.

**Figure 6: Descriptive statistics by region according to Hall *et. al* (2011) [14]**

Interestingly, the most common source of infection for sepsis was for both countries pneumonia (see Figure 6). In the USA the second most common cause was urosepsis whilst in Europe the infection site had an abdominal source.

Also ICU patients are at increased risk for nosocomial infections and have a prevalence of nosocomial infections between 5% and 17%[54]. Additionally there is now a global spread of drug resistance among common respiratory pathogens, including streptococcus pneumonia and mycobacterium tuberculosis[54], and in addition the proportion of coagulase-negative staphylococci, methicillin-resistant staphylococcus aureus and enterococci has been rising worldwide. Furthermore, the amount of fungal infections has been greatly rising, especially caused by candida species, and their mortality rate is over 50% [55]. Halting the further spread of bacterial resistance will help in reducing sepsis rates, because pneumonia is with 44,6 % the most common type of infection for sepsis with a mortality of 36,6%[9]. The PROGRESS registry Promoting Global Research Excellence in Severe Sepsis found out that in Europe after pneumonia the most common loci of infection are the abdomen or pelvis in 22.9%, the urinary tract in 7.7%, blood in 6.4%, skin 5.0%, other 5.2%, unknown 2.6%, meninges 1.5%, bone and joints 1.4%, indwelling catheter or vascular access site 1.4%, and dialysis access site 0.7% [53]. Nevertheless, 41.4% of patients had gram-negative organisms, 32.4% had gram-positive organisms, and in 34%, the infection agent was not determined [53]. The location of infection has changed during past decades [56] as earlier gram-positive bacteria predominated. Additionally there is a difference between ICUs and general wards. In the former, respiratory tract infections are the most common, whereas in the latter, urinary tract infections predominate. Mortality is associated with the severity of sepsis, the cause of infection and bacterial or fungal aetiology. A Croatian study showed that the overall mortality of patients with sepsis in Croatian ICUs was high, but outcomes of their treatment were comparable with those in other European countries. The most common isolates from positive blood cultures were Escherichia coli (11.6%), Pseudomonas species (9,9%), and methicillin-resistant staphylococcus aureus (9.3%)[57]. At the Sisters of Mercy University Hospital in Zagreb (Croatia) an observational study showed that sepsis was present in 100 (31.8%), severe sepsis in 89 (28.6%), and septic shock in 125 (39.8%) patients with mortality rates 17%, 33.7%, 72.1%, respectively[58]. Interesting is that their data revealed that the most common source of infection was urosepsis, present in 168 (53.5%) patients, followed by skin or soft tissue infections in 58 (18.5%)[58]. This differs from the

other American and European studies as mentioned above. Nevertheless, early recognition and prompt treatment in an appropriate environment as well as competent medical personnel remain pivotal.

## Pathophysiology of Sepsis:

The pathophysiology of sepsis will be discussed briefly, as it is still not fully understood and a detailed description of all the known pathways would go beyond the scope of this thesis.

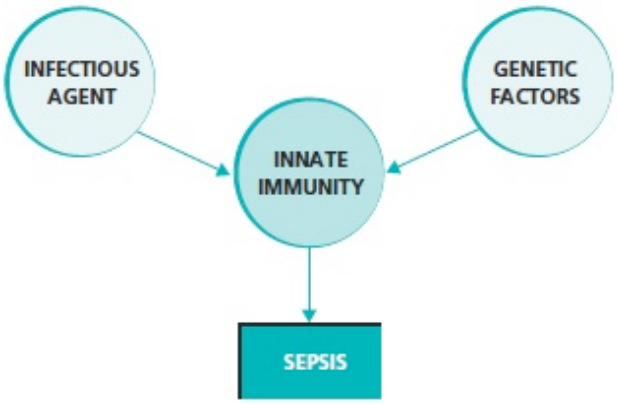



Figure 7: : Interaction between host and agent in the development of sepsis, with permission from WIley Blackwell[1]

The current literature describes generally that our defence against microbes has been divided into two basic types of reactions. First, the reactions of innate immunity and later reactions of the adaptive immunity.

Both innate and adaptive immunity can be seen as two equally important parts of our immune system. The innate immune system consists of cells and proteins that are always present and ready to mobilize quickly and fight microorganisms at the site of infection. However, genetic polymorphisms of toll-like receptor 4 (TLR-4) are associated with a predisposition to shock with gram-negative organisms, and mutations in the tumour necrosis factor α (TNF-α) receptor affect outcomes from severe sepsis [1].

The main components of the innate immune system are: physical epithelial barriers, phagocytic leukocytes, dendritic cells, natural killer (NK) cell, and circulating plasma proteins[59]. The adaptive immune system is the second line defence system against those pathogens that are able to evade or overcome the innate immune defences. Their components adapt to the presence of infectious agents by activating, proliferating, and creating efficient mechanisms for neutralizing or eliminating the microbes. There are two types of adaptive immune responses: humoral immunity, mediated by antibodies produced by B-lymphocytes, and cell-mediated immunity, mediated by T-lymphocytes.

Under normal condition the host response to an infection is initiated when innate immune cells, particularly macrophages, recognize and bind to microbial components. Pattern recognition receptors (PRRs) on the surface of our immune cells recognize and bind to the pathogen-associated molecular patterns (PAMPs) of microorganisms. There exist three types of PRRs: toll-like receptors (TLRs), nucleotide-oligomerisation domain (NOD) leucine-rich repeat proteins, and retinoic-acid-inducible gene I (RIG-I)-like helicases[59]. The binding of host immune cell surface receptors to microbes has several effects.

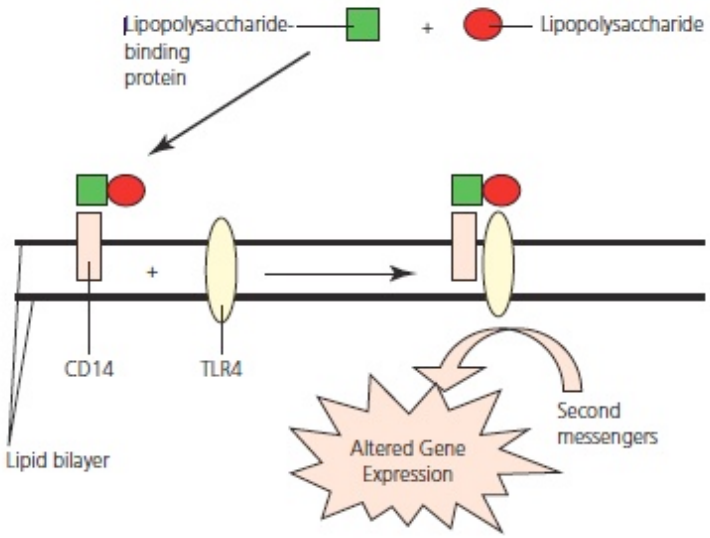



**Figure 8: The role of toll-like-receptors (TLRs) in the development of sepsis, ABC of Sepsis (2009) with permission from Wiley Blackwell [1]**

The activation of TLRs produces a signalling cascade via the activation of cytosolic nuclear factor-kb (NF-kb). Activated NF-kb moves from the cytoplasm to the nucleus, binds to transcription sites, and induces activation of a large set of genes, such as proinflammatory cytokines (tumour necrosis factor alpha [TNFα], interleukin-1 [IL-1]), chemokines (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1]), and nitric oxide[59]. Furthermore polymorphonuclear leukocytes (PMNs) become activated and express adhesion molecules that cause their aggregation and margination to the vascular endothelium. The release of mediators by PMNs at the site of infection is mainly the cause for the main signs of local inflammation as *calor* (warmth), *rubor* (erythema) induced by local vasodilation, hyperemia, and protein-rich edema due to increased micro vascular permeability. This process is

highly regulated by a mixture of pro-inflammatory and anti-inflammatory mediators secreted by macrophages, which have been triggered and activated by the invasion of tissue by bacteria [60,61]. While the pro-inflammatory environment leads to the recruitment of more PMNs and macrophages, the anti-inflammatory mediators inhibit the production of TNFα and IL-1[1]. In other words they suppress the immune system by inhibiting cytokine production. The balance of pro-inflammatory and anti-inflammatory mediators influences the inflammatory cascade and if it is not restored sepsis or SIRS is the result.

During sepsis, the balance is shifted towards cell death and a state of relative immunosuppression[1]. At this late stage, accelerated lymphocyte apoptosis occurs with decreased production of pro-inflammatory ensues, which may lead to end-organ failure. Various mediators, including tumour necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), induce nitric oxide production [14]. It causes a decrease in systemic vascular resistance but also causes myocardial depression and left ventricular dilatation with decreased ejection fraction[1]. This leads to an elevated cardiac output and generalized vasodilatation, which is described as septic shock. Over time myocardial depression becomes more pronounced and may result in a falling cardiac output. Capillary leakage occurs with peripheral and pulmonary oedema that may progress to acute lung damage and acute respiratory distress syndrome (ARDS). A surge in catecholamines, angiotensin II and endothelin causes renal vasoconstriction and increases the risk of renal failure developing.

In addition to those changes the coagulation cascade shifts towards a pro-thrombotic and anti-fibrinolytic state mediated by decreased anti-thrombin III, protein C, protein S and tissue factor pathway inhibitor levels and prolonged clotting time[1]. The blood clots when it should not. Virchow's classic triad consists of changes in coagulability, endothelial cell injury, and abnormal blood flow. In septic patients, all three of these classic alterations are present and result in reduced blood flow to vital organs. Septic patients frequently have poor tissue perfusion in addition to inappropriate use of oxygen with resulting cytopathic hypoxia[16]. Increased thrombin levels leads to endothelial and platelet activation. As a result, there is fibrin deposition and micro-vascular thrombosis that may insult end organs. The development of disseminated intravascular coagulation (DIC) in severe sepsis is a predictor of death and the development of multi-organ failure[1].

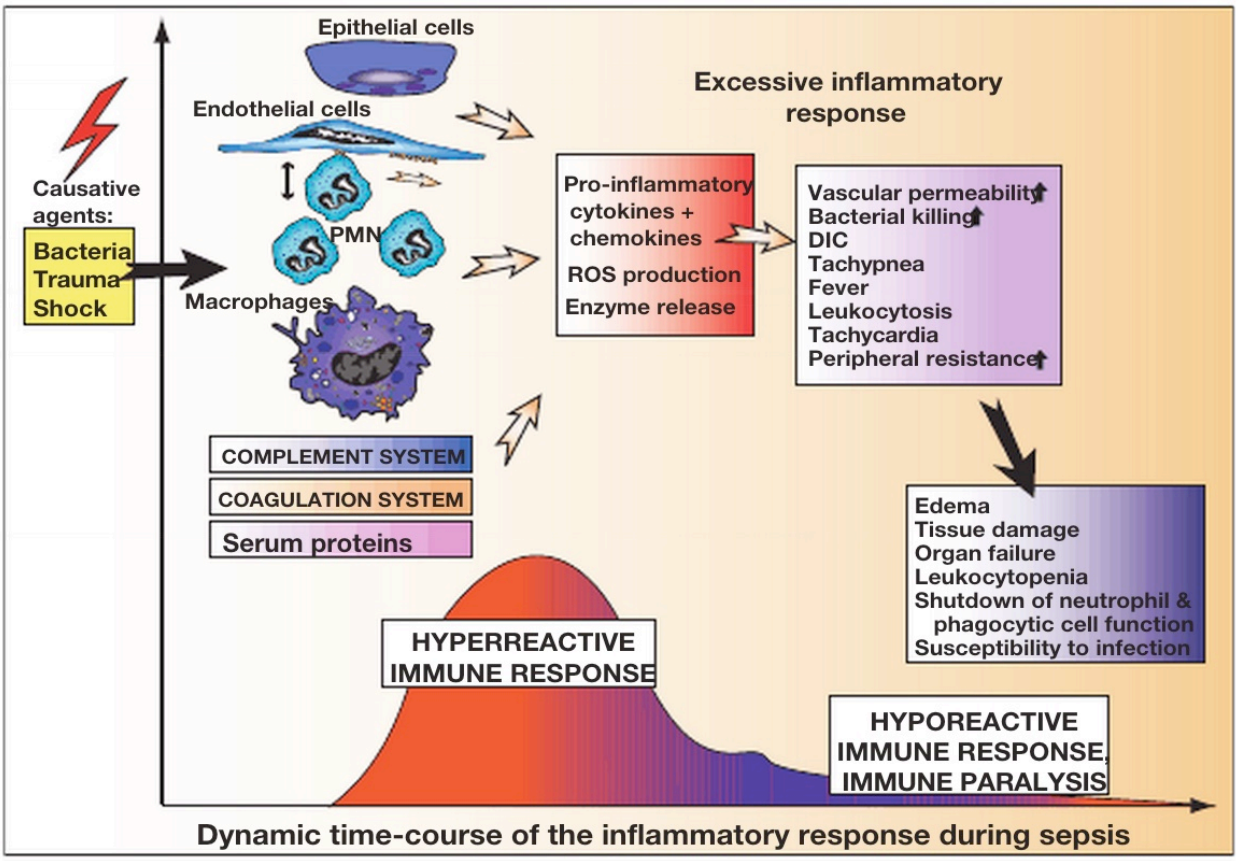



Figure 9: Overview of the inflammatory response during sepsis, with permission from Nature Publishing Group (2009) [62]

In summary, multiple stimuli can cause initiation of different cell types or proteins, as well as the complement and coagulation systems. This leads to a higher production of pro-inflammatory chemokines and cytokines and up-regulation of adhesion molecules on endothelial and polymorphonuclear leukocytes[62]. Subsequently there is a surge of granular enzymes and generations of reactive oxygen species in response to the initial stimulus that occurs in the early hyper-reactive phase. As a consequence vascular permeability increases, tissue damage and organ failure occur and the innate immune system becomes defective. This leads to the hypo-reactive phase of the immune response, sometimes resulting in immune paralysis. Finally, in Figure 9 shows an overview of the inflammatory response during sepsis.

## Clinical presentation and diagnosis of sepsis:

Basically the best approach to evaluate any patient admitted to the hospital with a suspicion of infection. Unfortunately daily clinical work is not that straightforward, especially with infants. Identifying a patient with sepsis remains the cornerstone of success in its therapy. There is no typical presentation but most likely the patient presents with fever, tachycardia and tachypnea.

Table 2: Diagnostic criteria for sepsis and severe sepsis. According to Surviving Sepsis Campaign Guidelines (2012) [63]

**SEPSIS: INFECTION, DOCUMENTED OR SUSPECTED, AND SOME OF THE FOLLOWING**

**General Variables**

Fever (temperature >38.3°C)

Hypothermia (core temperature <36°C)

Pulse rate >90/min or more than 2 SDs above the normal value for age

Tachypnea

Altered mental status

Significant edema or positive fluid balance (>20 mL/kg during 24 h)

Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

**Inflammatory Variables**

Leukocytosis (WBC >12,000 μL)

Leukopenia (WBC <4,000 μL)

Normal WBC with >10% immature forms

Plasma C-reactive protein more than 2 SDs above the normal value

Plasma procalcitonin more than 2 SDs above the normal value

**Hemodynamic Variables**

Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or less than 2 SDs below normal for age)

**Organ Dysfunction Variables**

Arterial hypoxemia ($PaO_2/FiO_2$ <300)

Acute oliguria (urine output <0.5 mL/kg per hour for at least 2 h despite adequate fluid resuscitation)

Creatinine-level increase >0.5 mg/dL

Coagulation abnormalities (INR >1.5 or aPTT >60 s)

Ileus (absent bowel sounds)

Thrombocytopenia (platelet count <100,000 μL)

Hyperbilirubinemia (plasma total bilirubin >4 mg/dL)

**Tissue Perfusion Variables**

Hyperlactatemia (>1 mmol/L)

Decreased capillary refill or mottling

**SEVERE SEPSIS: SEPSIS-INDUCED TISSUE HYPOPERFUSION OR ORGAN DYSFUNCTION (ANY OF THE FOLLOWING THOUGHT TO BE DUE TO INFECTION)**

Sepsis-induced hypotension

Lactate level above upper limits of laboratory normal levels

Urine output <0.5 mL/kg per hour for more than 2 h despite adequate fluid resuscitation

Acute lung injury with $PaO_2/FiO_2$ <250 in the absence of pneumonia as infection source

Acute lung injury with $PaO_2/FiO_2$ <200 in the presence of pneumonia as infection source

Creatinine level >2.0 mg/dL

Bilirubin level >2 mg/dL

Platelet count <100,000 μL

Coagulopathy (INR >1.5)

*SBP*, Systolic blood pressure; *MAP*, mean arterial pressure; *INR*, international normalized ratio; *aPTT*, activated partial thromboplasmin time.

Diagnosing sepsis includes two or more of these conditions: temperature > 38 ° C or < 36 °, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or PaCO2 < 32 torr (< 4.3 kPa), and WBC

> 12 000 cells/mm3 or < 10% immature forms. Table 2 summarizes all diagnostic variables according to the current SCC guidelines.

Some of these criteria need, as already mentioned, should lead to a high index of suspicion. For example an altered mental status will always be difficult to identify in older people with dementia or with neonates. At the same time this emphasizes how important teamwork between nurses and physicians is.

In order to make diagnosing sepsis as timely as possible, medical professionals can use the Modified Early Warning Score (MEWS) and a Screening Tool developed by the British National Health Services (NHS). MEWS uses four physiological parameters (systolic blood pressure, heart rate, respiratory rate and body temperature) and one observation (level of consciousness, AVPU scale) [64], as seen in Table 3. It is an important risk management tool, which not only helps to diagnose sepsis or SIRS cases[65]. With a higher score the parameters should be repeated more frequently. A score of higher than 5 indicates that the patient has an increased risk of mortality.

Table 3: Modified Early Warning Score (MEWS), AVPU = Alert, Verbal, Pain, Unresponsive - adapted from Lee Jr. (2014) [66]

| Categories | Scores | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | 1 | 2 | 3 |
| Respiratory rate (breaths/min) | | <9 | | 9-14 | 15-20 | 21-29 | ≥30 |
| Heart rate (beats/min) | | ≤40 | 41-50 | 51-100 | 101-110 | 111-129 | ≥130 |
| Systolic blood pressure (mmHg) | ≤70 | 71-80 | 81-100 | 101-199 | | ≥200 | |
| Temperature (℃) | | <35 | | 35-38.4 | | ≥38.5 | |
| AVPU score | | | | Alert | Reacting to voice | Reacting to pain | Unresponsive |

The Screening Tool for Sepsis incorporates the MEWS (see Figure 8). Once sepsis is diagnosed or suspected, the physician should proceed with the 3 hour and 6 hour treatment guidelines as discussed below.

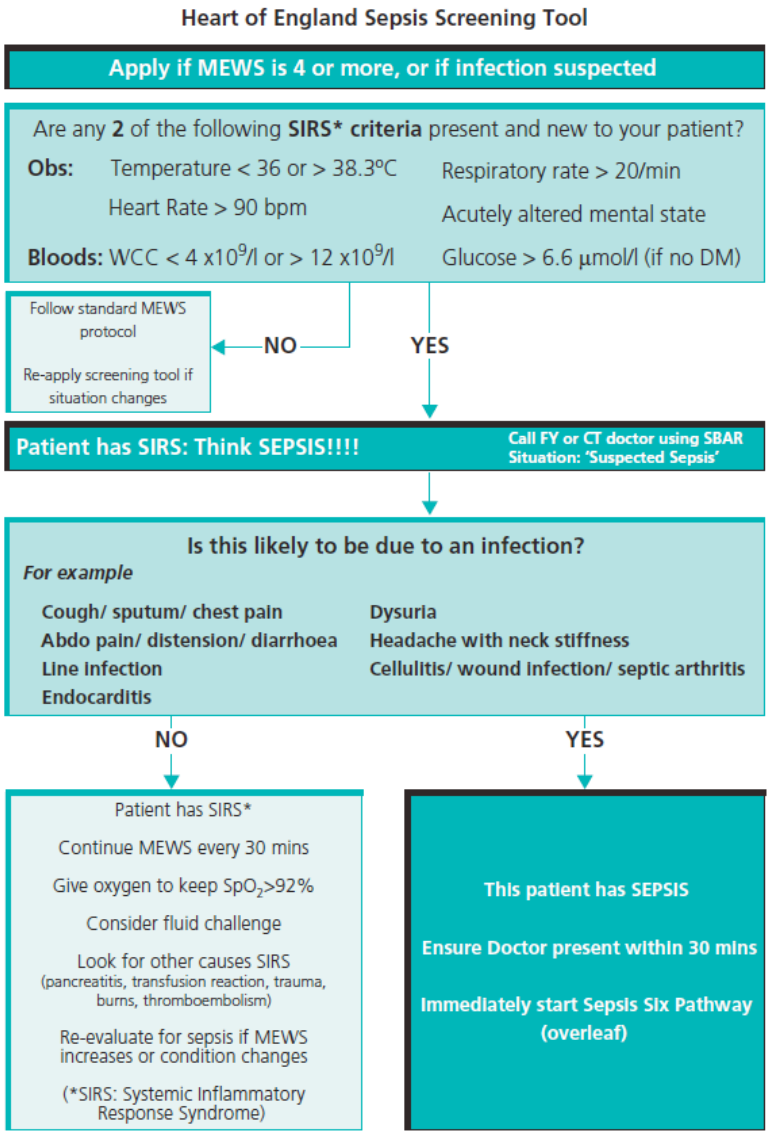



Figure 10: Heart Of England Sepsis Screening Tool, according to ABC of sepsis with permission from Elsevier (2009) [1]

## Complications of sepsis and scoring systems:

Complications of sepsis include severe sepsis, septic shock and multiple organ dysfunction syndrome (MODS), earlier called multiple organ failure (MOF). Severe sepsis is often accompanied by respiratory failure, due to diffuse alveolar damage, which can lead to pulmonary oedema and failure of oxygenation, also called acute respiratory distress syndrome (ARDS). The cardiac output is decreased due to the dilatation of veins and arterioles through the effect of nitrous oxide and increased levels of lactate, which acts as a cardiac depressant[67] - a vicious circle in regard to the hypo-perfusion of our body. Furthermore, renal failure is also seen as complication of sepsis and increases the mortality in severe sepsis. The nervous system is affected in up to 70% by septic-associated-encelopathy (SAE) and presents as delirium up to and including deep coma in severe cases [68]. Polyneuropathy has also been found on septic patients, which was mostly diagnosed when weaning patients from mechanical ventilation[69]. In multiple organ dysfunction syndrome the body's homeostasis can not be maintained without intervention. MODS is classified into primary and secondary. Primary MODS can be attributed to the direct insult itself (eg: renal failure due to rhabdomyolysis), and secondary MODS is organ failure that is not in direct response to the insult itself, but is a consequence of the host's response (eg: acute respiratory distress syndrome (ARDS) in patients with pancreatitis) [70]. The over activation of intravascular coagulation (DIC) can lead to micro-thrombosis in end-organs, cutaneous haemorrhage (purpura fulminans) or even necrosis of peripheral limbs (see Figure 11). DIC or also consumption coagulopathy is often seen in gram-negative sepsis (such as meningococcal sepsis).


Figure 11: Necrosis of distal fingers in a case of meningococcal sepsis with permission from Globalskinatlas.com (2014)

The aetiology of MODS is still not fully understood but generally tissue injury due to infection, distributive or haemorrhagic shock, trauma, or inflammation (such as pancreatitis), induces local and systemic responses. These responses can lead to a shock, reperfusion injuries, and systemic inflammation where organ dysfunction becomes progressive and leads to death. The patient can also recover and enter a phase of prolonged rehabilitation. Interestingly the progressive organ dysfunction usually follows some kind of predictable course [71]. During the first 72 hours of the original insult, respiratory failure (acute respiratory distress syndrome, ARDS) commonly occurs [71,72], which can also remain as interstitial lung fibrosis and be a lifetime restriction for the patient's lung function. In 5 to 7 days hepatic failure ensues and gastrointestinal bleeding occurs most likely in the following 10 to 15 days, and finally renal failure in 11 to 17 days [71,72]. Even though in mild cases the liver seems to be resistant, additionally cholestatic jaundice can occur [70]. However, there exist a handful of hypotheses as to the mechanisms that initiate and perpetuate MODS. In the current literature they talk about so-called "one-hit", "two-hit" and "sustained insult". Whereas in the one-hit model the initial insult (eg trauma, sepsis) is the cause, in the two-hit model a subsequent insult (such as catheter induced infection) is the explanation, and in the sustained model a continuous insult such as ventilator associated pneumonia is the origin for MODS [73]. The pathophysiology models such as the "gut hypothesis" is just one of the elaborated models, but seems to be amongst most cited ones. Their theory is that due to splanchnic hypo-

perfusion and endotoxin release the gut mucosal injury increases gut permeability which increases translocation of bacteria and their subsequent escape into the systemic circulation to activate the host's inflammatory response[71,72]. In the end, the patient that survives sepsis, has an increased risk for developing depression and posttraumatic stress disorder (PTSD). Up to 38% of patients after abdominal sepsis reported elevated levels of PTSD symptoms in a study performed at the University of Amsterdam [74].

There are no overall accepted criteria for single organ dysfunction in MODS. However, progressive abnormalities of the following organ-specific parameters are commonly used to diagnose MODS and scoring systems are used to predict their fatality.

Table 4: Parameters to predict organ dysfunction in MODS adapted from www.uptodate.com [75]

| | | |
|---|---|---|
| PaO2/FiO2 ratio | Platelet count | Serum bilirubin Serum |
| creatinine (or urine output) | Glasgow coma score | Hypotension |

Scoring systems estimate the risk of hospital death based on severity of disease, to help in clinical decision making, standardizing research, and comparing the quality of patient care in critical care medicine. There exist four different systems: the Acute Physiologic and Chronic Health Evaluation (APACHE) system, Simplified Acute Physiologic Score (SAPS), Mortality Prediction Model (MPM), and Sequential Organ Failure Assessment score (SOFA). The APACHE Score and SOFA are most frequently used. APACHE has different versions from II to IV. II and III seem to be the most cited ones. The data is collected during the initial 24 hours of ICU admission, taking into account the most critical values. The required data differ among the versions, but mostly include factors such as age, diagnosis, prior treatment location, and numerous acute physiologic and chronic health variables. The maximum points attainable are 71, whereas more than 35 indicate a probable mortality risk of over 80%[76].

Table 5: Sequential Organ Failure Assement (SOFA), each graded from 0 to 4 points according to the degree of dysfunction.

| Collected values | points | +4 | +3 | +2 | +1 | 0 | +1 | +2 | +3 | +4 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Temp. rectal °C** | | ≥ 41° | 39 - 40,9° | | 38,5 - 38,9 | 36 - 38,4° | 34 - 35,9° | 32 - 33,9° | 30 - 31,9° | ≤ 29,9° |
| **Mean arterial pressure mmHg** | | ≥ 160 | 130 - 159 | 110 - 129 | | 70 - 109 | | 50 - 69 | | ≤ 49 |
| **heartrate /min** | | ≥ 180 | 140 - 179 | 110 - 139 | | 70 - 109 | | 55 - 69 | 40 - 54 | ≤ 39 |
| **Respiratory frequency /min** | | ≥ 50 | 35 - 49 | | 25 - 34 | 12 - 24 | 10 - 11 | 6 - 9 | | ≤ 5 |
| **Fraction of insprired oxygen FiO2** | | ≥ 500 | 350 - 499 | 200 - 349 | | < 200 I > 70 | 61 - 70 | | 55 - 60 | < 55 |
| **pH** | | ≥ 7,7 | 7,6 - 7,69 | | 7,5 - 7,59 | 7,33 - 7,49 | | 7,25 - 7,32 | 7,15 - 7,24 | < 7,15 |
| **Na+** | | ≥ 180 | 160 - 179 | 155 - 159 | 150 - 154 | 130 - 149 | | 120 - 129 | 111 - 119 | ≤ 110 |
| **K+** | | ≥ 7 | 6,6 - 6,69 | | 5,5 - 5,59 | 3,5 - 5,4 | 3,0 - 3,4 | 2,5 - 2,9 | | ≤ 2,5 |
| **creatinine mg/dl** | | ≥ 3.5 | 2,0 - 3,4 | 1,5 - 1,9 | | 0,6 - 1,4 | | < 0,6 | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **haematocrit %** | ≥ 60 | | 50 - 59,9 | 46 - 49,9 | 30 - 45,9 | | 20 - 29,9 | | < 20 |
| **leukocyte count (x1000)** | ≥ 40 | | 20 - 39,9 | 15 - 19,9 | 3 - 14,9 | | 1 - 2,9 | | < 1 |
| **Glasgow Coma Scale (GCS)** | points= 15 - current GCS | | | | | | | | |

The difference between APACHE II and III is, that more variables have been added (such as diagnosis or prior treatment location). Crucial is also that the data should be collected on a daily basis, which makes APACHE III more accurate.

In contrast, the Sequential Organ Failure Assessment (SOFA) uses simple measurements for major organ function to calculate a severity score. The variables are collected 24 hours after admission to the ICU and every 48 hours thereafter. The score has 0-24 points, and thereby higher scores have a predictability of severe outcome. The mean and highest SOFA scores are useful predictors of organ dysfunction. If the initial score during the first 48 hours is elevated there is a 50 % risk of mortality [77]. In a prospective cohort study by Alan E. Jones the SOFA score showed good results in predicting in-hospital mortality when applied to patients with severe sepsis with evidence of hypo-perfusion at the time of emergency department admission[78]. Another study showed that SOFA was not any better than APACHE II score in predicting outcome[79]. Nonetheless it is simpler and might therefore be better for everyday use in ICUs.
On the other hand, a prospective study by Meyer *et al.* [80] showed that among patients who were predicted by clinical assessments and APACHE II scores more likely to die, more than 40% of them actually survived. In summary there is no method that is 100% reliable for predicting mortality. This shows that a patient's life should not be evaluated by a statistic; instead it should make therapeutic decision easier for physicians in ICUs and should serve as a tool for research purposes and comparison.

## Treatment strategies:

A standardized approach to any patient with sepsis should include performing Airway, Breathing, Circulation, Disability, and Exposure (ABCDE) assessment to initiate immediate therapy. The first steps should include airway support, high-flow oxygen, cannulation, fluid challenges, urinary output monitoring, blood glucose monitoring and temperature regulation.

Establishing vascular access and initiating fluid boluses remain crucial when managing patients with severe sepsis or septic shock. Afterwards the physician should re-evaluate the high-flow oxygen, cannulation, and fluid challenges if the patient is compromised. The 3rd step is to perform diagnostics specific to sepsis consisting of blood cultures, lactate measurement, CBC with differential and other tests including imaging to identify the source of infection. The last step is to start empiric antibiotic therapy and treat the infection, whilst re-evaluating the therapy 48 hours later.

Figure 11 shows the 3 hourly and 6 hourly therapeutic goals that need to be reached as adapted from the recent Surviving Sepsis campaign guidelines.

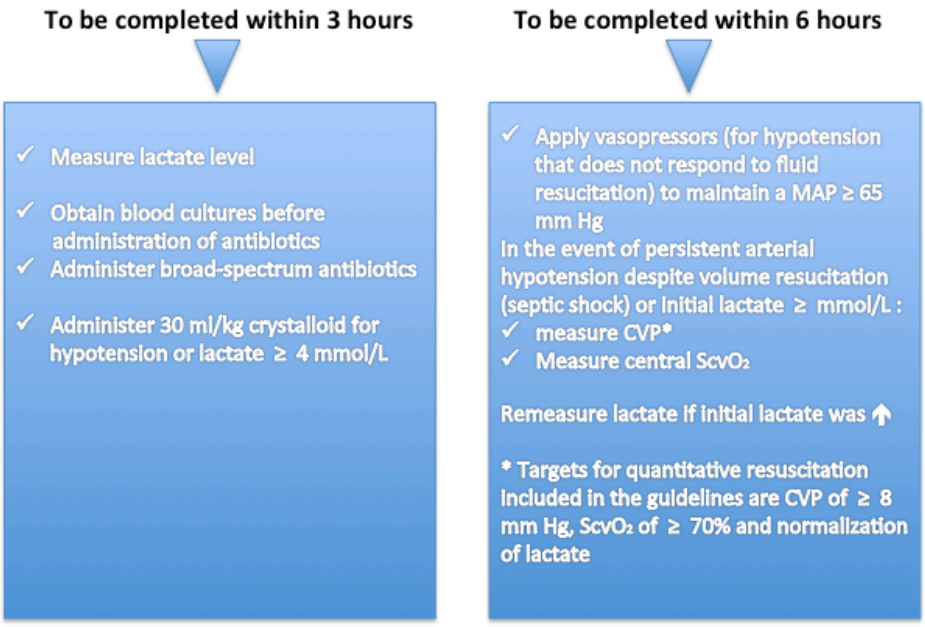



Figure 12: Treatment guidelines adapted from Surviving Sepsis Campaign 2012 [63]

Early recognition is the cornerstone of initiation for the initiation of sepsis treatment strategies. Screening tools as mentioned earlier should be used in order to help the physician start the therapy without any delay. It is important to take careful blood cultures samples, as the microbiologist can only give you accurate results with properly taken samples. The SSC guidelines recommend obtaining at least two sets of blood cultures (aerobic and anaerobic) before antimicrobial therapy, with at least one drawn percutaneously and one drawn through each vascular access [63]. In the case of suspected fungal infection they further suggest the use of the 1,3 b-D-glucan assay and mannan and anti-mannan antibody assays, as those assays showed positive results earlier than the standard culture methods [81-83], which especially is crucial as fungal sepsis has worse outcomes.

Regarding antibiotic therapy initial empiric therapy should most likely include one or more drugs which are effective against all possible pathogens and that penetrate in sufficient concentrations into the tissues suspected to be the loci of infection [63]. The choice of therapy remains a complex issue, in an era of increasing resistance – that is why de-escalation is crucial for success in therapy. De-escalation consists of the practice of administering broad-spectrum empirical antibiotic therapy together with early re-evaluation and subsequent narrowing down or discontinuation of therapy based on clinical improvement and the results of cultures and antibacterial susceptibility tests[84].

The physician should take into account the patient's history, including drug allergies and intolerances, underlying disease (such as COPD or diabetes), the clinical syndrome, recent treatment with antibiotics and the susceptibility patterns of microorganisms in the local hospital or area. The British National Health Services developed guidance for antibiotic therapy that I summarized in Figure 12.

Antibiotic therapy usually lasting 7-10 days, except if bone is the source of infection in which case treatment lasts usually from 14 days to 4 weeks.

**NOTE:** All doses that are recommended in this guide are for those with normal renal function

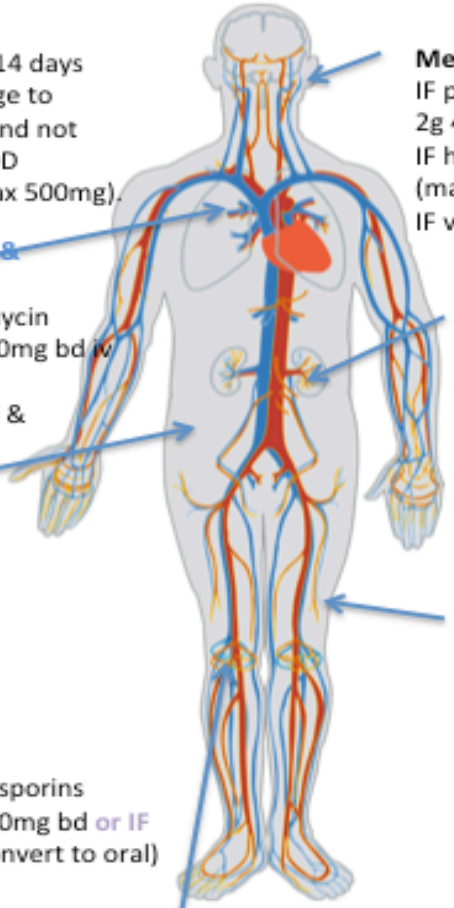
# Guidance on Initial Antibiotic Therapy by Body Site

**Review antibiotic choice with culture results !**

**CENTRAL LINES:**
**Remove line + Vancomycin IV**
Line-associated bacteraemia due to S. aureus should be treated with a min. of 14 days antibiotic therapy after line removal. Change to Flucloxacillin IV 2g qds if MSSA is isolated and not allergic. If severe sepsis or septic shock: ADD Gentamicin IV 5 mg/kg as a single dose (max 500mg).

**PNEUMONIA:**
*Mild – Moderate*: **amoxicillin 500mg tds orally & clarithromycin 500mg** bd orally
Severe: Co-amoxiclav IV 1.2 g TDS & clarithromycin 500mg bd iv (if penicillin allergy levofloxacin 500mg bd iv & clarithromycin 500mg bd iv)
ICU admission: only benzylpenicillin 1.2g qds IV & levofloxacin 500mg bd IV

**ABDOMINAL/BILIARY INFECTION:**
perforation of abdominal / gynaecological viscus – which is usually polymicrobial:
**Piperacillin/tazobactam IV 4.5g tds**
Or
If rash with penicillins: Cefuroxime IV 1.5g tds (Not to be used in serious penicillin allergy)
+ Metronidazole IV 500mg tds
Or
IF severe penicillin allergy or allergic to cephalosporins
Ciprofloxacin PO 500mg bd (or if vomiting IV 400mg bd or IF severe sepsis give 1st dose as IV 400mg then convert to oral)
+ Metronidazole IV 500mg tds
IF the patient has severe sepsis or septic shock:
ADD Gentamicin IV 5 mg/kg
as a single dose (max 500mg)
Or if risk of MRGNB Meropenem IV 1g tds



**Meningitis**: **ceftriaxone 2g bd iv**
IF patient > 55 yrs, immunocompromised ADD IV Amoxicillin 2g 4-hourly (covers listeria)
IF history of allergy , IV Chloramphenicol 12.5mg/kg qds (maximum dose 1g qds )
IF viral etiology suspected: IV Aciclovir 10mg/kg tds

**UROSEPSIS:**
Pyelonephritis is usually due to Gram negative bacilli:
**Piperacillin/tazobactam IV 4.5g tds**
Or IF non severe penicillin allergy Cefuroxime IV 1.5g tds Or
In severe penicillin allergy Ciprofloxacin 500mg PO bd (or if severe sepsis give 1st dose as IV 400mg then convert to oral)
IF severe sepsis/septic shock, add Gentamicin IV 5 mg/kg as a single dose (max 500mg)
If there are no culture results to indicate narrow spectrum therapy, convert Piperacillin/tazobactam to Co-amoxiclav PO 625mg tds. OR If risk of MRGNB Meropenem IV 1g tds

**CELLULITIS:**
**Flucloxacillin PO 500mg-1g qds** or if penicillin allergy Clarithromycin PO 500mg bd
When more severe or failed adequate doses of oral flucloxacillin give IV 2g qds (switch to oral if stable)
Penicillin allergy: Clindamycin PO 450-600mg qds or IV 600mg qds IF vomiting/ severe sepsis (change to oral when stable)
Nosocomial / MRSA is a possibility Vancomycin IV.

**BONE & JOINT INFECTION:**
Patients < 75 years old **Flucloxacillin IV 2g qds**
IF Penicillin allergy, Clindamycin IV 600mg qds (change to oral 300-450mg qds when stable)
or Cefuroxime IV 1.5g tds
IF MRSA infection is a possibility
Vancomycin IV + Piperacillin/tazobactam IV 4.5 g tds

Patients ≥ 75 years , immunocompromised , suspected/proven Gram negative infection:
**Piperacillin/tazobactam IV 4.5 g tds**
IF risk of MRGNB or non-severe penicillin allergy: Meropenem IV 1g tds
IF suspected/proven gonococcal infection:
Ceftriaxone IV 1g od

Figure 13 : Antibiotic guidance therapy by body site, tds – three times a day, PO – per os, qds – 4 times a day, bd – twice a day, OD – once a day, MSSA – methicillin sensitive staphylococcus aureus, MRGNB – multi resistant gram negative bacteria

The antibiotic therapy needs re-evaluation after 48 hours in order to de-escalate if needed. Furthermore the SCC guidelines suggest the use of low procalcitonin levels (or C-reactive protein) to help the clinician in the discontinuation of empiric-prescribed antibiotics in patients where there is no continuous evidence for infection [63].

According to the British NHS guidelines the initial therapy for a sepsis of unknown origin should be amoxicillin 1g tds IV plus metronidazole 500mg tds IV and gentamicin 5mg/kg IV. Nevertheless, in dealing with complex cases the attending doctor should consult the duty microbiologist and a senior physician.

## Conclusion:

In summary, sepsis is a condition that we will be facing more and more in the future. The demographic shift of our civilization has led to a higher rate of older people who need more medical interventions with a subsequent risk of infection due to numerous comorbidities and their age, respectively. Increasing awareness of sepsis is just the first step towards decreasing their mortality. Knowing the early signs of sepsis is crucial. The human factor in every hospital, community, nursing home, and rehabilitation clinic is important for that awareness. Every hour won from sepsis onset to sepsis treatment decreases mortality [15]. As long as sepsis is not represented in national disease reports, it will be even harder to get it included in the Global Burden of Disease Report. To date, the Global Burden of Disease Report (GBDR) and the WHO website list only "maternal sepsis" and "sepsis in new-borns". As sepsis can affect to nearly everyone, this is not acceptable. However, it will probably need further clinical trials to achieve this. As stated earlier, those facilities participating in the Surviving Sepsis Campaign reduced their mortalities up to 20 % of relative risk reduction. The initial goal of the sepsis campaign was to reduce sepsis rates by 25% within 4 years. It took in total approximately 8 years to reduce it by 20 % [14]. This is an achievement but still needs more support globally. The rising resistance to effective antibiotics does not make it any easier to fight sepsis, that is why we need to stress the importance of de-escalation therapy in the treatment of any infectious condition.

In the future sepsis awareness needs to be better outlined for laypeople and professionals – starting with the medical student and up to the senior physician. Unfortunately the human race likes to procrastinate, as in the meantime the problem becomes bigger. The answer is probably somewhere in the middle and increasing the awareness of sepsis is has definitely needed to be addressed for many years. This urges us all to follow the current literature on sepsis, to reach beyond the margins of our specialties and follow the published guidelines on topic of sepsis.

## Acknowledgements:

I would like to highlight the unwavering support, guidance, and motivation provided by my mentor Assistant Professor Vesna Degoricija, MD, PhD. An inspiring teacher and physician is truly to be treasured, and without her agency this paper would not have been written. I also wish to recognize the continuous and unconditional love and support of my parents.

## References :


1. Ron Daniels (Editor) TNE. ABC of Sepsis: John Wiley and Son; 2009.
2. Hodgin KE, Moss M. The epidemiology of sepsis. Current pharmaceutical design. 2008;14(19):1833-1839.
3. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Critical care medicine. 1992;20(6):864-874.
4. Opal SM. Concept of PIRO as a new conceptual framework to understand sepsis. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2005;6(3 Suppl):S55-60.
5. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Critical care medicine. 2001;29(7):1303-1310.
6. Martin GS, Mannino DM, Eaton S, Moss M. The Epidemiology of Sepsis in the United States from 1979 through 2000. New England Journal of Medicine. 2003;348(16):1546-1554.
7. World Sepsis Day Steering C. 2014; http://world-sepsis-day.org. Accessed 27.03.2014.
8. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical care medicine. 2006;34(6):1589-1596.
9. Slade E, Tamber PS, Vincent JL. The Surviving Sepsis Campaign: raising awareness to reduce mortality. Critical care. 2003;7(1):1-2.
10. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. NCHS data brief. 2011(62):1-8.
11. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. New England Journal of Medicine. 2001;345(19):1368-1377.
12. Shankar Santhanam M. Pediatric sepsis. 2014; http://www.emedicine.com/ped/topic3006.htm. . Accessed 25.04.2014
13. ECDC. Antimicrobial resistance surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: European Centre for Disease Prevention and Control. ; 2013.
14. Levy MM, Artigas A, Phillips GS, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. The Lancet infectious diseases. 2012;12(12):919-924.
15. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Critical care medicine. 2010;38(2):367-374.
16. Remick DG. Pathophysiology of sepsis. The American journal of pathology. 2007;170(5):1435-1444.
17. Nelson CL. Prevention of sepsis. Clinical orthopaedics and related research. 1987(222):66-72.
18. Joiner GA, Salisbury D, Bollin GE. Utilizing Quality Assurance as a Tool for Reducing the Risk of Nosocomial Ventilator-Associated Pneumonia. American Journal of Medical Quality. 1996;11(2):100-103.

**19.** Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. The New England journal of medicine. 2006;355(26):2725-2732.
**20.** Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Critical care medicine. 2004;32(10):2014-2020.
**21.** Jain M, Miller L, Belt D, King D, Berwick DM. Decline in ICU adverse events, nosocomial infections and cost through a quality improvement initiative focusing on teamwork and culture change. Quality & safety in health care. 2006;15(4):235-239.
**22.** Warren DK, Zack JE, Cox MJ, Cohen MM, Fraser VJ. An educational intervention to prevent catheter-associated bloodstream infections in a nonteaching, community medical center. Critical care medicine. 2003;31(7):1959-1963.
**23.** Warren DK, Zack JE, Mayfield JL, et al. The effect of an education program on the incidence of central venous catheter-associated bloodstream infection in a medical ICU. Chest. 2004;126(5):1612-1618.
**24.** Babcock HM, Zack JE, Garrison T, et al. An educational intervention to reduce ventilator-associated pneumonia in an integrated health system: a comparison of effects. Chest. 2004;125(6):2224-2231.
**25.** Cocanour CS, Peninger M, Domonoske BD, et al. Decreasing ventilator-associated pneumonia in a trauma ICU. The Journal of trauma. 2006;61(1):122-129; discussion 129-130.
**26.** Salahuddin N, Zafar A, Sukhyani L, et al. Reducing ventilator-associated pneumonia rates through a staff education programme. The Journal of hospital infection. 2004;57(3):223-227.
**27.** Boyce JM, Pittet D. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control. 2002;51(Rr-16):1-45, quiz CE41-44.
**28.** Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet. 2000;356(9238):1307-1312.
**29.** Raad, II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America. 1994;15(4 Pt 1):231-238.
**30.** Parenti CM, Lederle FA, Impola CL, Peterson LR. Reduction of unnecessary intravenous catheter use. Internal medicine house staff participate in a successful quality improvement project. Archives of internal medicine. 1994;154(16):1829-1832.
**31.** Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. The American journal of medicine. 2005;118(1):11-18.
**32.** Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999;354(9193):1851-1858.
**33.** Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. Bmj. 2001;323(7316):773-776.

**34.** Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA : the journal of the American Medical Association. 2001;286(8):944-953.
**35.** Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. Annals of surgery. 1999;229(4):467-477.
**36.** Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. The New England journal of medicine. 2009;360(13):1283-1297.
**37.** Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. Archives of surgery. 1999;134(2):170-176.
**38.** Silvestri L, van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. The Journal of hospital infection. 2007;65(3):187-203.
**39.** Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. Critical care medicine. 2007;35(2):595-602.
**40.** Geffers C, Zuschneid I, Eckmanns T, Ruden H, Gastmeier P. The relationship between methodological trial quality and the effects of impregnated central venous catheters. Intensive care medicine. 2003;29(3):403-409.
**41.** Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. JAMA : the journal of the American Medical Association. 1999;281(3):261-267.
**42.** Cherif H, Landgren O, Konradsen HB, Kalin M, Bjorkholm M. Poor antibody response to pneumococcal polysaccharide vaccination suggests increased susceptibility to pneumococcal infection in splenectomized patients with hematological diseases. Vaccine. 2006;24(1):75-81.
**43.** Davies JM, Barnes R, Milligan D. Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. Clinical medicine. 2002;2(5):440-443.
**44.** Landgren O, Bjorkholm M, Konradsen HB, et al. A prospective study on antibody response to repeated vaccinations with pneumococcal capsular polysaccharide in splenectomized individuals with special reference to Hodgkin's lymphoma. Journal of internal medicine. 2004;255(6):664-673.
**45.** William BM, Thawani N, Sae-Tia S, Corazza GR. Hyposplenism: a comprehensive review. Part II: clinical manifestations, diagnosis, and management. Hematology. 2007;12(2):89-98.
**46.** Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive care medicine. 2007;33(6):970-977.
**47.** Knaus WA, Sun X, Nystrom O, Wagner DP. Evaluation of definitions for sepsis. Chest. 1992;101(6):1656-1662.
**48.** Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA : the journal of the American Medical Association. 2011;306(20):2248-2254.
**49.** Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. The Journal of infectious diseases. 1983;148(1):57-62.
**50.** Labelle A, Juang P, Reichley R, et al. The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment*. Critical care medicine. 2012;40(7):2016-2021.

**51.** Shorr AF, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infection: A distinct entity? Insights from a large U.S. database. Critical care medicine. 2006;34(10):2588-2595.
**52.** Jawad I, Luksic I, Rafnsson SB. Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. Journal of global health. 2012;2(1):010404.
**53.** Beale R, Reinhart K, Brunkhorst FM, et al. Promoting Global Research Excellence in Severe Sepsis (PROGRESS): lessons from an international sepsis registry. Infection. 2009;37(3):222-232.
**54.** Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2008;46(2):155-164.
**55.** Ziegler EJ, Fisher CJ, Jr., Sprung CL, et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group. The New England journal of medicine. 1991;324(7):429-436.
**56.** Fomsgaard A, Baek L, Fomsgaard JS, Engquist A. Preliminary study on treatment of septic shock patients with antilipopolysaccharide IgG from blood donors. Scandinavian journal of infectious diseases. 1989;21(6):697-708.
**57.** Gasparovic V, Gornik I, Ivanovic D. Sepsis syndrome in Croatian intensive care units: piloting a national comparative clinical database. Croatian medical journal. 2006;47(3):404-409.
**58.** Degoricija V, Sharma M, Legac A, Gradiser M, Sefer S, Vucicevic Z. Survival analysis of 314 episodes of sepsis in medical intensive care unit in university hospital: impact of intensive care unit performance and antimicrobial therapy. Croatian medical journal. 2006;47(3):385-397.
**59.** Remi Neviere M. Pathophysiology of sepsis. 2014; Post TW (Ed):http://www.uptodate.com. Accessed 14.04.2014
**60.** Barriere SL, Lowry SF. An overview of mortality risk prediction in sepsis. Critical care medicine. 1995;23(2):376-393.
**61.** van der Poll T, Lowry SF. Tumor necrosis factor in sepsis: mediator of multiple organ failure or essential part of host defense? Shock. 1995;3(1):1-12.
**62.** Riedemann NC, Guo RF, Ward PA. Novel strategies for the treatment of sepsis. Nature medicine. 2003;9(5):517-524.
**63.** Dellinger RP, Levy M, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. Intensive care medicine. 2013;39(2):165-228.
**64.** Fullerton JN, Price CL, Silvey NE, Brace SJ, Perkins GD. Is the Modified Early Warning Score (MEWS) superior to clinician judgement in detecting critical illness in the pre-hospital environment? Resuscitation. 2012;83(5):557-562.
**65.** Gardner-Thorpe J, Love N, Wrightson J, Walsh S, Keeling N. The value of Modified Early Warning Score (MEWS) in surgical in-patients: a prospective observational study. Annals of the Royal College of Surgeons of England. 2006;88(6):571-575.
**66.** Lee JR, Choi HR. [Validation of a modified early warning score to predict ICU transfer for patients with severe sepsis or septic shock on general wards]. Journal of Korean Academy of Nursing. 2014;44(2):219-227.
**67.** Avontuur JA, Biewenga M, Buijk SL, Kanhai KJ, Bruining HA. Pulmonary hypertension and reduced cardiac output during inhibition of nitric oxide synthesis in human septic shock. Shock. 1998;9(6):451-454.
**68.** Gofton TE, Young GB. Sepsis-associated encephalopathy. Nature reviews. Neurology. 2012;8(10):557-566.

**69.** Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. Brain : a journal of neurology. 1987;110 ( Pt 4):819-841.
**70.** Remi Neviere M. Sepsis and the systemic inflammatory response syndrome: Definitions, epidemiology, and prognosis. 2014; http://www.uptodate.com/. Accessed 05.06.2014, 2014.
**71.** Cerra FB. Multiple organ failure syndrome. Disease-a-month : DM. 1992;38(12):843-947.
**72.** Cerra FB. Metabolic manifestations of multiple systems organ failure. Critical care clinics. 1989;5(1):119-131.
**73.** Osterbur K, Mann FA, Kuroki K, DeClue A. Multiple Organ Dysfunction Syndrome in Humans and Animals. Journal of Veterinary Internal Medicine. 2014:n/a-n/a.
**74.** Boer KR, van Ruler O, van Emmerik AA, et al. Factors associated with posttraumatic stress symptoms in a prospective cohort of patients after abdominal sepsis: a nomogram. Intensive care medicine. 2008;34(4):664-674.
**75.** Mark A Kelley M. Predictive scoring systems in the intensive care unit. 2014; http://www.uptodate.com. Accessed 20.05.2014.
**76.** Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Critical care medicine. 1981;9(8):591-597.
**77.** Rapsang AG, Shyam DC. Scoring systems in the intensive care unit: A compendium. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2014;18(4):220-228.
**78.** Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Critical care medicine. 2009;37(5):1649-1654.
**79.** Hwang SY, Lee JH, Lee YH, Hong CK, Sung AJ, Choi YC. Comparison of the Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation II scoring system, and Trauma and Injury Severity Score method for predicting the outcomes of intensive care unit trauma patients. The American journal of emergency medicine. 2012;30(5):749-753.
**80.** Meyer AA, Messick WJ, Young P, et al. Prospective comparison of clinical judgment and APACHE II score in predicting the outcome in critically ill surgical patients. The Journal of trauma. 1992;32(6):747-753; discussion 753-744.
**81.** Alam FF, Mustafa AS, Khan ZU. Comparative evaluation of (1, 3)-beta-D-glucan, mannan and anti-mannan antibodies, and Candida species-specific snPCR in patients with candidemia. BMC infectious diseases. 2007;7:103.
**82.** Oliveri S, Trovato L, Betta P, Romeo MG, Nicoletti G. Experience with the Platelia Candida ELISA for the diagnosis of invasive candidosis in neonatal patients. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2008;14(4):391-393.
**83.** Sendid B, Poirot JL, Tabouret M, et al. Combined detection of mannanaemia and antimannan antibodies as a strategy for the diagnosis of systemic infection caused by pathogenic Candida species. Journal of medical microbiology. 2002;51(5):433-442.
**84.** Masterton RG. Antibiotic de-escalation. Critical care clinics. 2011;27(1):149-162.

## Biography:

Nikola Blajic, was born on November 18 in 1986 in Brussels, Belgium and raised in Germany where he completed high school in March 2006. His interest in medicine led him to do his social service in Germany as a paramedic the following year. Then he enrolled in 2007 at the Universite Libre de Brussels for his medical studies. Eventually he transferred to the Zagreb Medical School in 2008.

After he graduates in July 2014 he plans to complete an internship and the board medical exam in Zagreb in order to be licensed in Croatia.

Besides medicine he got a B-license as a personal trainer. His hobbies vary from making music and doing sports.