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FIGHT AGAINST SEPSIS>
Call to Action

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Fight against Sepsis Regional Programme Technical Group

REGIONE TOSCANA

FIGHT AGAINST SEPSIS > Call to Action
Vision, Strategy, Action

"Suspect sepsis when a different diagnosis is not already evident to you. Then, if something about the diagnostic pathway you initiated does not convince you, suspect it again."

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ABSTRACT > People are dying of sepsis in increasing numbers. Diagnosing sepsis is not at all easy. Most cases originate in the community and can be identified at the patient's home or at Emergecency Dept. (ED) Units. In fewer cases, sepsis occurs in the place of treatment. This document presents strategies for its recognition and treatment in the various contexts in which sepsis can occur, as well as for the wide-ranging prevention of this serious pathology and of the infections that cause it; the impact of inappropriate care on the patient and on the community are also described. Our efforts nevertheless form an expansive and continuing work in progress, with evolving definitions and strategies. Changes during the process are an integral part of the initial project, and so is keen attention, which must never waver.

PURPOSE > This document is based on the Surviving Sepsis Campaign guidelines and on evidence reported in the literature concerning microbiology, clinical care, human factors, quality and safety of care. It proposes a vision of the critical issues that sepsis brings with it to the healthcare system, a vision not attributable to a single disciplinary perspective but rather an expression of multiple viewpoints of team members. The document suggests and indicates approaches that are integrated on both a strategic-organisational level and in clinical-care practice.

Introduction

The healthcare system has changed and is changing. Many of these changes are generated by results achieved in the past, such as the increase in life expectancy, also thanks to the widespread use of antibiotics. Ageing results in increased fragility in our elderly population, which needs care and is vulnerable to infections, although even young and active persons are victims of sepsis. **Antimicrobial resistance (AMR)** and **healthcare-associated infections (HAI)** are the outcome of inappropriate use of antibiotics, not only in the elderly population but also in the paediatric age group, and of strategies that are no longer suitable for current issues. Suffice to think about the results achieved by transplant surgery, which may be completely negated by the occurrence of infections. Sepsis, a disease known for 3,000 years, breaks out in this evolving context. **Why then do we talk so much about it now?** What is new is certainly not sepsis, but the context in which it occurs: more than 1 million people in Europe are affected by it. Septic shock can kill nearly one in two patients [1], and not because today's sepsis is more aggressive than the disease described by Machiavelli 500 years ago, but because our current healthcare systems and treatment habits, and the high standards reached, have created new possibilities of survival, in which infections adapt in previously unknown ways. This document aims to provide possible and sustainable solutions, to raise questions and suggest concrete responses to current issues, following three directions:

1. **Expand the vision** - "Who are the patients who develop sepsis? Why do they develop it? How many die and what happens to those who survive?"
2. **Set an integrated strategy to manage uncertainty** - "To manage the diagnosis of infection, an approach based on the stratification of the sepsis risk and septic shock is necessary; an integration of new management activities (called stewardships), of diagnostics and of treatments is required. What are these stewardships and why do they create discontinuities with the previous models?"
3. **Act promptly** - "How to address the challenge of sepsis? If it could not be prevented, it must be treated."

Chapter 1 **EXPAND THE VISION** "How many and who are the patients who develop sepsis? Why do they develop it? How many die? What happens to those who survive?"	We expand the vision to understand the problem. Why are sepsis and infections mutually related? Who are the patients who develop sepsis? How many die and what happens to those who survive? Why is it complex to identify sepsis? What can we do to reduce the uncertainty? How can Community Care and the Local Emergency Services respond to sepsis, and what action can ED implement? This section contains useful information to understand why, in order to defeat sepsis, it is necessary to understand the infection and its most serious complications (namely: sepsis and septic shock). To do so, methods and tools must be applied to make healthcare professionals and the organisation aware of the infectious risk. We will try to understand why the actions we put in place would have a limited impact without Community Care and the Local Emergency Services.
Chapter 2 **INTEGRATED STRATEGY** "The three stewardships. What are these stewardships and why do they create discontinuities with the previous models?"	The infection identification and management tools, namely antimicrobial stewardship, diagnostic stewardship and sepsis stewardship, can become the constituent elements of a healthcare organisation that identifies the infection and manages it effectively, offering a sustainable and safer pathway for the patients being cared for. The model proposed introduces new possibilities for comparison and cooperation between the clinical setting and health risk management. Such new procedures require careful planning. To transform discontinuity into a change useful for patient safety, it is necessary to fully understand the three stewardship activities and the related benefits. The lack of coordination in the use of resources might generate the risk of increasing costs without an actual benefit for all patients. In this chapter we present the hexagonal model of integration between the three stewardships and the stratification of risks, designed to manage uncertainty and increase patient safety.
Chapter 3 **ACT PROMPTLY** "How to address the challenge of sepsis? If it could not be prevented, it must be treated: How?"	How to address the challenge of sepsis? If it could not be prevented, it must be treated. This chapter presents the bundles in the Surviving Sepsis Campaign guidelines and their practical adaptation in the "Sepsis Six" guidelines, the diagnostic and therapeutic actions to be initiated within the first hour of diagnosis in cases of septic shock, and as soon as possible in cases of sepsis. The risk factors to be included in clinical care reasoning, the severity scores based on the detection of vital signs to be used to monitor deterioration in a perspective of pathway and treatments introduced in each clinical care setting, are presented.

1 - Expand the Vision

2 - Integrated Action

3 - Act Promptly

Expand the Vision

This section contains useful information to understand why, in order to defeat sepsis, it is necessary to understand the infection and its most serious complications (namely: sepsis and septic shock). To do so, methods and tools must be applied to make healthcare professionals and the organisation aware of the infectious risk. We will try to understand why the actions we put in place would have a limited impact without Community Care and the Local Emergency Services.

1.1 What is sepsis?

"Throughout the world, sepsis is the last stage, unfortunately often fatal, of a course triggered by many infectious diseases. It occurs when our immune system - in fighting an infection - loses control and begins to damage tissues and organs: this can lead first to organ failure and then to death."

Sepsis is a syndrome with a critical timeline. Despite being harder to identify in the early phases, it is easily treated with timely diagnosis and appropriate treatment. In the advanced phases it is easier to recognise but more difficult to treat. There is no single diagnostic test that can diagnose sepsis and septic shock with certainty. Sepsis and septic shock are clinical syndromes, defined as a constellation of signs, symptoms and abnormalities identifiable with laboratory tests and specific pathophysiological changes (see 1.5).

The old definition - Why are SIRS criteria not useful for the diagnosis of sepsis?

Some clinicians often incorrectly associate sepsis with Systemic Inflammatory Response Syndrome (SIRS) criteria, which include temperature, heart and respiratory rate and white blood cell count, but which have proven difficult applying both in the clinical setting and in randomised clinical trials.

SIRS 1991 and old criteria for the diagnosis of SEPSIS [2]

Infection-induced Systemic Inflammatory Response Syndrome is defined by at least two of the following parameters:

- Temperature >38°C or <36°C

- Heart rate >90 bpm

- Respiratory rate >20 breaths per minute or CO2 partial pressure <32 mmHg

- White blood cell count >12,000/mL or <4,000/mL or >10% immature forms (band cells)

The use of the SIRS criteria plus infection would define a large percentage of patients with an uncomplicated infection as sepsis cases: for these patients the sepsis label seems either out of place or irrelevant. For example, many children with middle ear infections often satisfy two or three SIRS criteria (fever, tachycardia and leukocytosis); defining them as septic based on SIRS criteria would not have clinical significance, considering that many are treated at home with oral antibiotics. Furthermore, in a large number of patients, especially those for whom antibiotics have been started empirically, finding bacteria in the blood or in body fluids is often a problem: no pathogen is identified in about 30% of cases of presumed sepsis. In many cases, the infection is suspected radiologically or from other haematological findings. The old term septicaemia refers to sepsis with positive blood cultures; it is now an obsolete term. Blood cultures in sepsis can be negative, partly because some patients have been treated with antibiotics empirically before sampling, partly because bacteria do not need to circulate in the blood to induce sepsis.

The recent definition [3] describes sepsis as **life-threatening organ failure caused by a dysregulated host response to infection**. This definition encompasses a new concept, that of sepsis as a **medical emergency,** therefore as a syndrome, whose severity increases until death in a rapid passage of time: a concept that necessitates a profound change in community and hospital management.

The new definition of sepsis and the role of the immune system response> The new definition of sepsis and septic shock in 2016 [3] is based on the clinical reality described by easily obtainable physiological and laboratory parameters. What distinguishes sepsis from other infections, whether localised or not, is the **host response**, defined as dysfunctional, generalised and which contributes to the multiple alteration of organs and tissues, even if not directly involved in the infectious process; potentially, sepsis develops into septic shock. A rapid assessment of organ injury at the patient's bedside was proposed, using easily obtainable clinical measurements. The early evidence of septic shock manifests in tissue hypoperfusion with resulting dysfunction and possible organ failure, which occurs simultaneously with or close to the time of the inflammatory event. The term **septic shock** is defined as a state in which sepsis is associated with cardiovascular dysfunction that manifests with persistent hypotension despite adequate fluid administration - this rules out the possibility of volume depletion as the cause of hypotension. Hypotension in turn is defined as the need for vasopressors to maintain average blood pressure >65 mmHg and the plasma lactate level <2 mmol/L. An increased serum lactate level is a clear sign of tissue hypoperfusion and septic shock, and is useful for early diagnosis. The usual cut-off value for an abnormal lactate level is >2 mmol/L (increased to 4 mmol/L for inclusion in clinical trials).

The new definition stems from the third international consensus conference on the definition of Sepsis and Septic Shock (**SEPSIS-3**), and considers the infection as an interaction between a host and a pathogen that induces a response (local or systemic) in the host.

SEPSIS: life-threatening organ dysfunction caused by a dysregulated host response to infection.

SEPTIC SHOCK: a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

NOTE. Organ dysfunction can appear from the onset far from the infection site. Septic shock is operationally defined as requiring vasopressor therapy to maintain an average blood pressure >65 mmHg, and as the presence of increased plasma lactate level (>2 mmol/L)

The WHO resolution to combat sepsis > Sepsis is a complication of infection. Acting when sepsis occurs and is full-blown is more complex and difficult than acting when it can be prevented. Preventing sepsis means preventing infection through the management of risk factors that make it possible to classify the infection in the context (healthcare-related infections and lifestyles) and response of the host. It is, therefore, necessary to consider both the patient's risk factors (fragility, comorbidity) and clinical history (recent surgery, immune response). The World Health Assembly WHA 70.7 resolution of 29 May 2017 urges Member States to act "for the improvement of sepsis prevention, diagnosis and clinical management" [4]. The resolution closely links, on the one hand, the prevention of healthcare-associated infections, the correct use of antibiotics and the training of healthcare professionals on the risk of progression from infections to sepsis and, on the other hand, clinical management, i.e., access to early diagnosis and efficient services. The response to sepsis can be obtained thanks to an integrated approach that involves the various roles (see Table 4) in relation to the different *settings*.

1.2 Why are sepsis and infections mutually related?

"What is an infection? Why can an infection generate an abnormal response of our immune system? Why does the infection lead to sepsis in some cases, and remain a localised infection in others? The infection, its early diagnosis and timely treatment remain a central point"

Sepsis is a pathological condition that always has an infection as its origin. Any infection, whether contracted in the community or in a hospital or healthcare service, can generate an abnormal host response. The infection, its early diagnosis and timely treatment are, therefore, a central point. The infection is a complex disease in which the **environment** and **human being** confront each other and clash. Microbes live in the environment that surrounds us, in plants and in animals, but also inside us and on us. They always live in symbiosis with us, but sometimes in conflict with our body. So, we share the environment in which we live with microbes, with all their qualitative and quantitative variability.

The 4 combined theories of infection >

1) The **germ theory** tells us that there can be no infection without the presence of microbes. This criterion is central: the knowledge of microbes and what their ability to attack might be is a task for Clinical Microbiology and its diagnostic methods, both classic and technologically advanced.

2) The environment can also influence the infection. The **ecological theory** of infections studies the environmental variation and can help us understand other risk factors related to the environment, which affect the host (us). Our response to infection changes depending on whether we live, eat, drink, sleep in a cold, warm, humid or unhealthy environment.

3) In the human host, we have to understand the status of the personal innate and adaptive immune response to the aggression of microbes. Immunological monitoring, thus far possible in all the components of immunity (including genetic and epigenetic elements), and the **immunological theory** - immunological response and tolerance - will allow us to understand other risk factors related precisely to the nature of the host response.

4) Lastly, we must take into consideration, always on the host side, the **genetic theory** and, therefore, all the errors and possible risks of the genetically coded immune system, in both its innate and adaptive part. A human being exposed to microbes may have an infection, but its manifestation will be unique and the result of interaction of the factors described by these 4 theories: two related to the environment (germ theory and environmental theory), and two intrinsic to the host (immunological theory and genetic theory). Hence, the great phenotypic variability of the infection and, ultimately, of its most serious complications: sepsis and septic shock.

The infection can be difficult to diagnose because it can be asymptomatic and/or localised, but suddenly, or within a few hours - maybe three or six at most - it can give rise to systemic inflammation (SIRS - Systemic Inflammatory Response Syndrome), and generate first dysfunction and then failure of the vital organs, leading to septic shock and death. The careful study of all the risk factors that interact in the infectious process, expressed by the 4 theories (see Table 1), can help us to predict, and perhaps to preempt, the dangerous slippery slope towards death.

Environment	**Infectious risk factors related to the presence of microbes** Colonisation, altered microbiota, contamination, home or hospital working environment contaminated in air, water, surfaces	**Infectious risk factors related to environmental conditions** Unhealthy environment, economic inequalities, nutrition, alcoholism, drug use
Host	**Infectious risk factors related to immune response** Immunoparalysis, immunodeficiency, immunosenescence	**Infectious risk factors related to genetic coding of the immune response** Expression of genetic immunity components

Table 1 - The risk factors according to the 4 theories of infection

To be able to prevent an infection or at least to treat it early, appropriately and adequately, it is necessary to learn how we can identify the risks present and manifest in the patient's history, and then make a rapid diagnosis of infection. To **stratify the risk,** we propose an approach that integrates the use of severity scores (early warning systems) with some risk scores based on both biomarkers and on clinical evaluation. With the help of ergonomics and of the human factor, we suggest a decentralised management model that makes it possible, on the one hand, to stratify the risk that patients have according to the 4 theories of infection and, on the other hand, to shift in the shortest possible time from empirical antibiotic therapy to targeted therapy

(so as to reduce the impact of antibiotic resistance). We, therefore, recommend the development of a practical strategy that enables us to act in the complexity and narrowness of time (a few hours), and to be able to diagnose sepsis and septic shock early, where it is not possible to organise a complete logical-algorithmic procedure for each case of suspected sepsis.

1.3 How many and who are the patients affected by sepsis in Tuscany?

"Who are the patients who develop sepsis? How and when do they arrive in hospital? How many die?"

In Tuscany, over 15,000 cases of sepsis or septic shock are expected each year. This figure is calculated by referring to the estimates of incidence present in the literature, which vary between 300-400 cases per 100,000 inhabitants, currently revised upwards [5]. Overall, **hospitalisations** for *sepsis* or *septic shock* **in Tuscany in 2017 were 9,168**, marking a 33% increase, compared to 2012. This pathology, therefore, affects about 1.8% of patients hospitalised in Tuscany, with an incidence of 261 per 100,000 inhabitants (still below the expected number). Patients who do not resort to hospital treatment or who died at home must be added to this number. The number of ED visits for this pathology is also constantly increasing: in 2017 there were 6,116 recorded cases of sepsis or septic shock. Around 300 of these patients, or 5%, die during the time in the ED. This trend can be explained by population ageing and the increasing complexity of patients hospitalised in Tuscan hospitals. In fact, several studies show that the incidence of sepsis is higher in the elderly population. However, it should be highlighted that this increase is presumably also attributable to a greater focus on diagnosis, and a more correct coding of this pathology in the administrative databases: since 2012, hospitalisations in which a diagnosis code specifically indicates the presence of sepsis or septic shock have almost doubled. Over 80% of patients with sepsis arrive at the hospital from the ED and are urgently hospitalised for a medical condition; 50% are over 80 years old. These patients stay in hospital for an average of 12 days. Only 17% of hospitalisations for sepsis are surgical, and in these cases the duration of hospitalisation reaches 28 days. Overall, 10% of these patients are hospitalised directly in Intensive Care, while 1 in 4 pass through it during hospitalisation. The most frequently reported infections in the hospital discharge form (SDO) for these patients are in the urinary and respiratory tract, while the most frequent organ dysfunctions are renal and respiratory failure, as indicated by the use of assisted ventilation. It is interesting to note that between 30-40 cases of sepsis are observed every year in infants under the age of one year (about 1 per 1,000 births). The percentage of hospitalisations with which a positive blood culture is associated is 20%, a figure confirmed in the literature. **The most frequent bacterium is *Escherichia coli* (15% of cases), followed by *Staphylococcus epidermidis* (13%), which in half the cases occurs in association with other bacteria.** One in three patients dies during hospitalisation, and this share is higher among surgical admissions, with a mortality rate of 38%. This figure has been substantially stable since 2014. 20% of patients discharged alive are readmitted to hospital within 30 days of discharge. In half the cases, the new hospitalisation is attributable to an infection, and 1 out of every 5 cases is due to sepsis. An immediate way to evaluate the number of sepsis cases is the count of hospitalisations for this pathology: in 2016 there were 8,000 total hospitalisations, in 2018 there were 9,000. Although increasing, if we consider the new coding rules introduced by the Tuscan Regional Administration (Regional Council Decree 773 of 09-07-2018) and aligned with the new definitions of sepsis, the explicit coding of sepsis and septic shock still underestimates the expected figure.

SEPSIS CLINICAL CRITERIA	SEPTIC SHOCK CLINICAL CRITERIA
INFECTION (certain or suspected)	INFECTION (certain or suspected)
≥2 SOFA SCORE POINTS* (above baseline SOFA)	Requirement for vasopressors to maintain average blood pressure ≥65 mmHg Serum lactate levels >2 mmol/L despite adequate fluid resuscitation

Table 2 – Clinical criteria for coding sepsis according to the new definitions (*see Chap 3 – Instruments)

1.4 What happens to those who survive sepsis?

In Tuscany, in 2016, one in five patients requires a new hospitalisation for sepsis within 30 days of discharge. Furthermore, 4.8% are sometimes diagnosed with sepsis again.
The percentage is much lower if hospitalisations for surgery are considered separately (4% of readmissions). After sepsis, one in 5 patients requires a new hospitalisation within 30 days of discharge. This ratio does not seem to vary with the patient's age or even with their socio-economic conditions, while the trend of the hospitalisation stay duration index is increasing. Every year, around 19 million individuals develop sepsis [6], 14 million of whom survive with a variable prognosis: about half of them have a complete or almost complete recovery, 1/3 die in the current year and 1/6 have persistent severe disturbances [12,13], including:

- 1-2 new functional limitations (e.g., inability to wash or dress independently);
- Increase (from 6.1% before hospitalisation to 16.7% after hospitalisation) in the prevalence of moderate-severe cognitive disorders (poor memory, concentration, decision-making skills) [9];
- High prevalence of mental health problems, such as anxiety (32% of patients), depression (29%) and post-traumatic stress disorder (44%) [10].

The most common symptoms that accompany a patient who has survived a septic event include:

- Muscle weakness
- Asthenia
- Difficulty swallowing
- Difficulty reasoning clearly
- Poor concentration
- Poor memory
- Sleep disorders
- Sadness
- Anxiety

Further disorders are added to these problems in the period (weeks/months) following hospitalisation for sepsis: greater risk of contracting further infections, heart or kidney failure. In fact, about 40% of patients require subsequent hospitalisation in the 3 months after sepsis, for events potentially treatable even at a community level, such as recurrent infections (11.9%), cardiovascular events (5.5%) and acute renal failure (3.3%) [11].

The reasons for deteriorating health after sepsis are multifactorial, and include:

- accelerated progression of previouly existing chronic conditions;
- residual organ damage;
- altered immune system. The complications that occur after discharge from hospital for sepsis are not entirely clear, but include various factors [12]: pre-sepsis health status, characteristics of the acute septic episode (severity of the infection, host response to infection), and quality of hospital treatment (timeliness in the sepsis treatment, prevention of treatment-related damage). Although there is little clinical evidence to support a specific rehabilitation treatment following discharge after hospitalisation for sepsis [13], experts recommend the use of physiotherapy to improve exercise and the autonomous performance of common daily activities. These recommendations are supported by an observational study involving 30,000 sepsis survivors, in which rehabilitation in the 3 months following the septic event was associated with a lower risk of mortality at 10 years, compared to the control groups [14]. In conclusion, in the months following discharge from hospitalisation for sepsis, patient management should focus on [15]:
- identifying new physical, mental and cognitive problems and initiating appropriate treatment;
- reviewing and adjusting long-term drug treatments (adjust drug dosages according to the patient's body weight loss after sepsis, or reduced kidney function; consider vaccination to reduce the risk of infectious events);
- assessing the treatable conditions that commonly result from hospitalisation, such as infections, heart or kidney failure;
- promoting rehabilitation programmes (physiotherapy, occupational therapy, logotherapy) and supportive therapies (support network for patients who have survived critical illnesses).
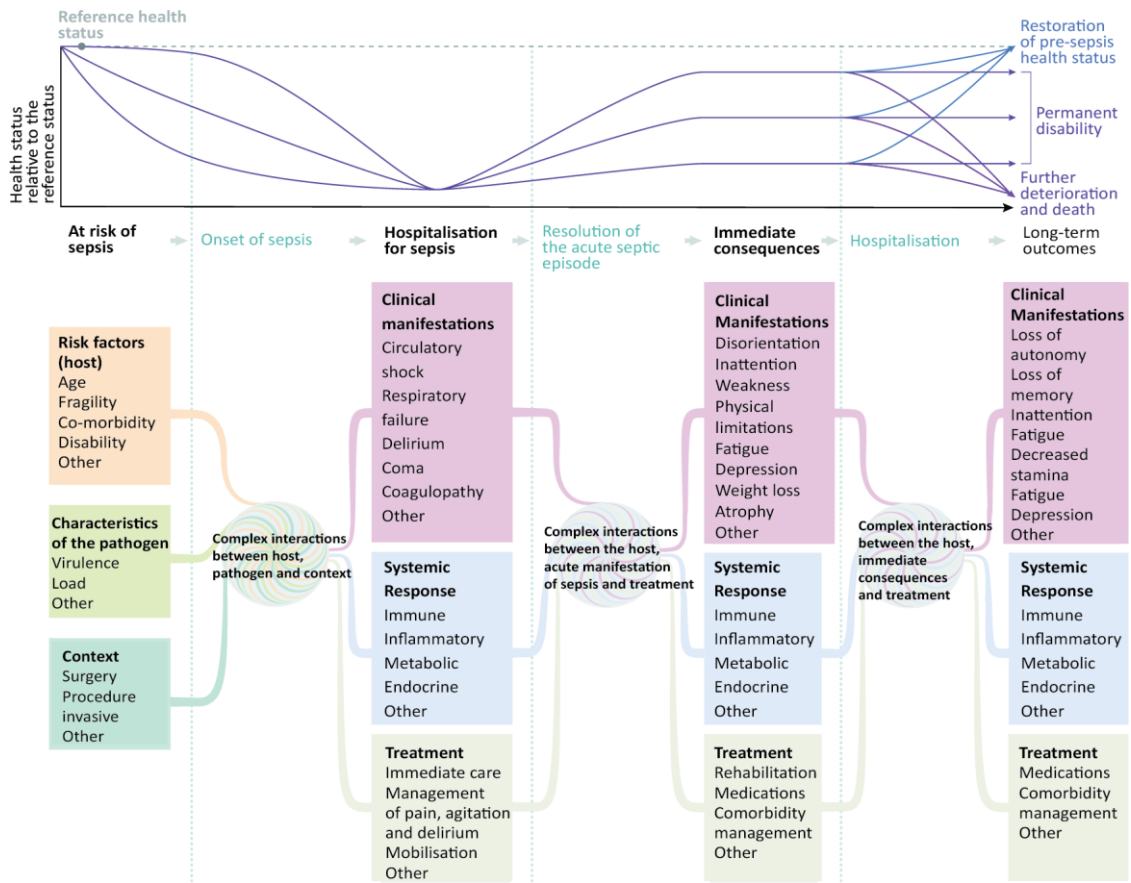
Fig. 1 – Post-sepsis: conceptual model representing the network of interactions that determine a patient's clinical progress and long-term outcomes after sepsis [15] (freely interpreted)

1.5 Entering uncertainty (with a plan) to manage sepsis

"The uncertainty in the diagnosis of sepsis can be defined as the lack of certain information or the presence of ambiguous information to perform a task"

In sepsis, the uncertainty arises from the difficulty of diagnosing the infection. In ergonomics, uncertainty is the lack of certain information to perform a task or the presence of ambiguous information to perform it [16]. If the uncertainty is not addressed and we simply avoid it, or manage it with inflexible models, then uncertain situations can turn into risks. If these risks can no longer be contained, they end up becoming fatalities, which could have been avoided. In the specific case, the uncertainty is amplified by the fact that sepsis is a pathology with a critical timeline.

What is certain in the management of sepsis:

- sepsis is a time-dependent pathology. The sooner it is identified, the better the chances of treating it effectively. The more time lost, the higher the chance of death (up to having only a 1 in 2 chance of survival);
- sepsis can be treated with the administration of antibiotics and fluids within the first 3 hours of diagnosis (see Chapter 3);
- sepsis develops in patients who have an infection;
- the improvement in mortality outcomes is attributable to early recognition and better adherence to the guidelines;
- antibiotic resistance and healthcare-related infections increase the chance of an at-risk patient developing sepsis.

What is a source of uncertainty in the management of sepsis:

- **inadequate diagnosis of sepsis:** the symptoms of sepsis are non-specific. Patients who develop sepsis have a reduced ability to fight infection, due to variable conditions (depending on individual factors, linked to the immune system, health conditions, the environment and the microorganism responsible for the infection);
- **poor identification ability**: patients with sepsis or with vague symptoms of sepsis are more likely to die, if they are not recognised as such and not classified within an early warning score (EWS)-based alert system;
- **poor cooperative capacity:** the appropriate diagnostic and therapeutic actions to manage sepsis require the activation of professional, technological and structural resources located in different sectors of the health organisation;
- **incomplete planning**: if a course of action has not been defined, therefore the resources that can be activated (human, technological and structural) have not been identified, the roles and responsibilities, times and procedures for activating the pathway and transitioning the information and the patient from one phase to another, are not known;
- **failure to verify**: if a system for monitoring the results and use of human, technological and diagnostic resources has not been defined.

The first source of uncertainty relates to the pathology, the rest depends on the healthcare organisation. The improvement in mortality outcomes is attributable to early recognition and better adherence to the guidelines [17] or to the organisation's response capacity. Our increased understanding of the pathogenesis of sepsis has generally failed to improve the chance of survival. It follows that – in the case of sepsis – if we can design the activity so that uncertainty is limited to the part deriving from the syndrome alone, lives can be saved. In the ergonomics of complex systems, the strategy to reduce the effect of uncertainty is to provide resources locally so as to manage the uncertainty before failure to manage becomes a risk, and ensure a result from effective communication between decision-making levels. Healthcare work, as in other complex sectors, is based on three types of resources interacting with each other: human resources, technological and structural resources (hardware), and cultural resources (software). A solution that focuses on improving only one aspect of the clinical management of sepsis, without considering how the service interacts with the rest of the hospital and of the healthcare system, does not reduce the possibility of error, even while increasing the efficiency of the single service.

For example, a medical-nursing team at the ED [Emergency Department] can quickly identify a sepsis originating from a urinary tract infection. However, the treatment may not be effective if either the times and procedures of communication for the activation of the infectious diseases, microbiological and surgical consultations have not been defined before the therapy regimens - i.e., the interaction between different resources. If we use the perspective of system ergonomics [18], collaboration between professionals is a way to enter uncertainty with a plan [16]. Nobody can be of help alone, but whoever joins others at the right time can. Below (Table 4) we propose a matrix where the main organisational functions are located in the clinical care settings in which the Local Emergency Medical Service and Community Care are included.

Components of the activity in the organisation systems		
1) Healthcare professionals	2) Technologies and Structures	3) Training, Procedures and Routine
They are the human component of the system, the holders of skills and of a personal communicative-relational, cognitive and emotional style. The flexible component that adapts by interacting with other parts of the system.	They are the machines, tools, equipment and materials, that is, the physical components of the system.	It is the culture of the organisation, understood as both declared values and implicit culture. They are the rules and procedures, the customs, the work plans, the adaptation strategies put in place to manage the organisation of work and routine activities.

Table 3 – Components of the activity according to ergonomics and human factors

Ergonomics and Human Factors > Ergonomics (literally: study of work) conceives human activity as a set of interactions between healthcare professionals and healthcare professionals, between healthcare professionals and tools, and between healthcare professionals and organisational structure. The study of human factors and ergonomics is the core discipline of patient safety. The work of healthcare professionals is influenced by tradition and culture, by the organisational system and by the instruments used. Over time, the healthcare organisation has developed ways of responding to and tolerating external forces, which on the one hand create solidity but on the other hand can disperse energy, instead of focusing it. In the case of the fight against sepsis, infections and antibiotic resistance, the contribution of system ergonomics is particularly relevant [19] because it can help more specialties to coordinate their work to reduce the degree of uncertainty and increase their clinical response capacity. However, new problems often require new ways of thinking and doing, which arise not only from learning from mistakes but are developed by individual professional experience and team work opportunities. The ability to redesign with a multidisciplinary approach is one of the fundamental characteristics of ergonomics and of human factors.

Functions	Community Care	Local Emergency Medical Service	ED/First AID	Medical Area	Obstetrics	Surgical Area	Intensive Care
Suspected identification of sepsis/septic shock	X	X	X	X	X	X	
Diagnosis and classification			X	X	X	X	X
Treatment			X	X	X	X	X
Follow-up	X			X	X		X
Rehabilitation	X						

Table 4 – Matrix of sepsis pathway of clinical care functions with respect to clinical care settings

1.6 What can the General Practitioner do to identify sepsis in the home?

"First of all, it is useful to ask: 'could it be sepsis?' for all those patients who present signs or symptoms of infection, even non-specific and non-localised"

According to British NHS estimates, 70% [20] of sepsis cases occur outside the hospital, and it is conceivable that the first contact of the patient at risk of sepsis or with sepsis is with Local Emergency Service healthcare professionals, consultants and General Practitioners. The role of General Practitioners and paediatricians in the timely identification of the sepsis patient is based on the systematic use of a simple and standardised assessment procedure that assigns a high, high-moderate, or low risk level (risk stratification), with consequent

response actions ranging from the timely activation of hospital intervention to maintenance in the local community with or without antibiotic therapy.

The following is a procedure adapted from the NICE guidelines. First of all, it is useful to ask "**could it be sepsis?**" for all those patients who present signs or symptoms of infection, even non-specific and non-localised (e.g., generalised malaise) even without fever, with particular attention also to changes in behaviour or mood, both in the negative sense (drowsiness, etc.) and positive sense (agitation, restlessness, etc.) manifested by the patient and/or reported by the *caregivers* or family members. Further attention should be paid in the event that an accurate history (e.g., language barriers or communication problems) cannot be collected. Through a **telephone consultation** using **qSOFA or clinical elements of the risk assessment**, it is possible to identify patients at risk of sepsis who need an urgent home visit (Table 5).

GP [Community Care] instruments: clinical evaluation at home with the search for conditions that increase the risk of sepsis
Age: <1 year or >75 years, or very fragile subjects
Immune system disorders caused by comorbidities or medications: immune deficiencies (e.g., diabetes mellitus, sickle cell anaemia, splenectomy), treatment with chemotherapy or immunosuppressants, prolonged treatment with corticosteroids
Surgery or trauma or other invasive procedures in the past 6 weeks
Non-intact skin (e.g., cuts, burns, blisters, skin infections)
Injection drug use
Permanent catheters
Women who are pregnant or who have given birth or had an abortion in the last 6 weeks, particularly if they: have gestational diabetes, diabetes mellitus or other comorbidities, or have had Caesarean section, use of forceps, emptying and revision of the cavity, prolonged rupture of the membranes, prolonged, current or previous contacts with subjects with group A streptococcal infections (e.g., scarlet fever), vaginal bleeding or foul-smelling vaginal discharge
Infants: maternal colonisation by beta-haemolytic group B streptococcus (GBS), bacteriuria or infection in pregnancy, GBS infection in previous birth, premature rupture of membranes, spontaneous preterm birth ≤37 weeks, preterm birth in suspected or confirmed membrane rupture for ≥18 hours, fever ≥38°C during childbirth or suspected or confirmed chorioamnionitis, suspected or confirmed infection in another infant in multiple pregnancy, parenteral antibiotic therapy to the mother in the 24 hours before or after childbirth for suspected or confirmed invasive bacterial infection.

Table 5 - GM instruments: conditions that increase the risk of sepsis in the home

The evaluation of subjects with possible infection involves the analysis of:

A. focus of infection (pulmonary, urogenital and abdominal);
B. conditions that increase the risk of sepsis;
C. signs or symptoms that could cause a clinical suspicion (e.g., unusual behaviour or disorder of the cardiovascular or respiratory system).

If sepsis is suspected: use a checklist to stratify the risk (see Table 6).
If neutropenic sepsis is suspected in patients on antiblastic therapy: request an immediate specialist evaluation.
It is important to carry out these three activities at the patient's home:

1. check body temperature, heart rate, respiratory rate, blood pressure, consciousness level, O2 saturation;

2. examine skin complexion (mottled or bruised appearance), peripheral or perioral cyanosis, non-blanching rash, skin integrity, presence of petechiae;

3. note the patient's urination quantity and frequency in the last 18 hours.

GP instruments: clinical evaluation at home and stratification of sepsis risk		
	High Risk	Moderate Risk
Level of consciousness	Evidently Altered	Altered
Respiratory rate	≥25 SaO2 92 or 88 (COPD)	21-24
Heart rate	≥130	91-129
	anuria ≥18 hours	anuria 12-18 hours
	0.5 mL/kg urine\hour	0.5-1 mL/kg urine\hour
Blood Pressure	systolic ≤90 mmHg or systolic 40 mmHg compared to normal	systolic 91-100 mmHg
Skin	Mottled or bruised Perioral or peripheral cyanosis Non-blanching rash	signs of infection, surgical wounds, or trauma, or pressure ulcers
Temperature (may be non-indicative)	>38°C <36°C (but also normal)	

Table 6 - GM instruments: clinical evaluation at home of conditions that increase the risk of sepsis

After the evaluation, the high risk patient will be hospitalised by contacting the emergency medical service according to the sepsis protocol (see following section); the moderate risk patient (except those under the age of 17 or immunosuppressed) or the low risk patient will be kept at home and re-evaluated respectively within 24-48 hours or 48-72 hours after having established reasoned empirical antibiotic therapy and started the search for the pathogen with determination of the antibiogram for possible targeted antibiotic therapy.

1.7 What can the Local Emergency Services do to identify sepsis?

"The mission of the local emergency-urgencyservice systems is to reduce mortality and disability. Hence the need to prepare instruments to stratify the risk and diagnose sepsis at an early stage."

The mission of the local emergency-urgency service systems is to reduce mortality and disability. Hence the need to prepare instruments to stratify the risk and diagnose sepsis at an early stage. We have described how, in order to diagnose sepsis, it is important to promptly identify the interaction between infection and organ failure. To define organ dysfunction, the authors (see detailed study box 4) recommend using the **Sequential Organ Failure Assessment score** (SOFA see - 3.2.2-3), or a scoring system aimed at determining the extent of a patient's organ function. However, this score is difficult to apply in the pre-hospital and triage phase of care, as it requires diagnostic and laboratory tests. The authors, therefore, propose the use of an even more simplified and rapid scale, which is particularly suitable for the needs of the patient's pre-hospital management: it is the "quick-SOFA Score" (abbreviated as "**qSOFA**").

It is an instrument (see 3.2.2 - 1) designed for the rapid identification - in the first phase of management - of patients with suspected infection at risk of negative evolution (death or prolonged hospitalisation in resuscitation).

Emergency service instruments: stratification of the risk of sepsis in the Local Emergency Medical Service - qSOFA	
Respiratory rate ≥22 breaths/min	Yes/No
Systolic blood pressure ≤100 mmHg	Yes/No
Alteration of the state of consciousness (GCS <13 AVPU score in *Verbal* or worse)	Yes/No
The qSOFA is defined as "positive" if at least two of the above criteria are met	

Table 7 - Instruments for the Local Medical Emergency Service: qSOFA for clinical evaluation of the sepsis

In the case of the Local Emergency Service, some criteria must be identified from the **telephone triage** phase for early identification of patients with sepsis or sepsis risk. If a body temperature >38°C is reported during the telephone interview, it should be assessed whether this is associated with 1) unconscious patient 2) tachypnoea. In the event of at least one of the aforementioned items being positive, a "red sepsis" ambulance dispatch code will be assigned. Once the team has arrived at the location and taken steps to detect the vital signs, the qSOFA score can be assessed and, if at least two of the criteria evaluated are positive, the red sepsis code is confirmed and the ED triage service will be alerted.

At this point the actions to be taken include:

Insertion of a large calibre venous access	Fluid infusion*	Administration of O2 therapy
Additional actions. We recommend the definition of shared standards for communication between the Medical Emergency Service contact point and the ED [Emergency Department] according to the SBAR (*Situation Background Assessment Recommendation*) method		

Table 8 - Instruments for the Local Emergency Medical Service: immediate treatment for suspected sepsis* see specific section in Chapter 3.7

1.8 What can the ED team do to manage sepsis?

"One of the main duties of emergency-urgency medicine healthcare professionals is rapid recognition, and timely and adequate treatment of the critical (or potentially critical) patient. Among time-dependent diseases, sepsis is the most difficult to identify. Continuous teamwork is, therefore, necessary, as well as having easy-to-use tools and adequate organisation"

The early identification of patients with sepsis and the timely start of adequate treatment have a significant impact on survival and associated morbidity. The healthcare staff of all hospitalisation and EDs must know the main clinical features of sepsis (epidemiology, presentation, etc.), and be able to recognise and identify the initial manifestations. The Surviving Sepsis Campaign has repeatedly stressed that the "zero" time for the diagnosis of sepsis is the triage: the literature shows that missed identification has a strong impact on the patient's survival and on the possibility of employing appropriate strategies at appropriate times; it is, therefore, necessary to provide the triage nurses with tools for rapid identification of these patients.

1.8.1 Organisational and structural elements of the First Aid model:
role of the triage nurse, high intensity unit nurse and doctor

The First Aid model for homogeneous care pathways (Tuscan Regional Council Decree 806 of 24-07-2017) introduces a new First Aid model.

The course of action chosen represents the result of combining several aspects: "clinical conditions and evolutionary risk", "resources", "care needs". The objectives of the model are:

- reception of the patient according to clinical need and complexity of care (Table 8);
- integrated priorities and complexity to direct the patient to the appropriate pathway already during the triage stage, and thereby streamline procedures at the ED.

In order to achieve these objectives, a numerical coding is applied where 1 is the high priority code and 5 is the low priority code (Table 9).

	TYPE OF TREATMENT PATHWAY BY COMPLEXITY		
	high	intermediate	low
Clinical conditions and evolutive risk	Absence of a vital function or need for mechanical/drug support for at least one vital function	Need for rapid diagnostic-therapeutic intervention	Walking patients and/or those with reduced care needs
Resources	Maximum and immediate availability of multiple type 1 resources	Maximum availability of multiple type 1 resources with different timings	Up to a maximum of two type 1 resources
Care needs	Maximum care complexity	High care complexity	Medium/Low care complexity
Activity line	High complexity	Medium complexity	Low complexity

Table 9 - ED reorganisation: dimensions that determine the choice of treatment pathways

TRIAGE: priority coding, definition and maximum waiting times			
Code	Type	Detailed definition	Maximum waiting time for access
1	EMERGENCY	Interruption or impairment of one or more vital functions	IMMEDIATE
2	NONDEFERRABLE EMERGENCY	a) Risk of impairment of vital functions b) Stable condition with evolutive risk	WITHIN 15 MINUTES
3	DEFERRABLE EMERGENCY	Stable condition without evolutive risk with distress and effect on the general status that usually requires more than two Type 1 resources	WITHIN 60 MINUTES
4	MINOR EMERGENCY	Stable condition without evolutive risk that usually requires up to two Type 1 resources	WITHIN 120 MINUTES
5	NON-URGENCY	Stable condition without evolutive risk, non-urgent or of minimal clinical relevance, that usually does not require Type 2 resources	WITHIN 240 MINUTES

Table 10 - First Aid-TRIAGE priority codes

First Aid: the role of the triage nurse in identifying the patient at risk of sepsis (time 0)

Instruments for the triage nurse
Triage decisional algorithm
Shock Index ratio between HR/SBP [Systolic Blood Pressure] (see - 3.2.2 - 2)
Quick SOFA Score (suspected organ failure) (see - 3.2.2 - 1)

Table 11 - First Aid-TRIAGE instruments

Patients with suspected sepsis should be assigned a high priority code to prevent valuable time from being lost while waiting for the medical evaluation. The algorithm for suspected infection has been included in the new triage algorithms with the following objectives:

- early identification of the patient with suspected infection and correct attribution of the numeric priority code through the use of precise instruments;
- activation of the Sepsis Pathway within the DEA High Intensity area;
- awareness and sharing between nurses to be an integral part of teamwork.

The algorithm takes into account alarm elements and risk factors (for multidrug-resistant bacteria, immunosuppression, etc.).

Alarm indicators in the febrile patient
Neck stiffness
Photophobia
Headache
Clouded sensorium
Petechiae
Haemoptysis

Table 12 - Alarm indicators in the febrile patient

Risk factors for sepsis at triage
Immunodepression, extensive burn, chronic ethylism, drug abuse
Presence of Device (CVC, drainage, permanent CV)
Recent surgery, trauma or invasive procedure (within 6 weeks)
Patients <1 year and >75 years "fragile"

Table 13 - Risk factors for sepsis at triage - see also Table 4

The "type 1 resources" include diagnostic, radiological and laboratory tests, specialist consultations and all other services related to a higher level of complexity and which require an increase in the patient's length of stay in the ED. Conversely, "type 2 resources" are considered to be all activities of lesser complexity or performed routinely in the ED, which do not determine organisational variability in terms of significant lengthening of the stay in the ED - (see Table 2 Page 6 Tuscan Regional Council Decree 806 of 24-07-2017).

Depending on the type of presentation, the patient with sepsis will have a priority code 1 or 2 and will be assigned to the high intensity area of the Emergency Department.

MANAGEMENT OF PATIENTS WITH SEPSIS and SEPTIC SHOCK AT THE ED FROM 1st TO 3rd hour as of identification at TRIAGE			
Activity	Healthcare professionals (liveware)	Instruments and Structures (hardware)	Rules, practices, operating procedures (software)
Immediate management of patients with sepsis and septic shock	The triage and ED healthcare professionals (triage nurse, high intensity unit nurse and ED doctors) know the tasks to be carried out according to the sepsis six model (see 3.1) for which they are adequately trained (simulation - training on the job)	Environment equipped for patient treatment (ED high intensity zone). Test panel definition - sepsis panel *blood count with formula, coagulation (PT, PTT and possibly fibrinogen), creatinine, urea, blood glucose and serum electrolytes, total and direct bilirubin, AST, ALT, LDH, PCR, procalcitonin, troponin.*	Shared algorithms and protocols with the following objectives: application of the first interventions of the bundle independently by the nursing staff; immediate activation of the First Aid doctor - following coded alerts; sharing of protocols with the surgical area for control of the infection site.

Table 14 - Integrated activity for DEA - Surgery

ED: the high intensity unit nurse in the management of the patient with sepsis and septic shock (1-3 hours)

Monitors the patient: electrocardiogram, non-invasive blood pressure, oxygen saturation, respiratory rate.
Places 2 large calibre venous accesses. (IV)
Collects the "sepsis panel" of laboratory tests: blood count with formula, coagulation (PT, PTT and possibly fibrinogen), creatinine, urea, blood glucose and serum electrolytes, total and direct bilirubin, AST, ALT, LDH, PCR, procalcitonin, troponin.
Carries out blood gas analyses for the evaluation of blood lactates. Administers O2.
Collects blood for culture tests (subject to doctor's agreement) within 45 minutes of admission: 2 sets of blood for culture tests must be taken (one set consists of a bottle for aerobic germs and one for anaerobes) following the procedures provided for by standard procedures, and at a 20-minute interval, from two different venous accesses, or a set from a central venous catheter, if present for >48 hours.
Places bladder catheter (subject to doctor's agreement) for hourly diuresis monitoring.

ED: the high intensity unit doctor (1-3 hours)

Ensures that the lactates have been measured and that blood has been collected for culture tests.
Administers fluids (crystalloids) 20-30 mL/kg as a bolus and evaluates their response: the volume replenishment *fluid challenge* treatment must be implemented in patients with hypotension and/or signs of organ hypoperfusion (increase in lactates, oliguria, etc.) according to the recommendations (quantity, infusion times - see Chap 3.7). Bolus administration of 500 mL crystalloid is indicated in normotensive patients with clinical suspicion of sepsis. The response to infusion therapy must be closely monitored to evaluate the effects, orient subsequent treatments, and avoid possible complications from overload. Monitoring should include an integrated ultrasound evaluation in this phase (heart, inferior vena cava, lung).

Administers antibiotic according to the therapy regimens adapted to the site of certain or presumed infection (see Chapter 3.6).
If hypotension persists despite adequate filling (usually after the 1st hour), administer vasoactive drugs (norepinephrine): the administration of vasoactive drugs (norepinephrine as first choice, vasopressin, dopamine and adrenaline according to specific indications) is indicated, if there are indications of inadequate tissue perfusion even after appropriate fluid replenishment, in order to ensure a minimum vital flow to the organs. In particularly severe cases of septic shock, vasoactive therapy is indicated even during the resuscitation phase with fluids. The haemodynamic goal of treatment is an **average BP ≥65 mmHg**. The use of vasoactive drugs requires invasive monitoring of blood pressure by positioning the cannula preferably in the radial artery.
Once the results of the tests performed are obtained, calculate the SOFA score (see Chapter 3.2.2); if patient with dysfunction of 2 or more organs and/or respiratory impairment or likely rapid evolution, contact the Intensivist.
Researches the initial focus of infection with particular attention to possible treatable and eradicable foci: early identification of a potentially eradicable focus of infection and subsequent eradication treatment (asportation, drainage, removal, etc.), immediately after initial stabilisation, are essential to control the clinical picture.
If a treatable focus of infection is present, contacts the reference specialist (urologist, surgeon, orthopaedic surgeon, interventional radiologist) to remove the focus as soon as possible (approximately within 6-12 hours).

Table 15 nd 16 - The sepsis six (see chapter 3) medical-nursing team part

1.9 Can sepsis be an adverse event?

Some contributing factors, deriving from organisation of the pathway that is not consistent with the standards defined by the international guidelines [17], can contribute to impair the quality and safety standards of treatments. The term adverse event designates an unexpected and unintentional event related to the care process, and entailing harm to the patient. Adverse events can be either preventable or non-preventable. An adverse event attributable to error is "a preventable adverse event" [21]. The main categories of factors that can cause an adverse event in the sepsis management process are summarised below.

Contributing factors of organisational origin	Factors related to clinical care activities and coordination between sectors and services
The healthcare organisation does not carry out monitoring, control and surveillance actions - even microbiological - of the healthcare areas at risk of infections related to care and dissemination of multidrug-resistant germs	Incomplete knowledge of sepsis, septic shock and their clinical manifestations
	Delay in identifying deterioration
	Delay in starting treatment
The patient contracts a Healthcare-Associated Infection - HAI	Antibiotic therapy not appropriate for the site of infection, the type of infection or the patient

Contributing factors of organisational origin	Factors related to clinical care activities and coordination between sectors and services
Colonisation or infection with multidrug-resistant germs	Inappropriate resuscitation with fluids Delay in identifying the pathogen → aetiological diagnosis and delayed transition from empirical therapy to targeted therapy *Absent or unorganised handover* (passage of information and collaboration) Inappropriate or delayed control of the infectious source

Table 17 - Possible types of adverse event in the sepsis pathway

Integrated Strategy

The instruments of identification of the risk of infection integrated with the three stewardships (antimicrobial, diagnostic and sepsis) can become constituent elements of a healthcare organisation that identifies the infection to manage it effectively and to offer a sustainable and safe pathway for patients.

The model we propose introduces new possibilities for comparison and collaboration between the clinic and health risk management. Such new procedures require careful planning. The three stewardships introduce discontinuities with respect to the previous structures. To move towards a useful change for patient safety, it is necessary to be very familiar with the three activities and their potential benefits. A lack of coordination in the use of resources would risk producing an increase in costs without an actual benefit for patients. In this chapter we present the hexagonal model of integration between the three stewardships and the stratification of risks, designed to manage uncertainty and increase patient safety.

2.1 Integrate risk identification and new diagnostic-therapeutic pathways

"We propose a sepsis and septic shock management model based on the identification of infectious risk and on the integration of the three stewardships, diagnostic, antimicrobial and sepsis"

An important component of the sepsis and septic shock management model concerns the identification of infectious risk at a decentralised level. This component of the model is based on the ability of healthcare professionals to locally identify the level of infection-related risk and to choose the appropriate diagnostic-therapeutic pathways. The identification of situations of infectious risk is based on the use of three types of instruments: infection risk factors, severity scores and bioscore.

	Non Risk-Based Model	Risk-Based Model
Centralised	Define the organisational objectives and plan the activities to achieve them	Define the objectives on the basis of known risks and plan the activity accordingly
Decentralised	Prioritise organisational objectives and choose locally among predefined behaviours to achieve them	Define the reference framework and contextual analysis tools to identify emerging risks and management methods

Table 15 - Decentralised risk analysis model

1. The risk factors aim to identify, in the patient who comes in contact with the healthcare system, the conditions that favour infection, collecting adequate information: the lifestyle, the environment in which the patient lives and the healthcare environments in which the patient has been cared for are considered.

2. The severity scores detect the deterioration of vital signs, and are calculated at the time of contact between healthcare professionals and the patient.

3. The bioscore combines the biomarkers, prognostic and infectious risk scores in a multiparametric way (see 2.7). This tool aims to guide the patient towards the most appropriate pathway, based on processing of all the information collected.

1. Identification of the **risk factors** present (assessment of the previous situation)	2. Detection of vital signs through **severity score** (assessment of the current situation)
3. **Bioscore** (choice of the diagnostic-therapeutic pathway)	

Table 16 - Risk factors, severity score and bioscore

Infections and risk factors > When we talk about an already infected patient, the time of prevention is running out. The interval between the time of identification of the risk factor and the actualisation of a pathological state is narrow, especially because the infected patient often already has an underlying disease. Infectious risk factors, therefore, belong to a different level of complexity. They concern the effects of the interaction between the host organism and bacteria, mycetes or viruses. The human body is naturally inhabited by bacteria, which symbiotically support its many organic functions - such as digestion. It is the change in this interaction that dysfunctionally reshapes the relationship between the bacterium and the host organism causing an abnormal host response to the infection, which in the most extreme cases endangers life: sepsis and septic shock.

2.2 The role of risk factors

The identification of risk factors in the context of infection prevention aims to identify the presence of predisposing factors. The reconstruction of the recent medical history has the objective of investigating all those events that may have damaged or impaired the existing balance between host organism and bacteria (see 3.2.1) according to the model based on the theories of infection (see 1.2). Besides these factors, there are others that take account of the environment in which the patient lives and his lifestyle. If in the relationship with the patient it is important to know how to ask the right questions to detect predisposing factors, at an organisational level it is necessary to build a system that makes it possible to identify, trace and systematically map the areas of infectious risk, so as to have the most accurate possible knowledge of the factors involved. This system will always be based on the awareness and culture of the healthcare professionals, and will be implemented through highly integrated digital infrastructures for data collection and analysis. The mapping should involve healthcare environments through microbiological tests of the infrastructural and instrumental components (surfaces, instruments, air, water), healthcare professionals and their activities (hand hygiene and behaviour) and, lastly, hospitalised patients (colonisation screening). The mapping actions fall under *Infection Prevention Control* (IPC) and microbiological surveillance of the community and hospitals. It is one of the core pillars of the hexagonal model (see figure 2) for the management of infections, sepsis and septic shock.

2.3. The role of severity scores

"Assess the current clinical condition"

The severity scores (NEWS, MEOWS, qSOFA, SI, SOFA - see 3.2.2) help to detect and quantify patient deterioration in a systematic way and, therefore, help the healthcare professional to assess whether the patient's health is impaired. The assessment takes place both in the community and in a healthcare facility, at the time of contact with the patient. In this section we shall focus on what happens in the hospital. The purpose of the severity scores is to identify macroscopic signs of alteration of vital parameters - therefore a deterioration in the status of health - also attributable to an active infection. It is the task of the healthcare professional to establish a relationship with the patient to assess the health status manifested by vital signs. The severity scores are intended to classify a condition of instability and to trigger the appropriate treatment activities. As described in the proposal to manage the diagnosis of sepsis (fig. 3), if the severity scores give a positive result, they become the object of a collaborative, shared and timely communication between the nurse or midwife and the doctor. At this point healthcare professionals' activity becomes synergistic. Additional activities for the collection of elements useful for the construction of infectious risk scores may already be started by the nurse or midwife. For example, in the pre-diagnostic phase, it is important to rapidly obtain the results of blood tests (blood gas analysis, white blood cell count) to investigate the presence of a systemic inflammatory response syndrome (SIRS), to which biomarkers can be added.

2.4 The role of stratification of the risk of infection

"The choice of the diagnostic-therapeutic pathway"

The ability to stratify risk is the capacity that makes it possible to manage the uncertainty brought about by sepsis and infections, and to start the diagnostic, antimicrobial and sepsis stewardship pathways that are sustainable and consistent with the information collected. As illustrated so far, the infection-related risk stratification is based on 3 activities:

- identification of the risk factors
- systematic detection of vital signs through the use of severity scores
- application of the bioscore approach to integrate, in a multiparametric way, the post-infection risk of infection and mortality scores with biomarkers

The risk stratification consists in supplementing the information collected with the ability to decide the patient's diagnostic-therapeutic pathway, or with the construction of the bioscore that supplemenlaboratory data with specific infectious risk scores.
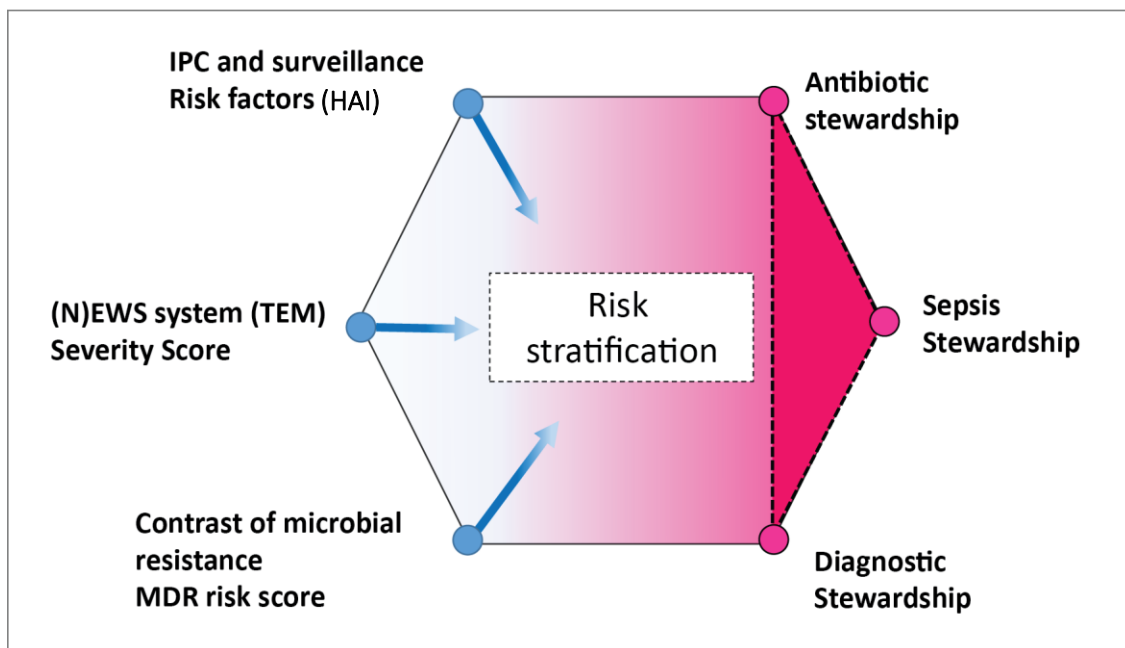
Fig. 2 - The integrated model of the 3 stewardships and identification of the risks related to infection

2.5 Manage the diagnosis of sepsis and septic shock in the ED and on the Hospital Ward: a proposal

"The more complete and shared the information collected from the search for risk factors and the determination of severity scores, the more the diagnosis will be able to reduce the level of uncertainty"

We propose what already exists in the literature with the intention of placing it within an organisational system that reduces the impact of antibiotic resistance and of infections in a sustainable way. The cornerstone of the proposal is the collaborative relationship between doctor and nurse. A sort of "universal couple" because they are present in all clinical settings where sepsis and septic shock need to be diagnosed. The 4 essential steps that spell out the diagnostic activities are listed below [22].

Portal of Entry	identify the infection's __portal of entry__ using clinical medicine and bedside ultrasound
Source control	assess the need to control the source of infection __(source control)__
Immune (status)	assess the patient's __immune__ status
Septic shock	__septic shock__ − assess if the patient is in a state of shock

Table 17 - Proposed steps to guide the diagnostic process of sepsis or septic shock [22].

Concerning the above, it should be emphasised that the more complete and shared the information collected, from the research of risk factors to the determination of the severity scores, the more favourable the conditions for attempting a diagnosis that reduces the level of uncertainty. The population of patients hospitalised at risk of death from sepsis includes patients recognised with sepsis at the Triage/ED, those with an evolving sepsis not evident on the first assessment, and those who develop sepsis during hospitalisation. Using the previous definition of sepsis based on the SIRS criteria, one in eight patients hospitalised in Intensive Care (ICU) with organ infection and dysfunction does not meet the SIRS criteria. SIRS-based screening algorithms are not optimal; one evaluation showed a positive predictive value of 71% and a negative predictive value of 55%. But the revised criteria based on the new definition of sepsis are less sensitive. About 4% of those who fall between the old and the new definition, i.e., patients who meet the SIRS criteria but not the organ damage detection criteria (SOFA see 3.2.2 point 3), die soon after admission to hospital [23]. Early identification facilitates timely treatment and gives time to choose appropriate antibiotics, while inappropriate use of broad-spectrum antibiotics can be followed by complications, such as *Clostridium difficile* [24] infection.
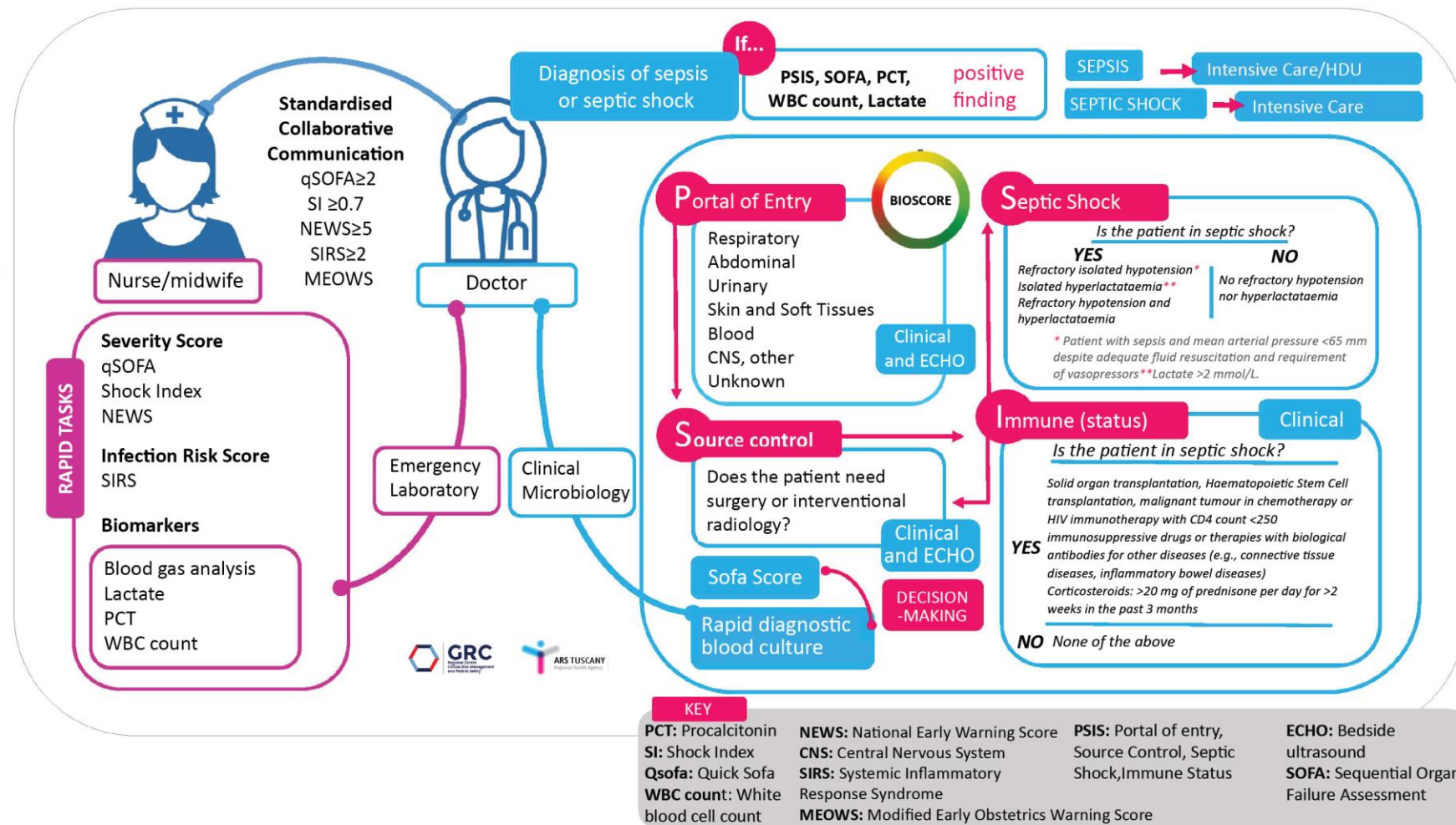
Fig. 3 - Suggested diagnostic-therapeutic approach based on cooperation between healthcare professionals on the 4 steps (PSIS) and application of the severity score and bioscore value (see 2.7 and 3.2.2.)

Collaborative, Shared, Timely Communication> At the time of communication, the collaborative communication model envisages the presence of a common ground that allows the speaker's and listener's attention to focus on a series of relevant details - in this case the severity score results. The advantages of this method are: 1) maximum use of shared attention (if the attention of a health professional is requested using a collaborative communication model, it means that the message is important and deserves attention); 2) guaranteed comprehensiveness of the communication (the use of a concise and shared communication model implies performance of a double check, if one of the two forgets one element, the other can request its addition). The communication is not closed until all elements have been communicated and understood; 3) Orientation to action: the communication takes place in order to activate an action and focuses on the content of the shared model designed to provide useful information for action. Loss of efficacy, if elements that are either irrelevant or connected to other spheres of activity are introduced within it, even if related to the professional sphere [25].

Early recognition of sepsis, the ability to consider infection with resistant germs (MDR) or not as the cause, and focus on prescribing antibiotics will increasingly be a priority [26]. More than one third of patients with septic shock visit the ED with vague symptoms that are not immediately attributable to an infection. These patients receive antibiotics late and have a higher mortality rate (even after a multivariate analysis by age, disease severity and timing of antibiotic therapy [27]). Three actions can assist the classification of these patients [28]:

1	Confirmation of the infection as the cause of the disease, via biomarkers (e.g., procalcitonin, C-reactive protein).
2	Stratification of patients into high, medium or low risk of inappropriate empirical therapy through the use of bioscores that supplement clinical judgment with organ dysfunction markers, such as lactate and disease severity scores (SOFA).
3	Aetiological diagnosis through rapid identification of the pathogen and of resistance mechanisms (for example, microbiological cultures and rapid identification via mass spectrometry, serology, amplification of the nucleic acid of microorganisms) in order to allow the transition from reasoned to targeted empirical therapy in the shortest possible time.

Table 18 - Three actions to classify patients with vague symptoms of suspected infection [28]

2.6   The three stewardships combined for the diagnosis and treatment of sepsis

"8 questions and 8 answers"

Two-thirds of bacterial infections are determined by gram-negative pathogens with an MDR (multidrug-resistance) rate of 50%, and this in itself is an independent factor associated with higher mortality [29]. To deal with sepsis effectively, it is absolutely necessary to manage the septic and/or septic shock patient in a diagnostic-therapeutic care pathway that provides for complete integration and correlation between *antimicrobial stewardship*, *diagnostic stewardship* and *infection control and prevention* (ICP), not forgetting the most recent concept of *sepsis stewardship*. The model we propose for patient management in hospital is **an integrated model of the three stewardships.** To do this, early and very rapid diagnostic and treatment interventions connected in a rationale of time-dependence, are necessary. The cornerstone of the treatment is the rapid and adequate antibiotic therapy that must, however, follow the modern "*shorter is better*" mantra. It is now established that in patients with septic shock, a delay of even just a few hours from the onset of symptoms in the administration of appropriate antimicrobial therapy is associated with a higher mortality rate [9]. However, even the reduction in intensity of the "*de-escalation therapy*", which must always be attempted when possible, is associated with a lower mortality rate for the same adequacy of antibiotic therapy [30], i.e., if the therapy is not reduced when possible even in the case of adequate therapy, the mortality rate is higher than in the comparator group where the *de-escalation* therapy was reduced.

1. What is meant by antimicrobial stewardship and what is its goal? The *antimicrobial stewardship* consists in managing the choice of antimicrobial therapy and has the objective of ensuring the correct interpretation of microbiological data, choosing the most suitable molecule (or molecules, in combination therapy) in order to improve the patient's outcome by avoiding inappropriate pharmacological choices. Another goal of the *antimicrobial stewardship* is to set a reasoned empirical therapy pending the microbiological data, evaluating the individual risk factors of the patient. A clinician must continually ask himself the question *"Why am I using this antibiotic at this dosage, or this combination of antibiotics at these dosages?".* Almost 1/3 of antibiotics used are unnecessary or, worse, inappropriate. In fact, the problem of antibiotic resistance is closely related to the selective pressure exerted by the same antibiotics and to the ecological impact this determines. Italy is among the European countries with the highest resistance rates, third after Greece and Turkey. In Italy, the phenomenon has increased from an average of 16-17% in 2005 to 33-34% in less than 10 years, so much so that today 1 in 10 patients experiences an infection caused by multidrug-resistant bacteria.

2018 - In Europe, over 4 million people are annually affected by hospital bacterial infections, with an estimated 25,000 deaths for resistant germ infections. Healthcare-associated infections (HAI) affect approximately 284,000 patients each year, causing 4,500-7,000 deaths.
2050 - Bacterial infections are estimated to cause around 10 million deaths per year, far outweighing deaths from cancer (8.2 million/year), diabetes (1.5 million/year) or traffic accidents (1.2 million/year) with a negative impact, according to recent estimates of the International Monetary Fund, of about 3.5% on world GDP. *(EMA, European Medicines Agency)*

2. What does diagnostic stewardship mean and what is its goal? Traditionally, the diagnosis of bacterial and fungal infections is based on the culture test of materials collected from the infection site, with relatively long response times (48-72 hours, but sometimes even longer) linked to the growth times of the main pathogenic microorganisms and their identification, which is crucial for the correct interpretation of susceptibility to antimicrobial drugs. It is evident that the clinical impact of this information is very low in a time-dependent pathology. In recent years, however, the availability of innovative diagnostic technologies that allow response times to be reduced to a few hours and, often, the analytical sensitivity of microbiological tests to be increased, puts the role of Clinical Microbiology back in the spotlight. The goal of *diagnostic stewardship* is to choose the right diagnostic pathway for each patient, generating clinically important and accurate results as quickly as possible in order to have a positive impact on patient outcome [31]. In fact, it is nothing other than the rapid management of microbiological diagnostics, strictly and temporally integrated with clinical diagnostics. *Diagnostic stewardship* focuses not only on identifying the individual aetiological agents of the patient but, more broadly, also operates depending on the community and hospital's local epidemiology. Furthermore, *diagnostic stewardship* is closely and inextricably linked to *antimicrobial stewardship* in a clinical perspective, but also to the IPC for health management.

3. What does sepsis stewardship mean and what is its goal? The goal and meaning of *sepsis stewardship* is the management of sepsis according to the clinical evidence reported in the literature, contained in the *Surviving Sepsis Campaign* (SSC) guidelines, now in their fourth edition, with the related *bundles*. Once again, the **synergy** between the 3 *stewardships* is the winning factor. All this means that *antimicrobial stewardship*, *diagnostic stewardship, sepsis stewardship* and the IPC represent a whole, recognising the word **integration** [32] as their founding element. The governance of this integrated pathway cannot be performed by the individual specialist, but must involve several figures in a multidisciplinary way, not only within hospital facilities, but also at a community level with General Practitioners, paediatricians, veterinarians, according to a *One Health* approach, where all the participants are protagonists. This approach must lead to a change in cultural attitude from the conventional individualistic vision of the doctor-patient relationship to a contextual vision, where one assumes responsibility for one's professional work, not only towards the individual patient, but with respect to the entire community. This is because each administration of an antibiotic drug generates a change in the microbial ecosystem that physiologically colonises the human being, in particular at the level of intestinal microbiota. Hence the need to understand that each prescription must embrace a rationale of correct risk-benefit ratio. Cognitive, educational and organisational aspects are fundamental elements of every advanced DASIP (*Diagnostic Antimicrobial Sepsis stewardship and Infection Prevention programme*) where the requirement for well-established multidisciplinarity is absolute.

4. How to optimise empirical therapy and what are the elements to be considered? First of all, empirical therapy can no longer be only empirical as it has a broad spectrum but, rather, **reasoned empirical**, where reasoned means **informed**, that is, based on the patient's clinical/epidemiological characteristics, on the suspected focus of infection (if identifiable) and on the data provided, in our case, by the Tuscan Regional Health Agency's SMART[1] network report. Usually, empirical therapy includes one or more broad-spectrum antimicrobials, active against possible pathogens (bacterial and/or fungal) at the dosages considered effective, optimising the PK/PD properties to the maximum and, of course, not neglecting the characteristics of penetration in the target site. It is important to always administer the loading dose (if necessary) and the appropriate maintenance dose to obtain effective plasma concentrations, since failure to reach peak plasma concentrations is associated with the risk of clinical failure.

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[1] https://www.ars.toscana.it/pubblicazioni.html

5. How to use the PCT biomarker and how to include it in the clinical assessment? The evidence in support of the PCT is impressive. In 2017 a systematic review of the literature conducted by Cochrane on 32 RCTs (Randomised Control Trials) definitively sanctioned the role of PCT in suspending antibiotic therapy in acute lower respiratory tract infections [33]. PCT, furthermore, has been included in all the most advanced antimicrobial stewardship programmes [34], especially for critically ill patients hospitalised in the ICU. Among other features, PCT has a high negative predictive power [127].

PCT - Use of the negative predictive value in clinical reasoning: an example? The negative predictive value differentiates PCT from other biomarkers used in the clinical setting. In the context of an initial structured diagnostic process administered to a patient, admitted to Intensive Care, evidently septic but without known infection foci, such as BSI (*Blood Stream Infection*) and IVAC (*Infection-related Ventilator-associated Complication*), the use of this marker, included within an integrated and complex clinical pathway, supports the clinician's diagnostic capacity by improving its accuracy. In the presence of a sepsis/septic shock patient with negative or extremely low PCT, for the severity of the clinical picture, it is necessary to direct the diagnosis towards the exclusion of syndromic conditions, such as deep and/or compartmentalised abscesses, meningitis/ventriculitis, endocarditis, specific atypical pneumonia or BSI from CoNS or from mycetes. In clinical practice, in such a patient setting, instrumental diagnostics should be further and rapidly extended by both CT and MRI advanced total body imaging with contrast agent, performing the MRI at the same time as the CT in cases where the site is better studied or characterised by this method (see particular deep muscle or CNS localisations). Next to the CT and/or MRI study with contrast agent, another diagnostic reference test is transthoracic, or better trans-oesophageal electrocardiography, which has the aim of excluding valve vegetation.

Speaking of empirical therapy, is it really true that combination therapy in the septic/septic shock patient is always better than monotherapy? In this regard, Ripa et al. recently reviewing a series of 576 consecutive patients with septic shock from monomicrobial infection and divided into two groups, of which the first (340) treated in appropriate monotherapy and the second (236) in combined therapy, did not find any difference in terms of mortality at 7, 15 and 30 days [35]. Only in the subset of patients infected with *Pseudomonas aeruginosa* and in the subset of patients with neutropoenia was there a beneficial effect, in terms of mortality, in patients treated with combined therapy. Even in the case of infection with *Klebsiella pneumoniae* a carbapenemase producer, the evidence is in favour of combination therapy [36]. In all other cases, therefore, adequate antimicrobial monotherapy is completely comparable with multidrug combination therapy, but the first is to be preferred due to the lower impact on the microbiological ecosystem.

How do I choose the right molecule for the isolated pathogen? Obviously the choice will be guided by the microbiology, by the epidemiological *cut-off* and by the clinical *breakpoint* of the pathogenic/antibiotic combination, by the pharmacokinetic/pharmacodynamic characteristics of the drug (also in relation to the patient's peculiar characteristics) and by its penetration at the site of the infection. The new BLBLI (beta-lactam/beta-lactamase inhibitor) combinations, such as ceftolozane/tazobactam and ceftazidime/avibactam are in our opinion molecules that require, except in rare cases, microbiology to confirm or not the presence of resistance patterns susceptible to treatment: in the case of ceftolozane/tazobactam, for example, the presence of resistance determinants, such as KPC, OXA and MBL must be excluded, in the case of ceftazidime/avibactam that of MBL.

6. After how long should the efficacy of the therapy in place be re-evaluated?   Any   antibiotic   therapy undertaken, whether monotherapy or combination therapy, needs to be systematically re-evaluated at 48-72 hours to establish whether or not clinical improvement has occurred and to proceed, consequently: towards a rapid *de-escalation*, in the event of a favourable trend, or to review the therapy itself. Above all, the change of treatment when initially setting a combined antibiotic therapy benefits both the community, by reducing the risks of developing bacterial resistance, and the individual patient (reducing the risks of superinfections and of mortality).

7. How long should antibiotic therapy last? Chastre et al [37] in one RCT demonstrated that 8 days of therapy in VAP vs. 15 days were completely comparable for clinical efficacy, but the duration differed significantly with respect to the second pulmonary infectious episode from MDR (42.1% vs. 62.3% in favour of the group treated for 8 days; P=0.04). In practice, in most cases, one week of treatment is sufficient to treat a VAP/IVAC, although there are some cases, such as non-fermenting Gram-negative infections, where discontinuation of therapy should be considered on a case-by-case basis, supplementing the decision with biomarkers, clinical/radiological assessment and documented microbiological eradication [38]. In most infections associated with sepsis and/or septic shock, 7-10 days of treatment are generally adequate. It should be noted, however, that more prolonged treatments are appropriate for patients with a slow clinical response, with non-draining infection foci, bacteraemia, in patients with immunodeficiency or in other particular types of infection, such as endocarditis or spondylodiscitis.

8. Does prolonging appropriate antimicrobial therapy always facilitate sterilisation of a colonisation? Or rather: is it correct to pursue the objective of always achieving complete eradication of a colonisation? Again, a thorough analysis of the literature helps us to confirm that the answer is yes if it is *Streptococcus pneumoniae, H. influenzae,* and *S. aureus,* but not if it is *Enterobacterales* and *Pseudomonas aeruginosa*. The last barrier concerning the duration of antibiotic therapy in BSI from *Enterobacterales* has also recently fallen: regimens reduced to 8 days, compared to prolonged regimens of 15 days, showed a similar mortality rate, however, subject to a lower number of recurrences and, especially, Gram-negative MDR recurrences [39].

Companion diagnostic for the introduction of new antibiotics > The term *companion diagnostic* designates one or more diagnostic tests used to appropriately place a particular new drug, customising its clinical efficacy to the utmost; in practice, the choice of a new molecule is supported by the result of a specific diagnostic test, in this case a molecular biology test, with the aim of exploiting the full potential of the new molecule in terms of efficacy, avoiding its undesirable effects or its total inefficacy unknown to the prescribing clinician. It is, in our opinion, a virtuous course of action that aims at *best practice* with the choice of the most appropriate therapy for the patient who always remains at the centre of the entire process. Within the *antimicrobial* and *diagnostic stewardship* integrated programmes today it is possible to include *companion diagnostic* strategies which aim, precisely, at the correct inclusion in therapy of new antimicrobial molecules. In fact, molecules such as ceftolozane/tazobactam and ceftazidime/avibactam have recently been introduced in the clinical setting, and have objectively increased the therapeutic possibilities of treating serious infections, such as those from *CRE* (*Carbapenem Resistant Enterobacteriaceae*) and *Pseudomonas aeruginosa* MDR, as well as offering a possible alternative to the use of carbapenems in increasingly diffuse *carbapenem sparing* strategies in the treatment of infections with *Enterobacterales*, ESBL producers; their correct use, however, requires a microbiological guide certifying or not the specific resistance pattern, also in order to maintain the efficacy of these important new molecules over time.

2.7 Bioscore: an instrument to choose the diagnostic-therapeutic pathway

"Who goes into rapid diagnostics? Or rather, who is the right patient who can best benefit by rapid diagnostics?"

Numerous innovative rapid microbiology diagnostic technologies have recently been developed (RMM), which allow a more rapid and accurate aetiological diagnosis of the infection. This translates into the possibility of starting targeted antimicrobial therapy earlier, reducing the use of unnecessary empirical therapies and improving patient outcomes, with particular reference to the septic patient [40]. Such RMMs have been introduced into clinical practice in recent times. This document has the aim of proposing a reference model that guides their adoption and use [41]. The reduction in response times is not the only advantage of the new rapid microbiology diagnostic technologies: they provide greater analytical sensitivity. Rapid diagnostics have overwhelmingly entered advanced programmes but, unfortunately, not everyone can afford them today, considering costs that are still too high. Risk stratification still emerges - this time out of practical need. Infection-conscious clinicians should stratify patients who need such a rapid diagnostic approach, based on several factors. The combined and integrated use of validated clinical scores can help the clinician in this arduous task. In fact, the bioscore is a heuristic procedure, that is, a practical approach to direct a rapid microbiological pathway with the aim of achieving an explicit and shared indication for the inclusion of rapid microbiological diagnostics into clinical practice. According to this model, once the positive blood culture is obtained, the microbiology laboratory should proceed at two different speeds, clearly differentiating the pathway of a routine specimen from the specimen collected from the critical septic patient, identified by the bioscore as being at high risk of infection with multidrug-resistant (MDR) bacteria. In fact, these two situations require completely different timelines. Today all identifications should be performed with mass spectrometry using Maldi-Tof (Matrix Assisted Laser Desorption Ionization - Time of Flight), currently a reference method for the rapid identification of bacteria. Depending on the result of the microbial identification, both rapid molecular and phenotypic diagnostics can be activated: the two methods give complementary but different information. Molecular methods are applied to identify genetic resistance patterns that, however, are not always reflected on the *in vivo* behaviour of the bacterium. For example, a bacterium devoid of resistance determinants may, however, not be sensitive to the action of a given antibiotic because it cannot penetrate the bacterial cell. Phenotypic methods are, instead, used to test live bacteria, which reproduce in the presence of antibiotic molecules, and their sensitivity is assessed.

A semi-targeted antibiotic therapy can be established in just 2-6 hours, having obtained all this important information (species identification, resistance pattern and susceptibility to the most common molecules).
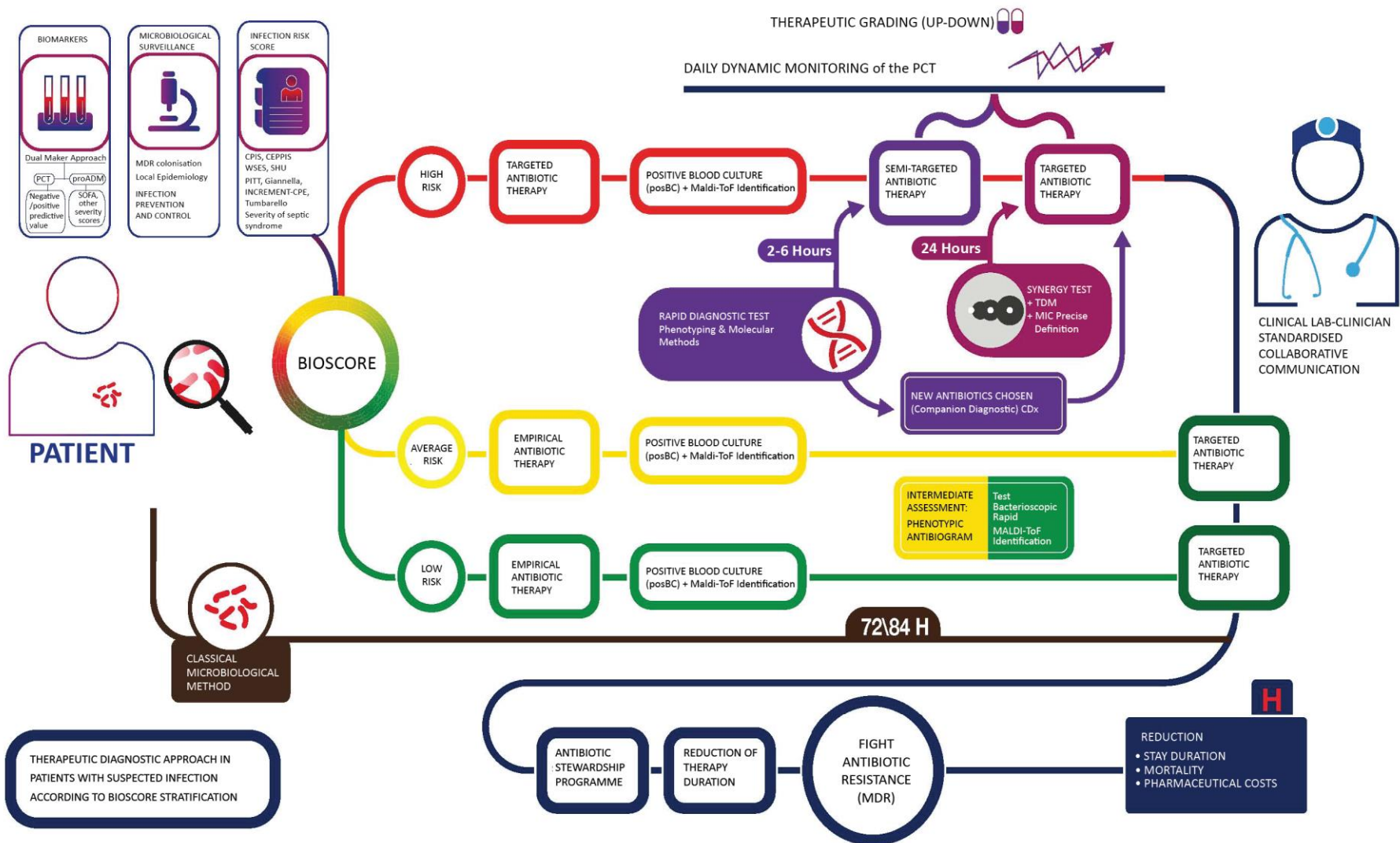
Fig. 4 - Therapeutic approach model for patient with suspected infection and risk stratification **in Intensive Care**
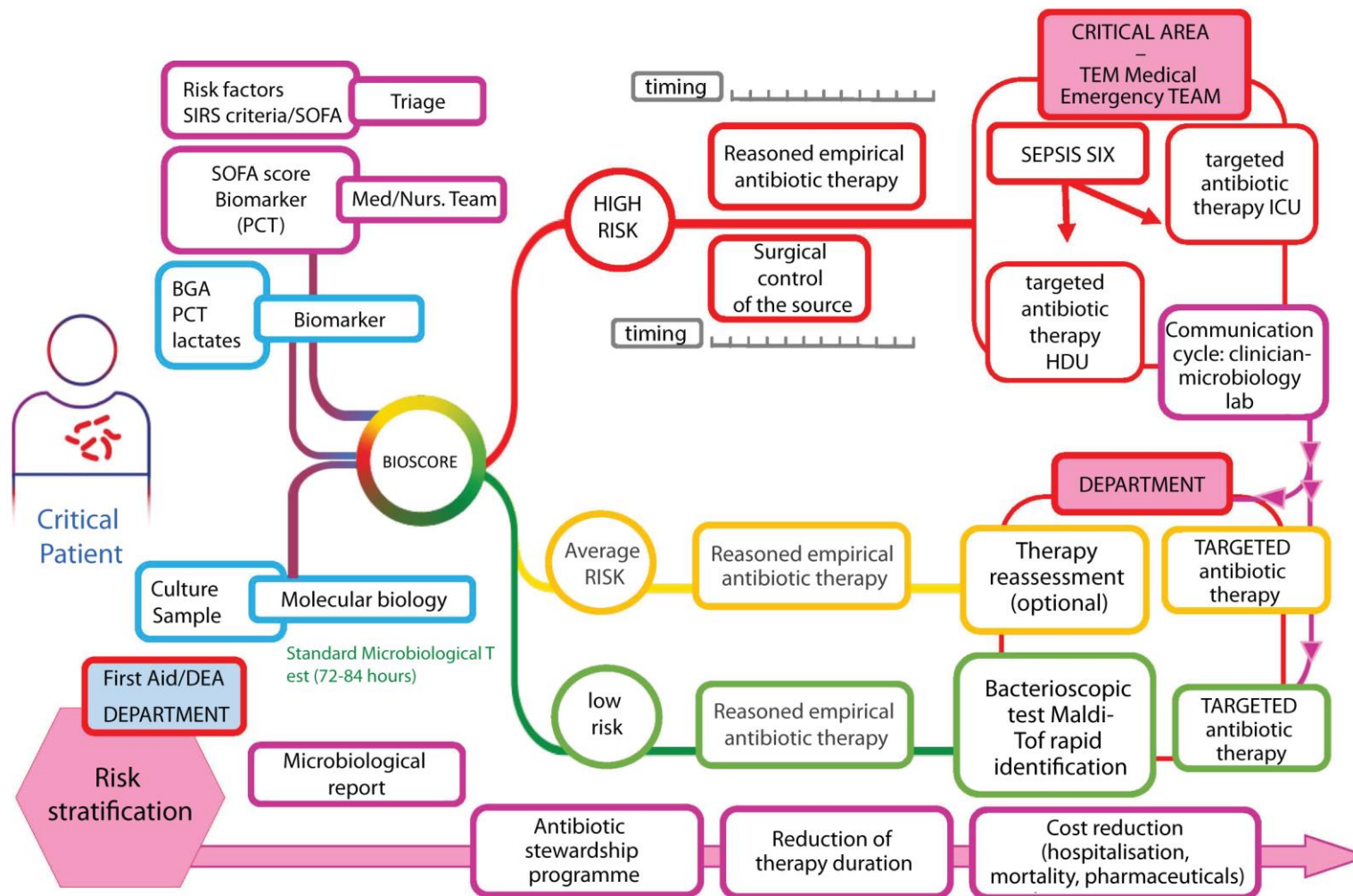
Fig. 5 - Therapeutic approach model for patient with suspected infection and risk stratification **in the DEA** and **on the Ward**

The model we propose provides for multiparametric stratification of patients who require such a preferential diagnostic approach. Among the scores used we find, in addition to those of severity, such as the SOFA (Sequential Organ Failure Assessment, described extensively in Chapter 3), some specific infection risk scores. We are proposing the CPIS (Clinical Pulmonary Infection Score) score, in its modified variant CEPPIS (Chest Echography and Procalcitonin Pulmonary Infection Score), which also includes thoracic ultrasound and procalcitonin, the PITT bacteraemia score and the scores that quantify the risk or not of having an ESBL or CRE infection. In this regard, the algorithm recently proposed by Cano [42] on the risk of developing an infection and mortality among patients colonised by KPC-kp using two validated scores is interesting; the first is the Giannella risk score (GRS) that, with an optimal cut-off set at <7 and ≥7, makes it possible to stratify patients colonised by KPC-kp into patients at low risk (if <7) or high risk (≥7) of developing KPC-kp infection. The risk of developing infection in patients with a low GRS (between 0 and 6) is only 6% vs. 85% of the group with GRS ≥7.

	Respiratory Infection	CPIS score (Clinical Pulmonary Infection Score) CEPPIS (Chest Echography and Procalcitonin Pulmonary Infection Score)
	Abdominal Infection	WSES score
	Urinary Infection	SHU score
	Blood Infection	PITT score
	KPC-kp colonisation	Giannella risk score (GRS) and INCREMENT-CPE
	KPC infection	Tumbarello Score
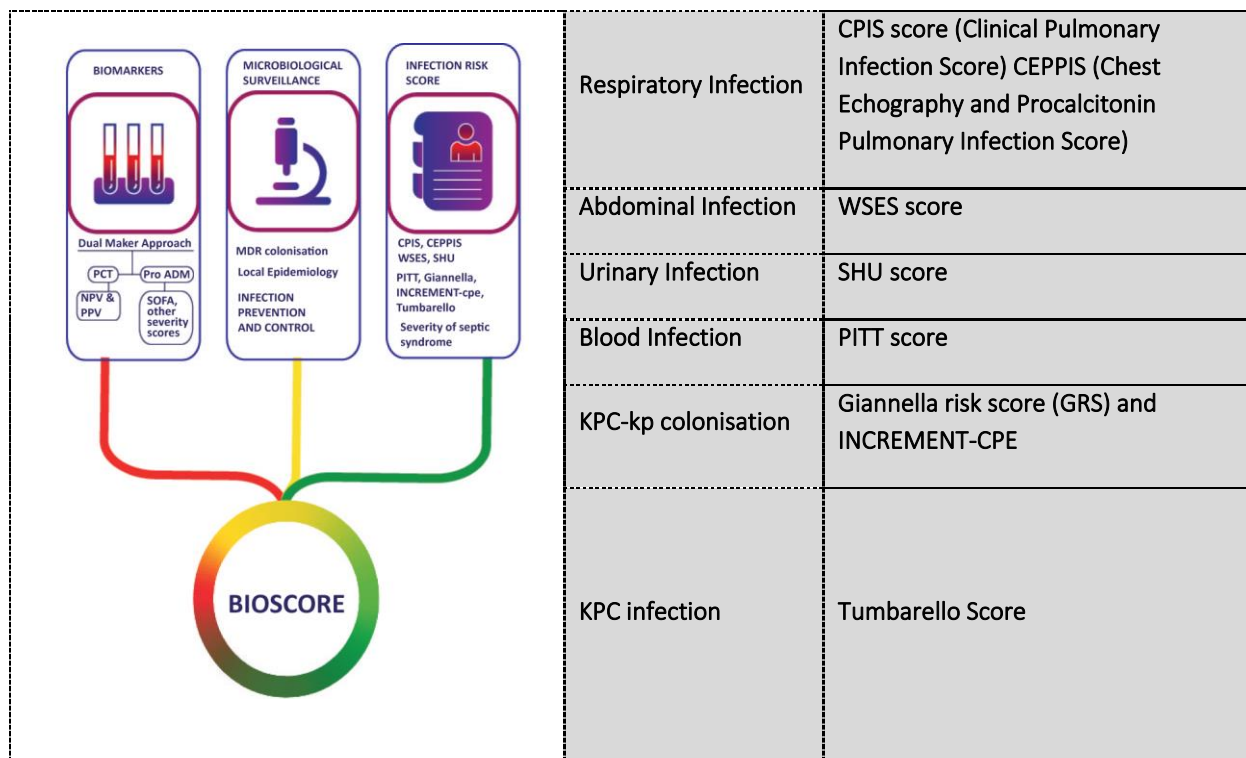
Table 19 - Scores that can be used for infection risk stratification in the Bioscore

High-risk patients with clinical suspicion of infection using the INCREMENT-CPE score [43] will be further divided into high or low mortality risk (low 0-7, high 8-15); those classified as high risk of mortality will require empirical antibiotic therapy in therapy regimens combined with the inclusion also of new molecules active on KPC-Kp. The latter are those whose samples will be sent for rapid microbiological diagnostics. For patients with KPC infection we indicate the Tumbarello score [44]. Next to the clinical evaluation through validated scores and identification of the degree of severity of the septic syndrome (sepsis/septic shock) in the multi-parameter global evaluation, we include biomarkers, essentially PCT, and essential microbiological data, such as accurate knowledge of local epidemiology, both department and hospital, and the patient's previous or current status of colonisation by MDR pathogens. The Bioscore thus identifies patients with high/medium or low risk of having an MDR infection.

Act promptly

How to address the challenge of sepsis? If it could not be prevented, it must be treated. This chapter presents the instruments to be applied when - since it could not be prevented - it is necessary to treat it trying to limit the damage. The risk factors, presented in a perspective of patient management and included in instruments for the classification of patients with suspected sepsis, the updated and validated scoring scales, which make it possible to classify the vital signs and monitor deterioration in terms of course of action, are the main TEM - medical emergency team activation tools. The components of the bundle are presented; or the diagnostic and therapeutic actions to be completed from the first hour of diagnosis and no later than three hours. Particular importance is given to controlling the source of infection. The instruments are identified in each clinical care setting: ED, Medical Area, Obstetrics, Surgery.

3.1 Clinical management of sepsis and septic shock: Sepsis Six and Bundle

"How to address the challenge of sepsis? If it could not be prevented, it must be treated. Standardised treatment that does not evaluate the risk contextually based on the patient's characteristics reduces the possible benefits of a timely approach"

Sepsis is a medical emergency, a life-threatening condition caused by an uncontrolled response of the body to infection. Sepsis and septic shock are pathologies with critical temporal evolution. The Surviving Sepsis 2017 Campaign guidelines [17] identify in resuscitation with fluids, administration of antibiotics, vasopressors and control of the infectious source the cornerstones of treatment. However, standardised treatment that does not emphasise the need to contextually evaluate the differences between one patient and another reduces the possible benefits of a timely approach [45]. In case of suspected sepsis and septic shock, it is necessary to act immediately by carrying out the actions envisaged for sepsis six [46], with the addition of infection source control.

	SEPSIS 6 + 1 *Start the treatment as soon as possible between the 1ˢᵗ HOUR and 3ʳᵈ HOUR of the diagnosis of sepsis*	
1	Oxygen	Assess the need for O2 and/or assisted ventilation
2	Blood culture	Collect at least 2 pairs of blood specimen bottles for culture tests (and any other biological samples, such as urine, sputum, wound swab, etc.) BEFORE starting antibiotic therapy.
3	Antibiotic therapy	Administer broad-spectrum empirical antibiotic therapy in accordance with protocols [2]
4	Lactates	Measure the lactates and perform blood chemistry tests including inflammation indices (biomarkers, such as PCR, Procalcitonin, etc.)
5	Fluids	Start fluid delivery
6	Diuresis	Start diuresis check
7	Consider the surgical check of the infectious source (within 6 hours)	

Table 20 - Summary table of patient with sepsis management within the first 3 hours of diagnosis

A timely diagnosis of sepsis is crucial particularly in patients with hypotension. In this category of patients, delayed administration of antibiotics increases the risk of mortality [47].

> In the case of septic shock it is necessary to act IMMEDIATELY by administering antibiotics, fluids and vasopressors in the first hour. Hydrocortisone can be used early to correct blood pressure.

In the management of septic shock, we propose the regimen suggested by Jean Luis Vincent [48], which provides for three categories of intervention:

> Haemodynamic management: fluids and vasoconstrictor agents

> Modulation of the host response: hydrocortisone and vasopressin

> Infection management: antibiotics and control of the source

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[2] See chapter 3.4

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Aggressive fluid resuscitation at 30 mL/kg is not recommended for everyone: aggressive fluid resuscitation, in fact, has little effect on pressure, fluid boluses can cause a drop in arterial elastance, boosting arterial vasodilation and the typical hyperdynamic state of septic shock; large volumes of fluids can cause severe pulmonary oedema and oedema in all other organs and cause "delayed" haemodynamic impairment (see section 3.7). Early administration of norepinephrine is, therefore, recommended: an increase in mortality for each hour of delay in administration has been demonstrated [49]. Recently, the authors of the SSC 2017 guidelines [50] proposed a one hour version of the bundle. However, the same Surviving Sepsis Campaign recommends against the application of that bundle[3]. In 2018 the American Infectious Diseases Society [45] distanced itself from the Surviving Sepsis Campaign 2017 guidelines because they are excessively inclined to propose standardised indications on the administration of antibiotic therapy, also for the clinical management of patients in whom the diagnosis of infection is uncertain. Patients with an uncertain diagnosis of infection need to be placed in a pathway that enables to obtain additional diagnostic information and, therefore, to re-evaluate their level of risk, as they would not receive benefits from standardised and prolonged antibiotic therapy.

> In patients with suspected sepsis, the goal is to start antibiotic therapy immediately but with the commitment of all healthcare professionals to reduce it to the shortest duration while maintaining all the safety margins and greatest possible benefits.

"Zero time" is the time of identification of sepsis or septic shock. It is defined as the triage time in the Emergency Department, or if the identification takes place in another care setting, as the time of first registration made by the doctor in the diagnosis chart consistent with the definition of sepsis (previously defined as severe sepsis) or septic shock and confirmed by reviewing the chart.

Strategy of Escalation and De-escalation

Adapted from P. E. Marik and J. D. Farkas, Crit. Care Med., 2018.
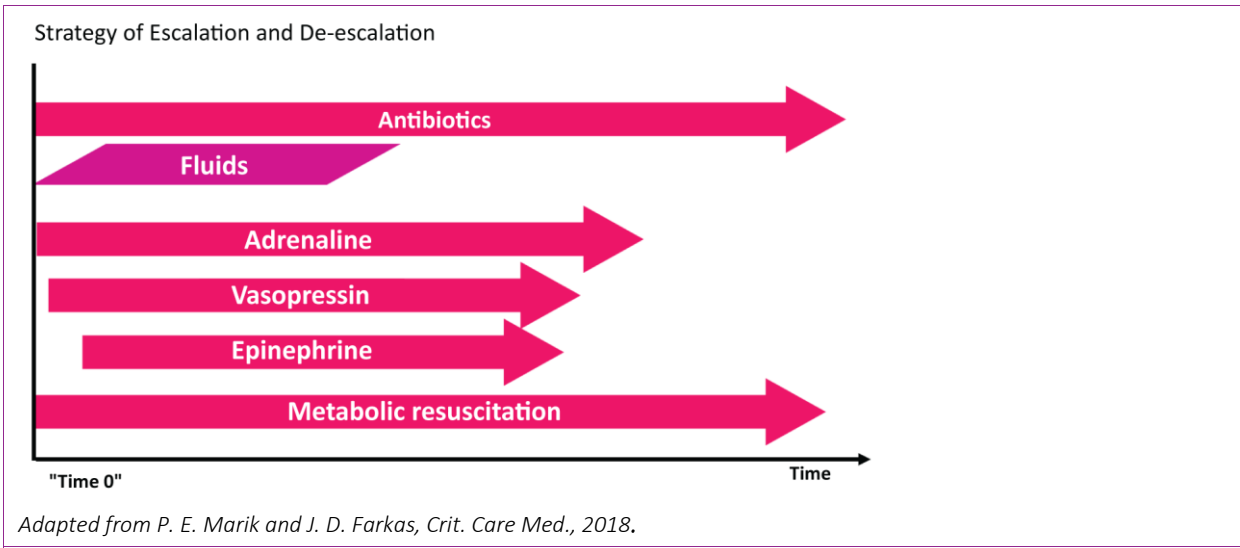
New paradigm for septic shock management The administration of antibiotics, fluid resuscitation and peripheral vasopressors are all started immediately. Additional vasopressors are administered within the first few minutes, if necessary. Always immediately, it is necessary to start metabolic resuscitation with hydrocortisone, ascorbate and thiamine. Upon improvement of the patient, vasopressors and metabolic therapy are suspended. The rapid increase in treatment stabilises the patient faster and reduces the need for Intensive Care stay overall, as well as reducing organ failure and decreasing the chance of death [51].

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[3] http://www.survivingsepsis.org/News/Pages/SCCM-and-ACEP-Release-Joint-Statement-About-the-Surviving-Sepsis-Campaign-Hour-1-Bundle.aspx *(access 19.11.2018)*

The Surviving Sepsis Campaign 2017 guidelines recommend that *"the specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically feasible after the diagnosis is made."* The sepsis six together with the identification and surgical control of the source of infection require an approach designed and defined before the healthcare professional meets the patient with sepsis. In order to reduce the uncertainties related to organisational methods (see 1.4), it is necessary to answer these 8 questions.

1. *If the infection presenting a risk of complication could not be prevented, how can the suspected sepsis be identified?*
2. *Which reasoned empirical therapy to choose?*
3. *When, how and which fluids to administer?*
4. *In which setting should the patient with sepsis be managed?*
5. *When and how to collect specimens for culture tests?*
6. *What is the role of lactates and of biomarkers?*
7. *What is the role of diuresis control?*
8. *What is the role of oxygen administration?*

3.2 Identifying suspected sepsis: risk factors and vital signs

"How can the suspicion of sepsis be confirmed?"

The clinical and care activities that can reduce sepsis and septic shock mortality, reducing the risk of adverse events, are the improvement actions implemented in the healthcare organisation (Chap. 2). Regarding the clinical management of sepsis, two functions that the healthcare organisation must be able to carry out are crucial:

1. Identification of the risk factors present (assessment of the previous situation)	2. Detection of vital signs through severity score (assessment of the current situation)
3. Bioscore (choice of the diagnostic-therapeutic pathway) see Chap. 2	

Table 16 - Risk factors, severity score and bioscore

We have already covered point 3 in Chapter 2. The first two points will be examined in detail in this section. An infection can be tracked in the clinical documentation; however, if this infectious picture is not monitored through severity scores (NEWS, qSOFA or MEOWS for the obstetric area), the probability of the patient being taken into care is reduced, the uncertainty and the situations that can generate errors and adverse events increases. Thus the risk increases. The resources and instruments to be activated for the timely identification of suspected sepsis are, on the one hand, the experience and sensitivity of the healthcare professional in recognising the risk factors, and on the other, the systematic use of severity scores (EWS - Early Warning Score) for the detection of clinical deterioration.

3.2.1 Risk factors

The most obvious risk factor is the presence of an infection. Any infection, from the weakest source (an insect bite, an abrasion, etc.) to the strongest (pneumonia, meningitis, etc.) can trigger an abnormal response that in certain conditions (see Table 1 Chapter 1) can lead to sepsis and septic shock. The infection can be bacterial, viral, fungal or parasitic. But in addition to the cause triggering the infection, some people have a higher risk of developing sepsis than others. Patients at higher risk of developing sepsis include:

GENERAL RISK FACTORS	
extreme ages (infants and elderly)	patients carrying devices
chronic diseases, such as diabetes, chronic lung disease, cancer and kidney disease	prolonged hospitalisation, trauma, extensive burns
patients with compromised immune systems due to certain conditions or their treatments	major surgery and invasive procedures
malnutrition	

Table 19 - Risk factors for sepsis

RISK FACTORS IN THE ADULT PATIENT	
Persons over 75 years or fragile	Compromised immune systems due to disease or drug-taking
People being treated for cancer with chemotherapy	Impaired immune function (e.g., people with diabetes, splenectomy or people with sickle cell anaemia)
People taking long-term steroids	Therapy with immunosuppressant drugs (e.g., rheumatoid arthritis)
Recent surgery or other surgery in the past 6 weeks	Skin wounds (e.g., cuts, burns, blisters or skin infections)
Intravenous drug abuse	Carriers of permanent catheter and permanent infusion lines

Table 20 - Risk factors for sepsis - adult patient

RISK FACTORS FOR PREGNANT AND POST-PARTUM SUSPECTED SEPSIS PATIENT	
Recent history positive for fever or chills	Myalgia/malaise/headache
Cough/sputum/wheezing	Dysuria or difficulty urinating
Anaemia	Onset of altered state of consciousness or confusion
Flu-like syndrome or active infections	Recent surgery/wound infection/cellulitis

RISK FACTORS FOR PREGNANT AND POST-PARTUM SUSPECTED SEPSIS PATIENT	
Abdominal pain not related to other causes/abdominal distension	Immunocompromised/chronic disease
Vomiting and/or diarrhoea	Suspected breast infections
Redness/swelling/pain infection associated with vascular catheter	Invasive manoeuvres in pregnancy (e.g., amniocentesis, cerclage, etc.)
Possible intrauterine infections (PROM, p PROM, MIF, prolonged labour, retention of placental material)	Previous pelvic or urinary infection
Previous urinary infection	Pregestational diabetes
Trauma	Strong concern of caregivers/family members
Low (<18.5) or high (>30) BMI	Heavy smoker
Social deprivation and/or marginalisation	

Table 21 - Risk factors for sepsis - pregnant, postpartum, post-abortion woman

3.2.2 Severity score - identify the patients with suspected sepsis and septic shock

The healthcare professionals who are able to understand weak signals and immediately think of an infection that is evolving into sepsis or septic shock are the best safety barrier. In order for awareness of the situation (see box below) to become a characteristic of the organisation and not just an individual healthcare professional's ability, it is necessary to know the main risk factors attributable to sepsis and to set up structured systems to detect vital signs (severity score) which, upon exceeding certain thresholds, authorise the healthcare professional to contact the reference doctor or TEM.

Situation awareness: Most healthcare professionals become aware of a potential risk to the patient and intervene to limit it. Unfortunately, it is not always as simple as it should be. There may be a gap between the individual ability to perceive a risk situation - giving a definite shape to the appearance and anticipating the actions to be taken - and the practical implementation of these actions in a healthcare organisation. In other words, despite the intuition of the individual, the organisational system is often not so receptive to start moving quickly in a univocal and coordinated way. By awareness of the situation we mean the ability to perceive the elements in the environment in a given unit of space and time, to understand their meaning and to project them into their future state with respect to the observer. To understand that a patient's condition is deteriorating following an infection and to act accordingly, a combination of the individual's action and the support of the organisational environment is needed [52].
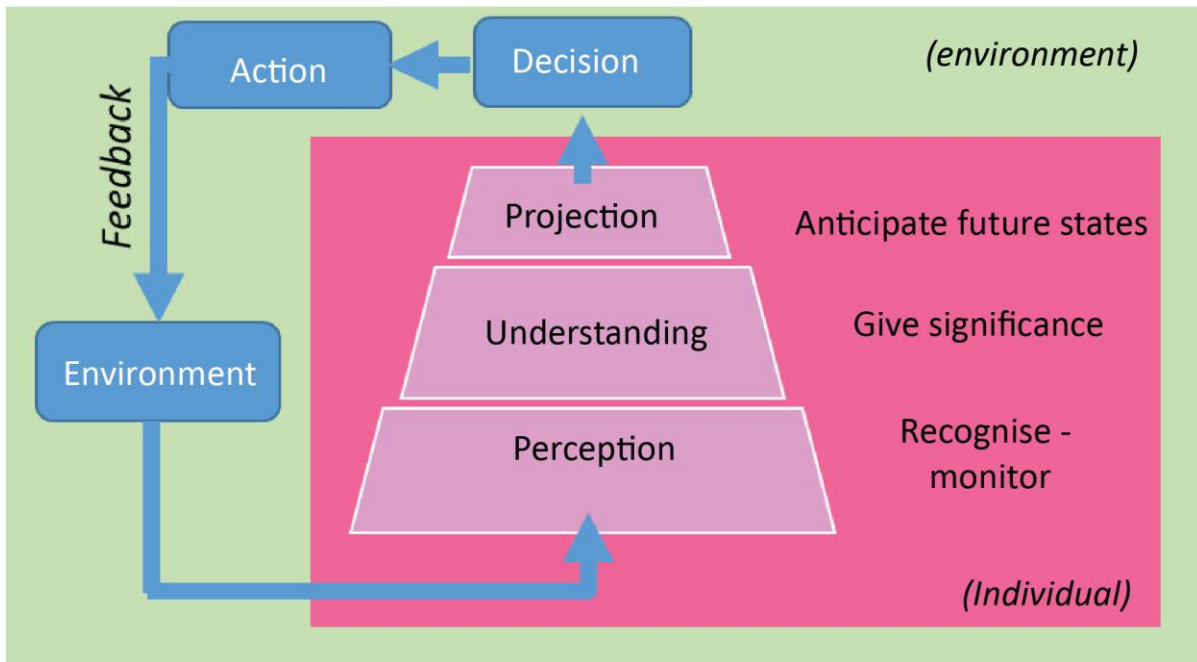
Fig. 7 - Descriptive model of awareness of the situation

Severity score The acute event in the hospital is never sudden but signalled by a progressive deterioration of the vital signs that precede the acute event from a few hours to 24 hours [53]. The nurse in the ordinary hospitalisation departments can first identify the signs of patient deterioration by using validated instruments, such as rapid alert systems (Early Warning Score). These instruments allow rapid recognition of patients with suspected sepsis and early treatment that reduces mortality and improves outcomes. Rapid alert systems are based on the interpretation of the detection of vital signs with respect to the degree of instability of the patient, and on the definition of an alert level that indicates the urgency of the clinical response and the level of competence. The rapid alert systems provide for the detection of vital signs, the level of consciousness and, in some systems, the use of oxygen therapy. A table accompanies the interpretation of the detected signs by attributing a score (from 0 to 3) to the detected sign. The more the measured value deviates from the physiological value, the higher the score attributed. After completing the record of vital parameter values, the nurse adds the scores attributed to the individual signs from the table and obtains the alert level and monitoring frequency. The effectiveness of rapid alert systems depends on this tool being recognised by all healthcare professionals (language and shared communication) and in the definition of a local response to the degree of patient instability (*track and trigger* system, TT), from *track*: identification of clinical worsening with regular observation of vital signs, and *trigger*: implementation of measures and interventions according to the severity level recorded.

The following are the main severity scores useful to classify the suspicion of sepsis and of septic shock

1) qSOFA - Quick Sofa
   Where to use it: Community Service, Emergency Medical Service, Triage

Quick Sofa or qSOFA was introduced by the Sepsis-3 Consensus, which produced the new definition of sepsis (see Chapter 1.1) based on the infection, which becomes more complicated and is linked to organ dysfunction. Hence the need to provide a less complex tool than the SOFA (Sequential Organ Failure Assessment, see below, point 3) that prefers the diagnosis of sepsis through rapid identification of patients with initial organ dysfunction outside Intensive Care. qSofa parameters are:

qSOFA	
Respiratory rate ≥22 breaths/min	Yes/No
Systolic blood pressure ≤100 mmHg	Yes/No
Altered mental status GCS <13 AVPU score in Verbal or worse	Yes/No
The qSOFA is defined as "positive" if at least two of the above criteria are met	

Despite all the limitations of this score (see in-depth below), qSOFA can be used in the community and at triage as an alarm element in patients with suspected infection for the identification of patients with organ failure. It should be noted that within the triage algorithm for suspected sepsis used by the Tuscan Regional Administration (see in-depth) the qSOFA>2 is one of the criteria for the assignment of code 2: "acute emergency that requires a medical examination within 15 minutes."

Further investigation > The Surviving Sepsis Campaign task force, the standing scientific committee that produced the guidelines [17] stressed that: not all patients with sepsis have qSOFA >= 2, not all patients with qSOFA >= 2 have sepsis. The qSOFA is easy to perform in triage and does not require the use of laboratory tests (with consequent reduction in waiting times). It can be used as a monitoring system at the patient's bedside and, despite the evidence being less robust than for the SOFA (rated better than SIRS criteria), the positive predictive value remains the same. Since the writing of Sepsis-3, various comments have followed, such as that of the Global Sepsis Alliance [54] and, above all, retrospective studies and meta-analyses that compared the SIRS and qSOFA criteria with results that are not entirely conclusive, and reducing the role of the qSOFA. In particular, the retrospective study of Tusgul [55] on 11,411 patients reported that sensitivity of the SIRS, qSOFA and *sepsis 3 definition* criteria is sub-optimal and does not allow to adequately select patients at risk of complications. In the observational study conducted by Askim [28] also, on 1,535 patients admitted to the ED with signs of sepsis, qSOFA failed to identify septic patients in 2/3 of cases and risk stratification in predicting mortality after 7 and 30 days. The authors conclude that qSOFA sensitivity was worse than other triage systems, such as SIRS. Another recent observational study of Williams [56] on 8,871 patients concluded that the SIRS criteria are associated with organ dysfunction and mortality, the qSOFA≥2 has high specificity but low sensitivity and this limits its use at the patient's bedside. Lastly, the meta-analysis conducted by Serafim [57], evaluating around 230,000 patients from various studies, concluded that the SIRS criteria are more sensitive than qSOFA to the diagnosis of sepsis, while qSOFA is slightly higher in predicting hospital mortality

2) Shock Index
Where to use it: Triage, ED

The Shock Index (SI) is defined as the ratio between Heart Rate (HR) and Systolic Blood Pressure (SBP), with a normal range in the healthy adult of 0.5-0.7; it is a simple, zero-cost tool that is useful in the initial assessment of patients at risk of sepsis.

$\dfrac{HR\ (Heart\ Rate)}{SBP\ (Systolic\ Blood\ Pressure)}$	≥0.5-0.7

Allgöwer and Buri [58] introduced this concept in 1967 as an easy tool to highlight the degree of hypovolaemia in the haemorrhagic and septic patient. Experimental and clinical studies have shown that the SI is inversely correlated with other physiological parameters, such as cardiac index, stroke volume and average blood pressure. An SI ≥1.0 has been significantly associated with worse outcomes in patients with acute circulatory failure. In 1994, Rady et al [59] showed that an SI ≥0.9 correlated with higher clinical priority to triage, higher probability of hospitalisation as well as Intensive Care, compared to HR or SBP taken individually. This suggests that the SI can be a useful tool for early recognition and evaluation of critically ill patients in the Emergency Department, as well as for evaluation of the progression of hydroelectrolytic resuscitation. It can also help to identify and stratify septic patients from a prognostic point of view, when there is a correlation between the SI and the increase in blood lactates. The SI has above all a negative predictive value: patients with a normal SI (less than 0.7) have a 95% probability of not having an increase in lactates; conversely, SI >1 correlates with the increase in blood lactates >2 mmol/L. Patients who present with a suspected infection and an SI of less than 0.7 have a low risk of having occult sepsis (or rather of having hyperlactacidaemia). The SI can be used as an additional tool at the patient's bedside to identify critical patients, and is particularly useful when traditional clinical signs are apparently relatively "normal". It is a simple and easy-to-apply tool at triage to identify patients at risk of rapid negative evolution [60].

3) SOFA
Where to use it: ICU, ED

The SOFA (Sequential Organ Failure Assessment score) is the reference score for the assessment of organ damage and represents a key element of the new definition of sepsis. The SOFA consists of 6 distinct assessments, with individual scores from 0 to 4, which measure the functional status of systems, such as the respiratory, cardiovascular, hepatic, haemocoagulative, renal and neurological systems.

	0	1	2	3	4	Value
Respiration PaO2 / FiO2 (mmHg)	>400	≤400	≤300	200 In assisted ventilation	100 In assisted ventilation	....
Haemostasis Platelets (n/mm3)	>150	≤150	≤100	≤50	≤20	....
Liver Bilirubin (mg/dL)	<1.2	1.2-1.9	2-5.9	6-11.9	>12	....
Cardiovascular		MAP <70 mmHg	Dopamine ≤5 Y/kg/min or Dobutamine	Dopamine >5 Y/kg/min or Adrenaline or Norepinephrine ≤0.1 Y/kg/min	Dopamine >15 Y/kg/min or Adrenaline or Norepinephrine >0.1 Y/kg/min	....
Neurological (Glasgow Coma Scale)	15	13-14	10-12	6-9	<6	....
Renal Creatinine (mg/dL) Urinary Flow		1.2-1.9	2-3.4	3.5-4.9 or <500 mL/24 hours	5 or <200 mL/24 hours	....

Total ....

Fig. 8 - SOFA score table

The baseline SOFA score is assumed to be zero, unless the patient is already known to have previously existing organ dysfunction prior to the infectious episode. Organ dysfunction can be defined as an acute 2-point change from the SOFA baseline. Hospitalised patients with suspected infection and SOFA score of 2 or greater have a 10% higher risk of mortality than the general population with suspected infection but with SOFA score of zero.

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Where to use it: Medical and Surgical Departments

In December 2017, the Royal College of Physicians reviewed and updated the NEWS (National Early Warning Score), changing its acronym to NEWS2 [61]. The updating of the NEWS system was determined by 4 objectives: one of these is how to use the rapid alert system to identify patients who are at risk of sepsis, who have rapid clinical deterioration and, therefore, require urgent clinical intervention. The parameters detected by NEWS2 are the same as in NEWS, namely:

Respiratory rate	Systolic pressure
Oxygen saturation	Pulse rate
Body temperature	Oxygen therapy, if any
Level of consciousness	

Changes concern the recording of oxygen saturation and level of consciousness. Two scales are provided for oxygen saturation to better respond to patients with hypercapnic respiratory failure. In the level of consciousness the symptom/sign of "new-onset confusion" is introduced, which is added to the AVPU system, where A: Alert, V: Voice, responds to voice, P: Pain, responds to pain, U: Unresponsive, does not give any eye, voice or motor response to voice or pain. See Table 11- rating scale –NEWS2 [61].

PHYSIOLOGICAL PARAMETERS	Score						
	3	2	1	0	1	2	3
Respiratory rate (per min.)	≤8		9–11	12–20		21–24	≥25
SpO$_2$ Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO$_2$ Scale (%)	≤83	84–85	86–87	88–92 ≥93 in Air	93–94 Oxygen	95–96 oxygen	≥97 oxygen
Air or oxygen?		oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Heart rate (per min)	≤40		41–50	51–90	91–110	111–130	≥131
Level of consciousness				Alert			CVPU
Temperature (ºC)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Fig. 9 - National Early Warning Score, 2017

The risk levels have been redefined by introducing the **threshold 5** value that allows:

1. to place the diagnostic hypothesis of sepsis in any patient with confirmed infection, signs or symptoms of infection or high infectious risk;
2. to trigger the activation of the medical emergency team for the management of sepsis (Table 11).

NEW score	Risk	Response
0-4	Low	Response of ward
Red score Score 3 for a single parameter	Low - medium	Urgent response of ward
5-6	Medium	Threshold for urgent response*
≥7	High	Emergency or urgency response**

Table 22 - alert levels –NEWS2(2017)

Clinical responses were redefined on the basis of risk by identifying the two thresholds: that of action in urgency and that in emergency; see Table 3 - clinical response at alert level-NEWS2(2017).

The use of the score in the **surgical area** involves a few considerations:

1. sensitivity and specificity (in relation to the transfer of High Intensity/Sub Intensive or Intensive Care patients) of the instrument are optimal in patients with score ≥4;
2. increasing the threshold increases specificity but makes sensitivity values unacceptable;
3. clinical deterioration in the surgical patient is "subtle" in terms of onset, and "late" in manifestation in about 40% of cases, with admission to intensive care in stages that are too advanced; to improve the outcomes in this type of patient, an increase in awareness of the clinical urgency, the search of collaboration and the implementation of organisation and supervision are necessary.

The use of the score in all patients allows, regardless of the septic state, early classification of patients at high risk of rapid deterioration of clinical conditions and to activate medical re-evaluation.

NEWS score	Frequency Monitoring	Clinical response
0	Minimum every 12 hours	Routine monitoring of the NEWS
1-4	Minimum every 4-6 hours	• Communicate the change during the *handover* and share the alert signal in the nursing team • Nursing staff decide the frequency of monitoring and the alert level
3 for a single parameter	Minimum every hour	• The nurse informs the doctor, who decides the treatment
≥5 Threshold for emergency response	Minimum every hour	• The nurse immediately informs the doctor attending to the patient • The nurse requests urgent evaluation by a clinician or team for the treatment of acute patients • Provides care in an environment with a monitoring system
≥7 Threshold for emergency response	Continuous monitoring of vital signs	• The nurse informs the doctor attending to the patient and who should have emergency assessment skills • The emergency should be assessed by a team dedicated to clinical emergencies and airway management • Evaluate the transfer to Intensive Care • Treat the patient in an environment with a monitoring system

Table 23 - Clinical response to alert level-NEWS2 (2017)

5) **MEOWS**

Where to use it: Obstetrics-Gynaecology

Maternal sepsis is a life-threatening condition, it is an organ dysfunction following an infection contracted during pregnancy, childbirth, postpartum, puerperium, or after an abortion. It is more frequently associated with a group A Streptococcal infection. Requires trained personnel for diagnosis and management [54, 55]. The MEOWS (Modified Early Obstetrics Warning Score) is the early warning score used for the detection of vital signs related to sepsis in pregnancy or within 42 days of delivery.

SEPSIS ALGORITHM IN OBSTETRICS

GRC — Regional Centre Clinical Risk Management and Patient Safety

SEPSIS **6** — OXYGEN LACTATES CULTURE ANTIBIOTIC FLUIDS DIURESIS

⊞ Red warning signs

T (°C)	< 35, > 38
BP [mmHg]	< 90, > 160
HR	< 40, > 120
RR	< 10, > 30
VAS	-
Response to stimuli	Does not respond, responds to pain

If one or more risk factors are present and a red warning sign, measure the lactates and perform blood chemistry tests including phlogosis indices - biomarkers (PCR, Procalcitonin)

Notify the doctor, assess whether to continue the treatment and whether to contact the TEM-Emergency Medical Team

1. OXYGEN	Assess the need for O2 and/or assisted ventilation
2. CULTURE	Take at least 2 samples for blood culture (and any other biological samples, (e.g., Urine) BEFORE starting the antibiotic therapy.
3. ANTIBIOTIC	Piperacillin/Tazobactam 4.5 g every 6 hours +Vancomycin 25 mg/kg loading dose, then 500 mg every 6 hours
4. FLUIDS	Start volemic filling
5. DIURESIS	Start diuresis check
	Completion of childbirth or emptying of the uterine cavity Thromboembolic prophylaxis

⊞ Yellow warning signs

T (°C)	35-36
BP [mmHg]	150-160 o 90-100
HR	100-120 o 40-50
RR	21-30
VAS	2-3
Risposta agli stimoli	Response to stimuli

1. Re-evaluate the warning signs at least every 8 hours (at least 3 times in 24 hours)
2. If there is a worsening/variation of the warning signs, notify the doctor
3. If there are alterations with respect to the usual condition of the woman, notify the doctor
If one or more risk factors and yellow warning signs are present, start monitoring

Fig. 8 - Graphic algorithm for the identification and management of sepsis in obstetrics - regional safety practice (2018)

The proposed empirical therapy to be considered to treat sepsis in obstetrics is as follows (for in-depth information on the use of *off-label* drugs see section 3.6.1)

> Piperacillin/Tazobactam 4.5 g every 6 hours
> Vancomycin 25 mg/kg loading dose, then 500 mg every 6 hours

3.3 Rapid alert systems - role of the ward

Early recognition of the clinical deterioration of admitted patients in hospital *settings* constitutes an effective safety barrier: it allows intervention when the chances of success of a clinical/care-giving intervention with limited resources are still high for a patient at risk of evolving towards irreversible morbidity. Early recognition is a clinical care activity that depends on **situational awareness** [52], or on the ability of the individual healthcare professional, the group of healthcare professionals, the entire organisation, to perceive a risk condition, to interpret it and act to limit it. In this case, it is the ability to identify a condition of morbidity with the risk of unexpected outcome in patients with an evolution towards severe or irreversible morbidity by means of the systematic detection of vital signs and attention to other relevant signals coming from the patient – or sometimes from family members and *caregivers*. Exceeding coded and shared threshold levels triggers a coordinated therapeutic-assistance action that, in emergencies, has the features of an emergency intervention, with the activation of resources additional to those available in the original care *setting* (TEM). A late intervention in these patients, with inadequate timing or resources, can lead to avoidable damages and impair the quality and safety levels of treatments coded as "*failure to rescue*". The acute event in the hospital is never sudden but announced by a progressive deterioration of the vital signs that precedes the acute event by a few hours (up to 24 hours). In the initial stages, this deterioration can take on the characteristics of a weak signal - that is, difficult to perceive. The responsibilities of the pertinent department (inpatient wards), include the maintenance of NEWS-type monitoring standards (see 3.2.2), and verification of emergency station equipment (see regional PREIT document), recommended in these guidelines. In accordance with the PREIT working group, and on the basis of available evidence, the systematic use of qSOFA as a monitoring tool is not recommended. In the case of suspected sepsis or septic shock, correspondence with some of the proposed activation criteria is likely, in particular:

HR (News score)	SBP (systemic blood pressure News score), particularly in case of septic shock	Alterations of the level of consciousness (News score)	Healthcare professional's concern (additional criterion)

The alert system envisaged for inpatient wards is of the *ramp-up* type, providing for the gradual activation of resources based on the NEWS score.

NEWS 3-4	Intensify the monitoring process
On single element of the Score	Activate the ward's medical staff (get evaluation within 10 minutes).
NEWS 5-6	Activate the ward's medical staff (get evaluation within 10 minutes). Intensify the monitoring process
NEWS ≥7	Activate the TEM (Emergency Medical Team)

In accordance with the Tuscan Regional Administration's Intra-Hospital Emergency Plan (PREIT), we underscore the importance of suspected sepsis in all cases of NEWS >5 or of a "concerned" healthcare professional, especially in case of:

Presence of venous accesses and/or catheters	Immunity impaired by disease (diabetes) or treatments (patients taking steroids or immunosuppressants or receiving chemotherapy)
Age >75 years or very fragile persons	Recent trauma
Surgery or trauma or other invasive procedures (in the past 6 weeks)	Intravenous drug addiction
Skin lesions (e.g., cuts, burns, blisters or skin infections)	Recent childbirth

If suspicion of SEPSIS is placed (whether in TEM activation or not), the performance is recommended of:

specimen collection for blood gas analysis with blood lactate assay
sampling for PCT (procalcitonin)
sampling for 2 blood culture SETS

Pending the TEM, ward staff must ensure the basic response to urgencies and prepare for the arrival of the emergency team.

3.4 Rapid alert systems - role of the TEM

The specific skills of TEM in the context of the sepsis approach include:

Planning/prevention phase: check of devices and their sanitisation (in particular non-disposable devices: ultrasound probes, ventilation devices, etc.), check of the possibility of direct communication with the infectious disease specialist and microbiologist (a dedicated telephone number or other communication system available 24H is recommended)
Alert phase: response at urgency/emergency, triage
Intervention phase: patient stabilisation, monitoring; check of performance of blood gas analysis sampling for blood lactate assay, PCT (procalcitonin) sampling if not already performed by staff present, history collection.

Confirmation and activation of the TEM, if the septic suspicion is high and/or confirmed.

TEM aims to quickly define with the reference infectious disease consultant (or autonomously, if TEM with experience) the most appropriate therapeutic approach and the administration of antibiotic therapy, considering the diagnostics and monitoring targeted on clinical suspicion (diuresis, temperature, blood chemistry, etc.). The need for *source control* is decided by activation of consultants (surgeon, radiologist interventionist, etc.) based on the clinical and diagnostic picture.

3.4.1 Objectives of surgical *source control* in the Emergency Medical Team

Find the source when sepsis is suspected	E.g., objective of source search, including sources that may require surgical drainage (as part of the initial classification)
Targeted search of the source in clinical history and in objective findings	E.g., urine and chest X-ray in identifying source in suspected sepsis
Abdomen and pelvis imaging, if there is no evidence of source after clinical examination and initial tests	
Involve the Surgical/Gynaecology team early when suspecting intra-abdominal/pelvic infection (if surgical treatment is needed)	

If the patient has clinical instability or organ failure, transfer to the hospital area with greater intensity of care, and monitoring must be planned as soon as possible, including intensive and sub-intensive areas. Any transfer procedure must not postpone the therapy and diagnostics of the case.

Transfer: transfer of the patient to an inpatient area of greater intensity must be promptly managed and guaranteed by TEM with the support of the staff of the ward of origin, if it is an intra-hospital pathway, or managed by TEM and guaranteed by the Local Emergency Medical Service, if it is an intra-hospital pathway. However, TEM patient management is recommended up to *handover* to the Emergency Medical Service. Consider the opportunity of patient functional isolation, if indicated. Event recording: it is recommended that TEM draw up intervention consultations in a dedicated format or in the patient's medical record, clearly reporting: activation times, clinical notes on the intervention, antibiotic therapy administered, consultants activated, planning of monitoring and destination, indications on antibiotic *de-escalation*.

Time objectives	1st hour: time from triage to lactate control, sending blood cultures, PCT
	2nd hour: time between TRIAGE (TEM activation) and ATB therapy administration
	48 hours: antibiotic therapy reassessment time and opportunity for *de-escalation*

3.5. Summary – identification of patients at risk of sepsis in the hospital

Clinical and care-giving activities that can reduce sepsis and septic shock mortality are the improvement actions implemented in the organisation. Among these, if we are talking about the clinical management of sepsis, the timely identification of the suspicion of sepsis based on severity scores and a rapid clinical diagnosis are crucial. Individual professionals must know the risk factors related to sepsis and, as part of the organisation, they must be able to record vital signs through severity scores appropriate to the clinical care setting in which they operate. This provides the basic elements for risk stratification and treatment according to the recommendations, and for assigning a level of care of adequate intensity. Individual knowledge, diagnostic and therapeutic equipment, rules for effective coordination and shared communication are all elements that must carefully interact with each other in order to build a system capable of responding to sepsis.

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Severity scores have different characteristics and can be used in different settings. The common goal is to quickly identify patients at risk of sepsis.

	GP	Emergency Medical Service	DEA		Medical Area	Obstetrics	Surgical Area	Intensive Care
			Triage	ED				
QSofa	X	X	X					
Shock Index			X					
NEWS				X	X		X	
MEOWS						X		
SOFA				X				X

Table 24 - Tools for identifying sepsis applicable in different settings

Identification of Patients with Suspected Sepsis			
Two functions that the health organisation must be able to perform are crucial: identify the risk factors and record the signs related to sepsis			
Activity	Healthcare Professionals	Instruments and Structures	Rules, practices, operating procedures
Identify the risk factors for suspected sepsis	All healthcare professionals know the main risk factors for sepsis and septic shock, and know their main modes of presentation. The risk factors are used by the healthcare professionals to communicate with each other regarding patients at risk of sepsis.	The tables with risk factors are entered in the healthcare software and are included in the healthcare documentation.	The healthcare professionals organise and promote training courses on the correct identification of the patient with suspected sepsis. There are active working groups at hospital and unit level as part of actions to combat sepsis infections and septic shock. Risk factors and detection of parameters related to sepsis are considered closely related.

Activity	Healthcare Professionals	Instruments and Structures	Rules, practices, operating procedures
Place the patient with suspected sepsis in rapid alert systems	All healthcare professionals know the vital signs related to sepsis and use them to communicate. All healthcare professionals know the alert levels above which it is necessary to ask for support from the ward doctor or from the Medical Emergency Team (TEM). The TEM number is visible and known to the healthcare professionals. The rapid alert systems are used by the healthcare professionals to communicate with respect to patients at risk of sepsis.	The severity scores are available and included in the healthcare documentation, in the computerised record and in the handover forms.	The vital signs of patients are monitored at each shift change and noted in the medical records. In the case of patients at risk of deterioration, the detection of vital signs intensifies according to methods shared and known to all the healthcare professionals. The medical-nursing team knows the TEM activation rules.

Table 25 - structure of organisational resources in the identification of suspected sepsis

3.6 Proposals of empirical antibiotic therapy protocols in sepsis

"Which reasoned empirical therapy to choose?"

The *Surviving Sepsis Campaign* [17] guidelines, in the case of suspected sepsis and septic shock, recommend starting antibiotic therapy as soon as possible. It has been shown that in cases of sepsis with hypotension, a delay in starting antibiotic therapy increases the risk of mortality. It is therefore necessary to start treatment within the first hour of diagnosis (time 0); in the case of suspected sepsis or septic shock, the indication we support is that of promptly starting empirical antibiotic therapy, with the commitment of the entire care system to reduce its duration to the shortest possible time. In the model that we propose, this translates into stratification of infectious risk on the one hand, and integration of the three *stewardships* on the other. Both actions are based on systemic skills, organisation and technology. The SSC guidelines also identify some good practices with respect to antibiotic therapy:

- any antibiotic therapy undertaken, whether monotherapy or combination therapy, needs to be systematically re-evaluated at 48-72 hours to establish whether or not clinical improvement has occurred, and to proceed thereafter to rapid *de-escalation* or review of the same therapy;
- set dosage strategies based on the clinical/epidemiological characteristics of the patient and on the suspected infection focus (if identifiable);

- choose an empirical antibiotic therapy as reasoned as possible and limited to the presumed site of infection (to optimise tissue penetration);
- appropriate collection of cultures for microbiological tests (before starting therapy);
- prohibition of prolonged antibiotic prophylaxis;
- identification or exclusion of the infectious source;
- timely removal of any potentially infected venous access.

The empirical antibiotic therapy protocols aim to standardise prescribing behaviours, before switching to targeted therapy, in order to decrease improper use of antibiotics, which can determine both the onset and spread of resistance phenomena, and the appearance of side effects (such as enteritis from *Clostridium difficile*). The primary objective is to allow the prescriber to easily identify an adequate therapeutic regimen, by choosing molecule, dosage, duration and limitation of adverse events, for the most common infectious syndromes causing sepsis and septic shock.

Antibiotics are essentially divided into two main categories: time-dependent (T>MIC), where the therapeutic objective is to maximise the duration of exposure to the drug, and concentration-dependent ones (Cmax>MIC), where the goal to be achieved is to maximise concentration. However, and this is a more recent concept, there are also antimicrobial molecules that are concentration-dependent but with a component of time dependence within them (e.g., oxazolidinones and phosphomycin) where the goal is to maximise the amount of exposure to the drug [64].

Further details on the correct method of administration of some commonly used antimicrobial molecules > The best way to administer a **beta-lactam** is continuous or extended infusion [17]. **Linezolid**, typically bacteriostatic drug, being concentration-dependent with a time dependency component, has as target PK/PD AUC/MIC >100 and T>MIC=85-100%, with C_{min}>MIC; the registered method of administration is 600 mg every 12 hours, but it has been seen that with continuous infusion administration, preceded by a loading dose, it is possible to reach C_{min}>4-5 times the MIC obtaining a bactericidal effect [65]. **Meropenem** in high-dose extended infusion of 2 g every 8 hours can reach the therapeutic target T >40% 1xMIC up to an MIC of 32 or a maximum of 64 mg/L, considerably extending its range of action as the EUCAST breakpoint is set at 2 mg/L [66]; this is the basis of its use in *combo therapy* in the setting of infections from *KPC-kp* where locally the MICs for carbapenem are less than 32 mg/L; in Tuscany, unfortunately, the MICs extended to carbapenem are normally 512 mg/L or >1,024 mg/L, rendering this therapeutic option unusable. For **Daptomycin** in the critical patient, it is known that it must be administered at much higher dosages (10 mg/kg) than those registered (4-6 mg/kg) if we want to treat a BSI from MRSA [67]. Daptomycin at a dosage of 9 mg/kg in BSI from VRE has been related to a lower mortality rate, compared to the standard dosage of 6 mg/kg [68]. **Tigecycline** in *KPC-kp* to be effective, has to be administered at a double dosage, compared to the standard with an LD of 200 mg [69]. The European guidelines recommend using **gentamicin or tobramycin** at 3-8 mg/kg/day in monotherapy and **amikacin** at 15-30 mg/kg/day based on the severity of the infection, possibly for a maximum of 5 days in order to minimise its toxicity by making use only of the powerful bactericidal effect of aminoglycosides. Their efficacy can be checked in TDM: a target of C_{max} and C_{min} of 30-40 mg/L and <0.5 mg/L is suggested for gentamicin/tobramycin and 60-80 mg/L and <2.5 mg/L for amikacin. **Phosphomycin**, great partner in *combo therapy*, must be administered at very high dosages, at least 16 g or better 24 g per day in 4-6 administrations, as it is also a concentration-dependent molecule but which also requires a time dependency in order to function well. Obviously, since the latter is a hydrophilic molecule with low molecular weight and is excreted practically unchanged by the kidney, it requires dose adjustments in the presence of CrCL <50 mL/min. The best way to administer the reserve molecule par excellence, that is, of **colistin**, is an LD of 9 MU infused in 3 hours followed by two administrations of 4.5 MU at a distance of 12 hours from each other [70].

Some aspects to consider to correctly interpret the reported therapeutic protocols

The therapeutic indications contained in this document can be changed in the individual patient depending on the different clinical assessment and the analysis of particular risk factors, as well as adjusted to any changes in kidney and liver function or in the presence of interactions with other drugs.

Furthermore...

A. Perform biological sampling for culture tests (blood culture, urine culture, bronchoaspirate/BAL or other biological fluids based on the possible organ localisation), <u>if possible before the start of antibiotic therapy.</u>

B. In patients with reported penicillin allergy, if possible, do not use ß-lactam antibiotics. Evaluate the type and characteristics of the reactions reported in the case history (year of last episode - major or minor 5/10, type of reaction - skin with rash, systemic with urticaria, laryngeal oedema, shock, etc., time of onset - immediate or delayed). If allergic tests to penicillins are not available, consider performing them. If necessary, in any case, therapy with ß-lactam antibiotics, Carbapenems and III-IV generation cephalosporins show a lower cross-reactivity.

C. In infections from MSSA (*Methicillin-Sensitive Staphylococcus aureus*) ß-lactam antibiotics (cefazoline, oxacillin) are more effective than glycopeptides (Vancomycin, Teicoplanin) and are preferred.

D. Vancomycin and Teicoplanin are indicated in Methicillin-Resistant Staphylococcal aureus infections. The Coagulase-negative staphylococci (*S. epidermidis*, *S. hominis, S. haemolyticus*, etc.) resistance is higher for Teicoplanin than for Vancomycin.

E. In case of resistance to Vancomycin or MIC >1, use Daptomycin (in particular in case of bacteraemia), Linezolid (in particular in case of pneumonia or CNS), or Tigecycline as alternatives. Often, a high MIC for Vancomycin corresponds to a high MIC for Teicoplanin also.

F. Coagulase-negative staphylococci (CoNS) bacteraemia are to be considered true (and not likely to be contaminated) if: positivity of multiple bottles (aerobic/anaerobic) in the same collection set, multiple blood cultures within 48 hours, same pathogen positivity on multiple samples.

G. In the treatment of anaerobic infections, if protected penicillins (amox/clav., PIP/TAZ) or Carbapenems are used, the use of Metronidazole can be considered superfluous.

1) *sepsis/septic shock of community or nosocomial origin but with a stay <2 days [December. 2018]*

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL TEST RESULTS

SEPSIS/SEPTIC SHOCK OF COMMUNITY OR NOSOCOMIAL ORIGIN BUT WITH A STAY <2 DAYS

RISK FACTORS FOR MDR

YES

NO

MEROPENEM 2 G Q8H IV + LINEZOLID 600 MG Q12H

PIPERACILLIN / TAZOBACTAM 4.5 G Q6H IV
+
AMIKACIN 15 MG/KG/DAY
+
VANCOMYCIN 1 G LD + 2 G IN CONTINUOUS INFUSION

SUSPECTED ABDOMINAL ORIGIN

IF ALLERGY TO BETA-LACTAMS

SUSPECTED OTHER ORIGIN

TIGECYCLINE 200 MG LD + 100 MG Q12H
+
AMIKACIN 15 MG/KG/DAY
+
VANCOMYCIN 1 G LD + 2 G IN CONTINUOUS INFUSION

[MEROPENEM 2 G Q8H IV OR PHOSPHOMYCIN 4 G Q6H OR COLISTIN 9 MU LD (3H) + 4.5 MU Q12H (3H)]
+
AMIKACIN 15 MG/KG/DAY
+
VANCOMICIN 1 G LD + 2 G IN CONTINUOUS INFUSION

Gruppo Tecnico Programma Regionale Lotta alla Sepsi – Regione Toscana

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS

```
          ┌─────────────────────────────┐
          │  NOSOCOMIAL SEPSIS/SEPTIC    │
          │  SHOCK STAY >2 DAYS          │
          └─────────────────────────────┘
                        │
          ┌─────────────────────────────┐
          │  MEROPENEM 2 G Q8H IV        │
          │            +                │
          │  LINEZOLID 600 MG Q12H       │
          └─────────────────────────────┘
                        │
          ┌─────────────────────────────┐
          │       IF KPC CERTAIN         │
          └─────────────────────────────┘
              YES              NO
   ┌──────────────────────────┐   ┌──────────────────────────┐
   │ COLISTIN 9 MU LD (3H)     │   │ CONFIRM THERAPY IN       │
   │ + 4.5 MU Q12H (3H)        │   │ PROGRESS                 │
   │          +               │   └──────────────────────────┘
   │ TIGECYCLINE 200 MG        │
   │ LD+100 MG Q12H            │
   │          +               │
   │ GENTAMICIN 5 MG/KG/DAY    │
   │          +               │
   │ LINEZOLID 600 MG Q12H     │
   └──────────────────────────┘
```

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS

```
[AMOXICILLIN/CLAVULANATE 4.4 G Q8H          ┌──────────────────────┐          [PIPERACILLIN/TAZOBACTAM 4.5 G Q8H
 OR AMPICILLIN/SULBACTAM 3 G Q6H]           │ URINARY TRACT SEPSIS │           OR CEFTOLOZANE/TAZOBACTAM 1.5 G Q8H
           +                                └──────────────────────┘                    +
[GENTAMICIN 3 MG/KG/DAY OR                            │                        [GENTAMICIN 3 MG/KG/DAY OR
 AMIKACIN 15 MG/KG/DAY]                               │                         AMIKACIN 15 MG/KG/DAY]

         NO        NO                              YES         NO
              ┌────┐   ┌──────────────┐   ┌────┐
              │ CV │   │  RR FOR MDR? │   │ CV │
              └────┘   └──────────────┘   └────┘
         YES                                   YES

[PIPERACILLIN/TAZOBACTAM 4.5 G Q8H OR                     [PIPERACILLIN/TAZOBACTAM 4.5 G Q8H OR
 CEFTOLOZANE/TAZOBACTAM 1.5 G Q8H]                         CEFTOLOZANE/TAZOBACTAM 1.5 G Q8H OR
           +                                              MEROPENEM 1 G Q6H]
[GENTAMICIN 3 MG/KG/DAY OR                                          +
 AMIKACIN 15 MG/KG/DAY]                                   [LINEZOLID 600 MG Q12H OR
                                                          VANCOMYCIN 15 MG/KG FOR 12H
                                                          (LOADING 25 MG/KG)]
                                                                   +
                                                          [GENTAMICIN 3 MG/KG/DAY OR
                                                           AMIKACIN 15 MG/KG/DAY]
```

3-a) Urinary tract sepsis - In the case of patients colonised by specific MDR germs, if ABG are not available [December. 2018]

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS	
Klebsiella pneumoniae KPC	meropenem 2 g q8h + phosphomycin 4 g x4/day or tigecycline 100 mg q12h (loading 200 mg) + colistin 4.5 mln U x2/day (loading 9 mln U) or ceftazidime/avibactam 2.5 g q8h
Acinetobacter baumannii	meropenem 2 g q8h + ampicillin/sulbactam 3 g q6h + colistin 4.5 MU q12h (loading 9 MU) + rifampicin 600-900 mg/day

3-b) Urinary tract sepsis - In case of allergy to beta-lactams [December. 2018]

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS	
Empirical tp 1	ciprofloxacin 400 g q12h + phosphomycin 3 g q6h + gentamicin 3 mg/kg/day or amikacin 15 mg/kg/day
Empirical tp 2	ciprofloxacin 400 g q8h + phosphomycin 4 g q6h + gentamicin 3 mg/kg/day or amikacin 15 mg/kg/day
Empirical tp 3	ciprofloxacin 400 mg q8h or colistin 4.5 MU q12h (loading 9 mln U) + phosphomycin 4 g q6h + linezolid 600 mg q12h or vancomycin 15 mg/kg q12h (loading 25 mg/kg) + gentamicin 3 mg/kg/day or amikacin 15 mg/kg/day

4) Pulmonary sepsis [December. 2018]

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS

PULMONARY SEPSIS

RISK FACTORS

NO — **YES**

TREATMENT FOR COMMUNITY -ACQUIRED PNEUMONIA

COPD - SMOKING - DIABETES ALCOHOLISM – *ASPIRATION*

IDU - POST INFLUENZA

RISK OF INFECTION FROM MDR

HAP / HCAP

CEFTRIAXONE 2 G IV/DAY
+
[AZITHROMYCIN 500 MG *OR* CLARITHROMYCIN 500 MG Q12H]

PIPERACILLIN/TAZOBACTAM 4.5 G Q6H
+
CEFTRIAXONE 2 G IV/DAY
+
METRONIDAZOLE 500 MG Q6H
OR
AMPICILLIN/SULBACTAM 3 G Q6H

CEFTRIAXONE 2 G/DAY IV
+
VANCOMYCIN 1 G IV Q12H
OR
LINEZOLID 600 MG Q12H
OR
CEFTAROLINE 600 MG X Q8H

[CEFEPIME 2 G Q8H *OR* PIPERACILLIN/TAZOBACTAM 4.5 G Q6H]
+
[VANCOMYCIN 1 G IV Q12H *OR* LINEZOLID 600 MG Q12H]
CONSIDER ADDING LEVOFLOXACIN 750 MG
OR
AZITHROMYCIN 500 MG, IF SUSPECTED *LEGIONELLA*

IF *PSEUDOMONAS* AERUGINOSA RISK FACTORS

IF *ACINETOBACTER* BAUMANNII COLONISATION

IF KPC COLONISATION

PIPERACILLIN/TAZOBACTAM 4.5 G Q6H OR MEROPENEM 2 G Q8H
ALSO CONSIDER
GENTAMICIN 5 MG/KG/DAY
ALSO CONSIDER
[LEVOFLOXACIN 750 MG/DAY OR CIPROFLOXACIN 400 MG Q8H]
MDR (FROM PREVIOUS ISOLATIONS) MEROPENEM 2 G Q8H
+
COLISTIN 9 MU LOADING DOSE THEN 4.5 MU Q12H
OR
FOSFOMYCIN 4 G Q6H
+
COLISTIN AEROSOL
+
CIPROFLOXACIN 400 MG Q8H

COLISTIN 9 MU LOADING DOSE THEN 4.5 MU Q12H
+
MEROPENEM 2 G Q8H
+
RIFAMPICIN 600 MG/DAY
OR
AMPICILLIN/SULBACTAM 3 G Q6H

COLISTIN 9 MU 1ST DOSE THEN 4.5 MU Q12H
+
TIGECYCLINE 200 MG 1ST DOSE THEN 100 MG Q12H (OR FOSFOMYCIN 4 G Q6H)
+
MERO PENEM 2 G Q8H
ALSO CONSIDER
AMIKACIN 1 G/DAY
OR
CEFTAZIDIME AVIBACTAM 2.5 G Q8H
+
MEROPENEM 2 G Q8H
+
GENTAMICIN 240 MG/DAY

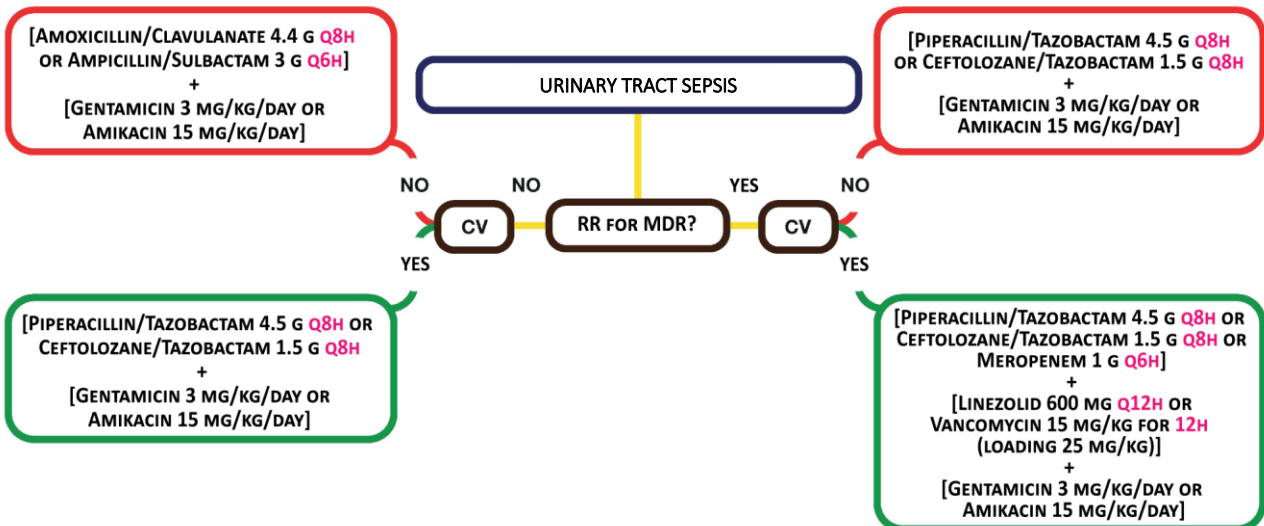## 5) *Abdominal sepsis [December. 2018]*

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS

ABDOMINAL SEPSIS

HEALTHCARE-ASSOCIATED?

NO → **BILIARY TRACT**

YES → **ANTIBIOTIC TP**

BILIARY TRACT
- YES → AMPICILLIN/SULBACTAM 3 G Q6H
  OR
  CEFTRIAXONE Q12H
  +
  METRONIDAZOLE 500 MG Q6H
- NO → PIPERACILLIN/TAZOBACTAM 4.5 G Q8H
  OR
  AMPICILLIN/SULBACTAM 3 G Q6H
  ALSO CONSIDER
  GENTAMICIN 3 MG/KG

ANTIBIOTIC TP
- YES → **C. DIFFICILE**
- NO → **Chirurgia**

C. DIFFICILE
- YES → VANCOMYCIN 125 MG x4 OS
  +
  METRONIDAZOLE 500 MG Q6H IV
  OR
  FIDAXOMICIN 200 MG Q12H OS
  NB: CONSIDER SUSPENSION
  OF THE ANTIBIOTIC TP IN PROGRESS

Chirurgia
- YES → PIPERACILLIN/TAZOBACTAM 4.5 G Q8H
  OR
  IMIPENEM 0.5-1 G Q6H
  OR
  CEFTOLOZANE/TAZOBACTAM 1.5 G Q8H
  +
  METRONIDAZOLE 500 MG Q6H
  +
  GENTAMICIN 3 MG/KG/DAY
  ALSO CONSIDER
  ECHINOCANDIN
- NO → PIPERACILLIN/TAZOBACTAM 4.5 G Q8H
  OR
  IMIPENEM 0.5-1 G Q6H
  OR
  CEFTOLOZANE/TAZOBACTAM 1.5 G Q8H
  +
  METRONIDAZOLE 500 MG Q6H
  +
  GENTAMICIN 3 MG/KG/DAY

KPC COLONISATION → COLISTIN 9 MU LOADING DOSE THEN
4.5 MU Q12H
+
TIGECYCLINE 100 MG Q12H
+
MEROPENEM 2 G Q8H
OR
CEFTAZIDIME AVIBACTAM 2.5 G Q8H
+
MEROPENEM 2 G Q8H
+
GENTAMICIN 240 MG/DAY

COLONISATION BY ACINETOBACTER BAUMANNII → COLISTIN 9 MU LOADING DOSE
THEN 4.5 MU Q12H
+
TIGECYCLINE 100 MG Q12H
+
AMPICILLIN/SULBACTAM 3 G Q8H

6) Sepsis associated with skin and soft tissue phlogosis [December. 2018]

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS

```
                    ┌──────────────────────────────────────────────────┐
                    │ SEPSIS ASSOCIATED WITH SKIN AND SOFT TISSUE        │
                    │ PHLOGOSIS                                          │
                    └──────────────────────────────────────────────────┘

   WITHOUT PURULENT          WITH SUBCUTANEOUS         WITH INVOLVEMENT OF THE MUSCULAR
   COLLECTION                ABSCESS                   FASCIA (NECROTIZING FASCIITIS)
```

GRAM-NEGATIVE RISK FACTORS

NO / **YES**

AMOXICILLIN/CLAVULANATE 2 G Q8H
+
CLINDAMYCIN 600 MG Q8H

[VANCOMYCIN 1 G Q12H OR
LINEZOLID 600 MG Q12H]
+
[PIPERACILLIN/TAZOBACTAM 4.5 G Q8H OR
ERATAPENAM 1 G/DAY OR
MEROPENEM 1 G Q8H]

[VANCOMYCIN 1 G Q12H OR
TEICOPLANIN 6-12 MG/DAY]
+
CLINDAMYCIN 600 MG Q8H
+
[PIPERACILLIN/TAZOBACTAM 4.5 G Q6H OR
ERATAPENAM 1 G/DAY OR
MEROPENEM 2 G Q8H]
OR
[LINEZOLID 600 MG Q12H OR
DAPTOMYCIN 10 MG/KG/DAY]
+
[PIPERACILLIN/TAZOBACTAM 4.5 G Q6H OR
ERATAPENAM 1 G/DAY OR
MEROPENEM 2 G Q8H]

CRE COLONISATION

FOSFOMYCIN 4 G Q6H
+
TIGECYCLINE 200 MG 1ST DOSE THEN 100 MG Q12H
+
MEROPENEM 2 G Q8H
ALSO CONSIDER
AMIKACIN 1 G/DAY

EMPIRICAL THERAPY TO BE REVIEWED WITHIN 48-72H ON THE BASIS OF MICROBIOLOGICAL RESULTS

CENTRAL NERVOUS SYSTEM SEPSIS

LIQUOR

CEREBRAL ABSCESS

turbid

Dexamethasone 10 mg q6h
Add before the dose
of antibiotic in the patient
with strong suspicion of
bacterial meningitis
+
Ceftriaxone 2 g q12h
+
Rifampicin 600 mg q12h
If risk factors* for *Listeria* add
Ampicillin 3 g q6h

POST-SURGERY (Neuro, ENT), TRAUMA, VENTRICULAR-PERITONEAL SHUNT

Cefepime 2 g q8h
or Meropenem 2 g q8h
+
vancomycin 1 g q12h
(with loading dose)
add Linezolid 600 mg q12h

limpid

Ceftriaxone 2 g q12h
+
Aciclovir 10 mg/kg q8h
If risk factors*
for Listeria add
Ampicillin 3 g q6h

Primary

Meropenem 2 g q8h
(alone)
or
Ceftriaxone 2 g q12h
+
Metronidazole 500 mg q8h

Post-surgery

Linezolid 600 mg q12h
+
Meropenem 1 g q8h]

Post-trauma

Ceftriaxone 2 g q12h
+
vancomycin 1 g q12h
(with loading dose)
Also consider
Gentamicin 3.5 mg/kg/day

*Risk factors for Listeria

Age>50 or age between 15-50 but with a history of alcohol abuse,
pregnancy, diabetes mellitus, use of immunsuppressive
drugs, oncological disease
or other causes of acquired immunodeficiency

KEY

q6h: Every 6 hours	**RF:** Risk Factors	**OS:** orally
q8h: Every 6 hours	**KPC:** Klebsiella Pneumoniae Carbapenemasi	**IV:** Intravenous
q12h: Every 6 hours	**MDR:** Multidrug-resistance	**CV:** urinary catheter
DD: days	**HCAP:** healthcare-associated pneumonia	**CRE:** Carbapenem-resistant
day: daily	**HAP:** hospital-associated pneumonia	enterobacteriaceae
LD: Loading Dose	**ENT:** Ear, Nose and Throat	**IDU:** Intravenous drug use
	NCH: Neurosurgery	**MU:** millions of units

3.6.1 *Off-label* antibiotic therapies

The *off-label* prescription provides for the use of a drug outside the conditions reported in the "Summary of Product Characteristics" (SmPC) authorised by the Italian Medicines Agency (AIFA) on the basis of registration studies. The *off-label* prescription can differ from what is stated in the SmPC for:

- therapeutic indication
- dosage
- method of administration (administration route, administration times, duration of treatment)

Regulatory Context

The use of *off-label* drugs is governed by the following regulations:

- Law 648/96
- Law 94/98 (DI BELLA'S LAW)
- Law 296/2006 art. 1 section 796 (Financial law 2007)
- Law 244/2007 art. 2 section 348 (Financial law 2008)
- Law 79/2014

The **diffuse and systematic** use of drug therapies payable by the Italian National Health Service outside the Marketing Authorisation conditions **is not allowed** for the treatment of diseases for which drugs with specific indications for treatment are authorised. Such a use is allowed **only in the context of clinical trials.**

The **sporadic use** of a drug outside the conditions of registration can occur exceptionally **in individual cases** characterised by:

1. Lack of a valid therapeutic alternative from documentable data
2. Acquisition of the patient's informed consent
3. Assumption of responsibility by the doctor
4. Presence of **phase 2 clinical trial favourable data**

It should be noted that the doctor's use of the option to prescribe a drug for *off-label* use cannot constitute the recognition of the patient's right to dispensation of the medicinal product payable by the NHS, i.e., the costs of the drug are charged to the patient. It remains understood that the use of the drug for a patient hospitalised in an accredited public or private facility is payable by the Italian National Health Service, since the hospitalisation fee includes the cost of the pharmacological treatment practiced.

Within the context of Law 648/96, it is allowed, **when there is no valid therapeutic alternative**, on the proposal of **Patient associations**, **Scientific societies**, **Hospitals**, **Universities**, **Scientific Institutes for Research/Hospitalisation and Healthcare**, to request the Scientific Technical Consultative Commission of the AIFA to include a medicinal product in the List of dispensable drugs payable by the NHS to be used for a therapeutic indication other than the authorised indication, provided that results of **phase two studies** are available.

Law 79/2014 introduced the possibility of requesting inclusion in the list of drugs pursuant to Law 648/96, **even where there is a valid therapeutic alternative in the context of authorised drugs**, of drugs to be used for a therapeutic indication other than the authorised indication, provided that such **indication is known and in accordance with research conducted within the national and international medical-scientific community, according to parameters of economy and appropriateness**.

- The *off-label* use of drugs must be limited to **single uses**, in situations of actual lack of therapeutic alternatives and supported by scientific evidence documented in the literature (**phase II clinical studies**).
- For *off-label* drugs used in **recurrent contexts** without valid therapeutic alternatives, the approach envisaged by current legislation for the request of **inclusion in the lists of Law 648/96** should be followed, so that the expenditure incurred can be correctly charged to the NHS.

3.7 When and how to start resuscitation with fluids

"When, how and which fluids to administer?"

Sepsis and septic shock, as defined in 2016 by Sepsis-3, from the haemodynamic point of view, are a combination of hypovolaemia, depressed vascular tone, microvascular insufficiency and cardiac dysfunction. The result is hypotension, inadequate supply of oxygen to the tissues and tissue hypoxia [71] [17]. The degree of each of these abnormalities varies from patient to patient.

Current guidelines recommend infusing intravenously to the limit 30 mL/kg crystalloid within the first three hours of resuscitation.

It is imperative to re-evaluate fluid response early in order to provide adequate therapy. Current guidelines recommend using dynamic variables to anticipate the risks of fluid response instead of static measurement of CVP (Central Venous Pressure - detected by Central Venous Catheter), which is not as effective [72]. As in the case of the administration of antibiotic therapy within the first hour for all patients, even in the case of fluid resuscitation, a standardised approach that does not include a case-by-case risk assessment reduces the expected benefit in many subgroups of patients. Also in this section, we will try to provide the main tools to anticipate the risks and allow the most appropriate fluid resuscitation to be chosen.

> *Criticality of an approach to administration of non-risk based fluids >* Arbitrarily establishing the volume to be infused has raised many doubts in the scientific community. Septic patients, in fact, have different volume deficits [73]. The administration of a predefined volume could lead, in some cases, to an oversized resuscitation and, in others, to an undersized one. The risk of fluid overload should be especially considered in patients with cardiovascular comorbidity. Furthermore, the indication to consider a three-hour interval does not guarantee an early reassessment of the haemodynamic status. Early reassessment is also recommended by the ESICM (European Society of Intensive Care Medicine) [74].

In the following detailed study box we suggest the main methods for the contextual evaluation of fluid resuscitation.

Evaluation of the response to fluid resuscitation - The fluid challenge > The *fluid challenge* - literally fluid test - does not make it possible to predict the response to fluids but, by the fact that the infusion takes place, directly assesses the consequences. The Fenice study has shown a great variability in carrying out the *fluid challenge* (in terms of volume and infusion rate) and found that in half of the cases, an additional bolus of fluids was administered with a negative result [74]. This misleading interpretation of the approach can eventually lead to fluid overload. Alternatively, especially in the operating theatre, a "mini-*fluid challenge*" has been proposed that consists in the infusion of only 100 mL of fluids [75] [76]. However, since a reduced volume of fluids can induce only small haemodynamic changes, it is necessary to have a very precise measurement of the cardiac output.

Predicting the response to fluid resuscitation - the dynamic variables > Over the years, methods for evaluating dynamic variables have been proposed, useful for predicting the response to fluids without the need to infuse them [77]. The *Pulse Pressure Variation* (PPV) - [78] and the *Stroke Volume Variation* (SVV) -[79] have been shown in many studies to effectively predict fluid response in patients with assisted ventilation in cases where the Current Volume is normal [80]. They have proven to be less reliable in ventilation with low current volume. This limitation can be overcome by increasing the current volume from 6 mL/kg to 8 mL/kg for one minute, and by simultaneously measuring the PPV and SVV response [81]. An increase in PPV or SVV of at least 3.5% or 2.5%, respectively, predicts the fluid response at 6 mL/kg [82]. Spontaneous breathing, cardiac arrhythmias, low pulmonary *compliance* and high frequency of ventilation limit the use of the PPV and SVV variables [83] to predict fluid response. Other dynamic variables that predict fluid response, such as **collapsibility of the superior vena cava** [84]**, distensibility of the jugular vein** [85]**, respiratory variation of the inferior vena cava diameter** [86] **or variation of the plethysmographic signal** [87] share the limitations of the PPV and SVV. Limitations that do not apply to **the end-expiratory occlusion** (EEO) test, also valid in cases of arrhythmia and spontaneous breathing activities. This test is performed in mechanically ventilated patients maintaining exhalation for 15 seconds. An increase in heart rate of more than 5% acceptably predicts the fluid response [88]. Due to the low threshold value, a very precise method of measuring the heart rate must be used, such as Pulse Code Modulation (PCM) or, rather, analysis with the *Pressure Recording Analytical Method* (PRAM). However, if ultrasound is the only instrument available to measure cardiac output in ventilated patients, an end-inhalation occlusion test should be combined with an end-exhalation occlusion test. [89].

The *passive leg raise* (PLR) test can be used in almost all patients including those with partial or total spontaneous breathing. Reliably predicts fluid response [90]. To be interpreted correctly, it is necessary to abide by the following 3 rules [91]:

I	the PLR must start from the semi-recumbent position
II	the effects of PLR must be assessed using real-time heart rate measurements.
III	precautions should be taken to prevent adrenergic stimulation, which may result in an unreliable interpretation of the test

Table 26 - The three rules for performing the passive leg raise test

What is the optimal fluid for resuscitation in sepsis? Multicentre studies did not find significant differences between the main types of fluid used (albumin and crystalloids). For a more in-depth review of the topic, see the reference literature [92][93][94][95]. The choice of fluid in sepsis resuscitation is still largely unknown and needs to be more clearly outlined. Furthermore, the choice of fluid once the initial resuscitation has been completed is unclear. Despite numerous studies, the role of colloids, how many to use and which type to use, is still unclear. Studies that distinguish between balanced crystalloids and 0.9% saline are needed; however, these studies should be more adherent to the daily behaviour of doctors and consider measurements of chlorine and discontinuation of administration if hyperchloraemia occurs. Given the heterogeneity of the aetiology of sepsis, the sepsis subgroups need to be further evaluated to determine whether there are specific groups in which the type of fluid has a real impact on the outcome. Finally, the possible choices of fluid in the areas of care with limited resources have not been exhaustively explored; studies are, therefore, needed to investigate the optimal type of fluid to be used in such *settings*.

History of the Early Goal Directed Therapy (EGDT) > In 2001 an aggressive step-by-step haemodynamic strategy was proposed, called "Early Goal Directed Therapy" (EGDT) [96], which was later adopted in 2004 by the Surviving Sepsis Campaign (SSC) and included in the first edition of the international guidelines. This step strategy was geared towards normalising central venous oxygen saturation (ScvO2) within the first six hours of resuscitation. As a first step, the infusion of fluids was recommended in order to obtain a central venous pressure (CVP) between 8 and 12 mmHg. As a second step, administration of the vasopressor was recommended, if the mean arterial pressure (MAP) was <65 mmHg. As a third step, in the case of ScvO2 <70% despite reaching the target for CVP and MAP, blood transfusions and possibly the administration of dobutamine (inotropic) were considered. In a study that included 263 patients, the application of EGDT significantly decreased mortality, compared to the control group where ScvO2 was not used. Applying EGDT, a higher volume of fluids in the first six hours, compared to the standard cure, was recorded (average 5,000 mL versus 3,500 mL). The EGDT protocol was fully adopted by the SSC [97] but many criticisms were raised about the protocol [98] [99]. Among these was the use of CVP to manage resuscitation with fluids, since there is strong evidence that CVP is an unreliable static measure of fluid response [72]. The administration of fluids up to a CVP value as high as 12 mmHg - a value five to six times higher than normal values - could lead to fluid overload. In a study with a large number of septic shock patients, those with a CVP <8 mmHg 12 hours after admission had a higher survival rate than those with CVP >12 mmHg [100]. Cumulative positive fluid balance has been shown to be an independent mortality factor in septic patients. In a cohort of 23,513 septic patients, the administration of more than 5 litres of fluids during the first day was associated with an increased risk of death [101]. Three multicentre studies (ProCESS [102] ARISE [103] and ProMISE [104]) were conducted to compare EGDT with the use of ScvO2 in standard care. In none of these studies did EGDT show benefit in terms of outcome, as recently confirmed by a meta-analysis [105]. It is important to note, however, that the patients from these three studies were less seriously ill than those enrolled in the original EGDT study [96] as they had fewer comorbidities, lower lactate levels and lower mortality rates. In the three multicentre studies, the average ScvO2 was already higher than the target (70%) set at the time of enrolment, so that these studies could not demonstrate any benefit from the application of EGDT. Therefore, these studies cannot exclude a benefit of reaching a ScvO2 target >70% when ScvO2 is lower than this value, as was the case in the original EGDT study (ScvO2 49% on average). CVP and ScvO2 were removed from the recommendations [17].

Rescue resuscitation phase (immediately) During the first phase of treatment, called the rescue resuscitation phase [106], the main objective of fluid therapy is to obtain blood pressure and cardiac output levels that are compatible with immediate survival.

*Administration of norepinephrine >*After the initial phase, the benefit/risk ratio of further volume expansion should be carefully assessed with dynamic measurements in each patient. Norepinephrine should be administered early in the event of life-threatening hypotension even when hypovolaemia has not yet been controlled.

Within the first hour of resuscitation (1 hour) When hypovolaemia is constant in the initial phase of septic shock, fluids should be infused urgently without using fluid response predictors. A rate of administration of 10 mL/kg within the first hour (30-60 minutes) of resuscitation appears to be a reasonable time. A higher infusion rate should be considered in cases of evident fluid loss, distribution of fluids in the third space as in the case of abdominal sepsis, high body temperature, mottling of the skin, high or low pressure capillary filling time of arterial pulse (suggesting low stroke volume). Lower infusion rates should be considered if signs of pulmonary oedema appear during fluid infusion in the event of severe lung injury.

After the initial phase of fluid resuscitation (3 hours) If the signs of shock have disappeared, there is no need to continue the volume expansion. If the shock persists, it is necessary to predict fluid response before deciding to continue infusion of fluids to prevent fluid overload in patients who do not respond to fluids, who represent about half the population of critically ill patients [107].

Patients with ARDS > Fluid administration is logical only in patients who respond positively to fluids, while alternative options should be chosen if patients do not respond. However, even in patients who respond to fluids, the benefit/risk ratio of continuing fluid therapy should be carefully evaluated, especially if associated with ARDS (*Acute Respiratory Distress Syndrome*). In the latter case, monitoring of cardiac output also through transpulmonary thermodilution could be an interesting monitoring technique, since it also allows the measurement of extravascular lung water (EVLW) and the pulmonary vascular permeability index (PVPI) [108]. Both are indicators of the risk of fluid administration and are independent factors that predict mortality in ARDS[109]. Pulmonary artery occlusion pressure measured with a catheter in the right heart could be an alternative [110]. *Hypotension due to depressed vascular tone>* If hypotension is mainly due to a depressed vascular tone, even when hypovolaemia has not yet been resolved [97] [111] [112], administration of norepinephrine should be initiated. Low diastolic blood pressure, especially in patients with tachycardia, is an easy way to identify such a situation [73]. Norepinephrine has the advantage of increasing cardiac output, if started early [113], redistributing venous blood from the "unstressed" volume to the "stressed" volume [110].

Fig. 9 - Algorithm for resuscitation with fluids

Patients who present with sepsis and septic shock

Infuse about 10 mL/kg crystalloid within the first hour (30-60 minutes)

Decrease the infusion rate in case of:
• Worsening of tachypnoea
• Fall in O2 saturation

Increase the infusion rate in case of:
• Evident fluid loss
• Abdominal sepsis
• High fever
• Mottling
• Increased capillary filling time
• Low arterial pulse pressure

If shock persists Fluid response test

Variation of ejection volume

Variation of pulse pressure

Flow volume test

Passive leg raising test

Inferior vena cava Change in diameter

End-expiratory occlusion

Preload response

Preload non-response

Patients without ARDS

Patients with ARDS

Consider another bolus of fluids

Assess the benefit/risk ratio of continuing fluid therapy

Benefit>risk
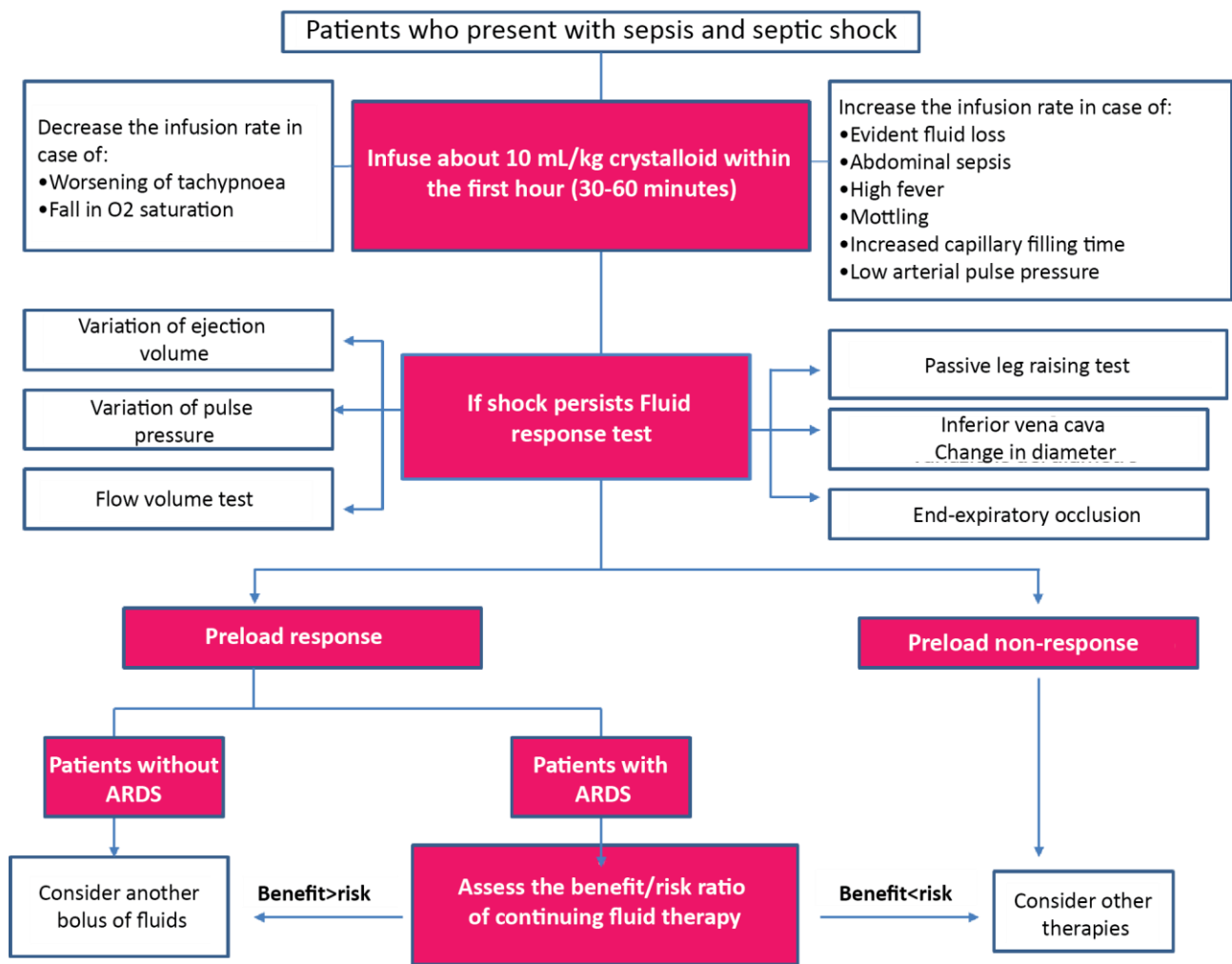
Benefit<risk

Consider other therapies

Fig. 9 - Algorithm for resuscitation with fluids

It is also stressed that early administration of norepinephrine could prevent fluid overload [115]. In patients with sepsis and septic shock, rather than following predefined therapeutic algorithms, it is much more reasonable to individualise fluid resuscitation to prevent damage caused by fluid overload.

What is the optimal approach for the selection, dosage and escalation of vasopressor therapy?

In shock patients, norepinephrine has been shown to be a better vasopressor choice, when compared to dopamine [116]. Adrenaline can be considered a substitute vasopressor when an inotropic action is required. As a non-catecholamine vasopressor, vasopressin has been shown to be safe as an adjunct agent to norepinephrine with an improvement potential found in a subset of patients with less severe septic shock [117]. Vasopressin was compared with norepinephrine as a primary agent. Compared to the latter, there was no difference with regard to acute kidney injury and did not confirm beneficial effects in patients with septic shock of lesser severity [118]. More recently, angiotensin II has shown efficacy in raising the mean arterial pressure (MAP) but the effects on the *outcome* are still to be demonstrated [119]. In contrast, it has been shown that non-selective inhibition of Nitric Oxide Synthase (NOS) increased mortality [120], highlighting that the evaluation of vasopressors should not be based on its haemodynamic effects only. Finally, a higher MAP target did not prove to be beneficial in patients with septic shock, although in a subset of patients with severe underlying hypertension, a higher MAP target was associated with a lesser need for renal replacement therapy (RRT) [121].

Based on the analysis of the literature, the tendency to use vasopressors earlier than previously can be detected. 5 good reasons for early use of vasopressors in case of septic shock can be listed.

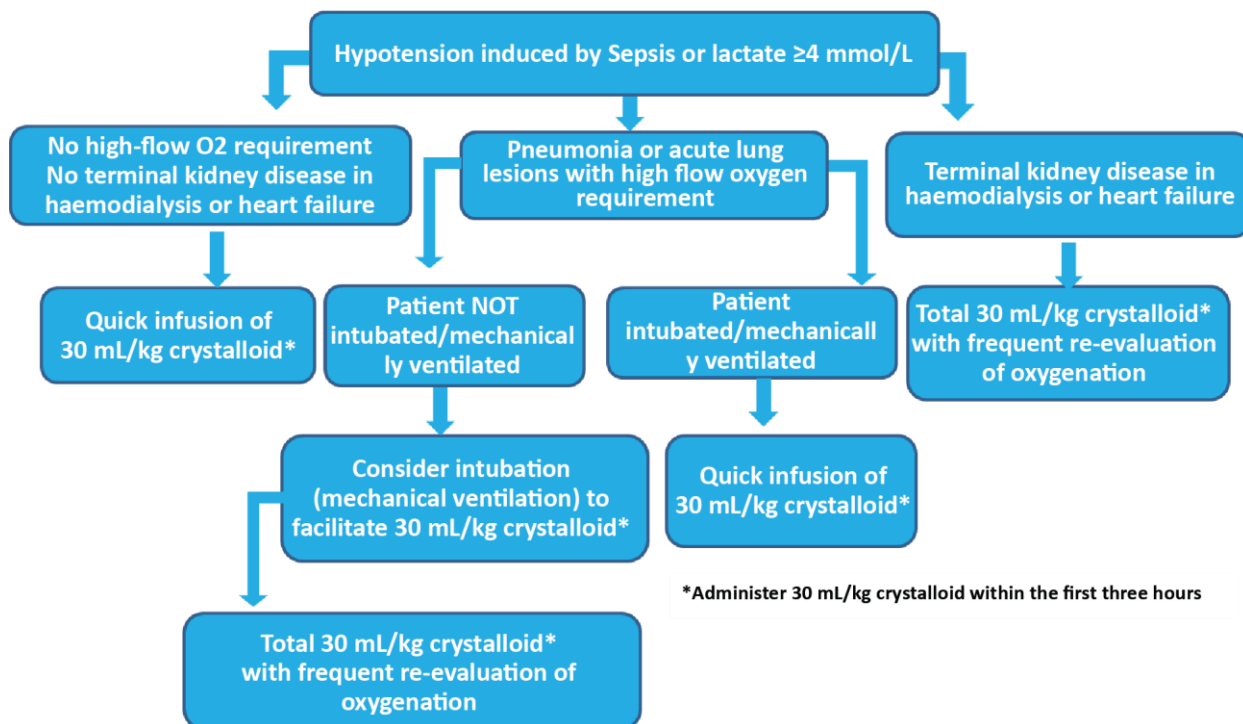| I	the duration and degree of hypotension are associated with an increase in mortality
II	the delayed start of vasopressors is associated with increased mortality
III	the early administration of norepinephrine increases cardiac output by increasing preload
IV	the early administration of norepinephrine in patients with severe hypotension improves microcirculation
V	early administration of norepinephrine prevents damaging fluid overload

Table 27 - The five reasons for the early use of vasopressors in case of septic shock

low diastolic blood pressure is an indicator of a depressed vascular tone: it is an easy way to identify which patients are suitable for early treatment with norepinephrine

In the last twenty years of research on septic shock, the type of objectives studied has been the subject of many variations, making it difficult to consistently evaluate the use of the various vasopressors. Studies have observed dosages, resuscitation strategies, clinical objectives and plans to increase the intensity of

different therapies. In other words, there is no common framework for the study of vasopressors. In fact, the current recommendations that support the use of vasopressors to maintain the MAP at 65 mmHg are based on observational data only. Many essential questions still remain unanswered; for example, a therapeutic approach is needed that compares a catecholamine (norepinephrine) to a non-catecholamine (vasopressin, angiotensin II) to raise the MAP and improve survival. In addition, the role of epinephrine as a second-line agent needs to be further assessed. Patient subgroups should be better assessed (heart failure, essential hypertension) by observing patients who suffer from adverse events generated by hypotension as well as those who suffer from adverse events of vasopressor therapy (arrhythmias and acute kidney injury).

Hypotension induced by Sepsis or lactate ≥4 mmol/L

No high-flow O2 requirement No terminal kidney disease in haemodialysis or heart failure

Pneumonia or acute lung lesions with high flow oxygen requirement

Terminal kidney disease in haemodialysis or heart failure

Quick infusion of 30 mL/kg crystalloid*

Patient NOT intubated/mechanically ventilated

Patient intubated/mechanically ventilated

Total 30 mL/kg crystalloid* with frequent re-evaluation of oxygenation

Consider intubation (mechanical ventilation) to facilitate 30 mL/kg crystalloid*

Quick infusion of 30 mL/kg crystalloid*

*Administer 30 mL/kg crystalloid within the first three hours

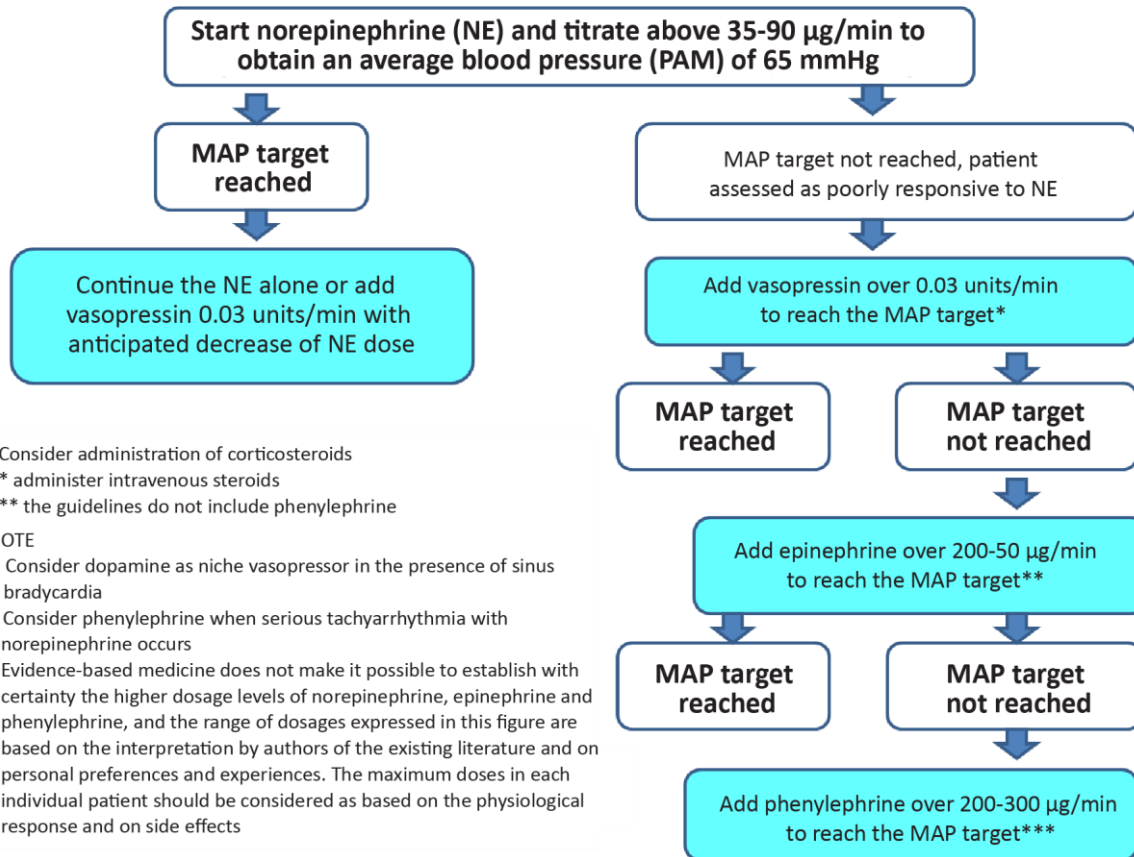Total 30 mL/kg crystalloid* with frequent re-evaluation of oxygenation

Continue to consider fluid resuscitation and the dose of vasopressors with attention to maintaining tissue perfusion and minimising interstitial oedema.

Implement combinations of haemodynamic monitoring (blood pressure response, heart rate; urinary output; cardiothoracic ultrasound; CVP, ScvO2; pulsatory pressure variation; normalisation of lactate clearance) with dynamic measurements (flow response to fluid bolus or PLR) to assist in further resuscitation choices, which may include additional fluids or inotropic therapy.

Consider resuscitation with albumin when large volumes of crystalloids are required to maintain intravascular volume.

Start norepinephrine (NE) and titrate above 35-90 µg/min to obtain an average blood pressure (PAM) of 65 mmHg

MAP target reached

Continue the NE alone or add vasopressin 0.03 units/min with anticipated decrease of NE dose

MAP target not reached, patient assessed as poorly responsive to NE

Add vasopressin over 0.03 units/min to reach the MAP target*

MAP target reached

MAP target not reached

Add epinephrine over 200-50 µg/min to reach the MAP target**

MAP target reached

MAP target not reached

Add phenylephrine over 200-300 µg/min to reach the MAP target***

*Consider administration of corticosteroids
** administer intravenous steroids
*** the guidelines do not include phenylephrine

NOTE
• Consider dopamine as niche vasopressor in the presence of sinus bradycardia
• Consider phenylephrine when serious tachyarrhythmia with norepinephrine occurs
Evidence-based medicine does not make it possible to establish with certainty the higher dosage levels of norepinephrine, epinephrine and phenylephrine, and the range of dosages expressed in this figure are based on the interpretation by authors of the existing literature and on personal preferences and experiences. The maximum doses in each individual patient should be considered as based on the physiological response and on side effects

Pragmatic approach to septic shock sepsis management using non-invasive techniques in spontaneously breathing patients	
Parameters	Possible clinical implications
Blood Pressure	
MAP ≥65 mmHg and diuresis ≥0.5 mL/kg/h	Titer the resuscitation consistently
Inferior vena cava and lung ultrasound	
Ø<1 cm, Vena Cava Index (VCI) ≥40% and absence of line B	Responds to fluids
1< Ø<2.5 cm	Undetermined
Ø>2.5 cm and VCI <40% and presence of line B	Does not respond to fluids
Echocardiography	
Left/right ventricular dysfunction	Inotropes
Normal left/right ventricular function	Vasoconstrictors
Lactate	
Lactate clearance	Titer the resuscitation consistently
VCI= Ø maximum inferior vena cava - Ø minimum inferior vena cava /Ø maximum inferior vena cava x 100 Lactate clearance 10% or more measuring the lactate in 2 assessments within the first 6 hours of resuscitation *Mearelli F. Sepsis outside Intensive Care Unit: the other side of the coin Infection 2015 ; 43:1-11*	

Table 28 - Non-invasive techniques in spontaneously breathing patients
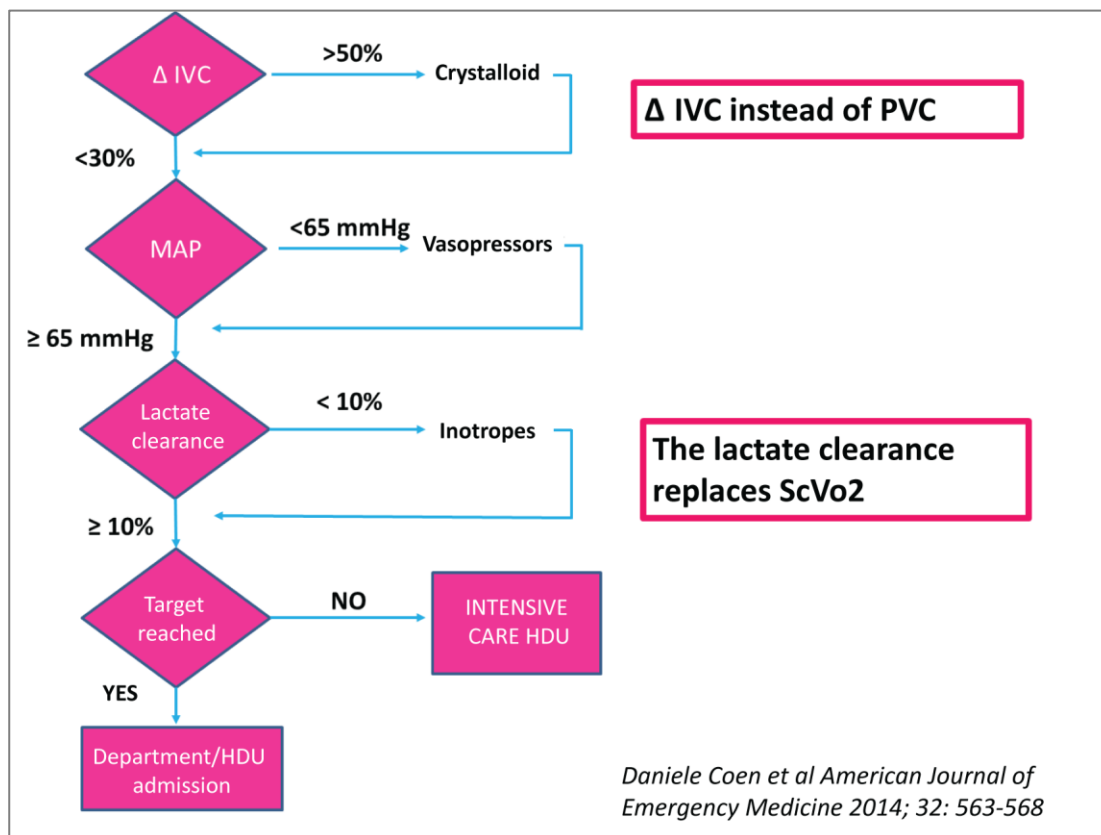
Table 29 - Approach to resuscitation based on the inferior vena cava and lung ultrasound

3.8 When should a patient be transferred to Intensive Care?

Transfer to an ICU bed from HDU or a ward/ED is appropriate whenever there is **immediate need** of support and/or substitution of one or more vital functions for neurological, cardiovascular and respiratory organ failure. ICU transfer is appropriate whenever there is **impending need** for support and/or substitution of one or more vital functions, that is, clinical cases that can deteriorate in a few hours. Transfer to an ICU bed is also appropriate for the need for minor substitution treatment of vital functions progressing towards a risk: e.g., non-invasive ventilation in patients with acute respiratory insufficiency requiring prolonged NIV treatments; this situation is very different from the patient in advanced respiratory *weaning* who requires short NIV trials alternating with increasingly prolonged periods of spontaneous breathing, or the patient in pulmonary oedema who needs contextualised NIV at the initial critical moment. A rapidly deteriorating **septic patient** should oblige an intensive care consultation and/or contact with the TEM (medical emergency team) to evaluate a possible shared transfer of the patient to a bed with more intensive care. In this regard, the difference in the number of beds/number of nurses is also of absolute importance.

3.9 Identification and control of the source: the role of surgery and interventional radiology

The eradication of the focus includes all the actions aimed at controlling an infection source and restoring optimal function of the infected anatomical site. Specifically:

- drainage of infected fluid collections;
- *debridement* of solid infected tissue;
- removal of foreign bodies;
- definitive surgical procedures to correct anatomical alterations that feed microbial contamination and to restore normal organ function.

Intra-abdominal, skin and soft tissue infections represent the anatomical sites where rapid eradication appears more feasible; hence the need for early diagnosis is greater. Catheter-related infections, urinary infections, thoracic infections and those related to implantable devices represent further attacks; therefore, the priority action for a correct and definitive eradication of the focus is its identification. It is mandatory to activate the *imaging* resources (see below: points 7 and 8) and dedicated healthcare staff (interventional radiologist and surgeon) in order to obtain a specific anatomical diagnosis of the infection. The collaboration of professionals *during the performance of the diagnostic investigation* will make it possible:

- to confirm or exclude as quickly as possible the need to intervene to eradicate the focus;
- to select the least invasive procedure (with equal efficacy) in case of identification;
- to re-evaluate the patient with other professionals in case of:
  - missed identification;
  - confirmation of the presence of an outbreak in the absence of indication for "mechanical" eradication (e.g., pneumonia without effusion).

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When the diagnosis is ascertained and shared, the procedure or procedures required for eradication must be implemented as quickly as possible in relation to the clinical and logistic variables. The invasiveness and control method of the infection focus guide the choice of procedure made by healthcare professionals (interventional radiologist and surgeon); in this phase, the inclusion of the anaesthesiologist/resuscitator in the decision-making process is crucial to establish:

- feasibility of the procedure;
- *setting* and any patient relocation (e.g., CT-guided drainage vs. ultrasound-guided drainage);
- times and methods of performance of the procedure based on the clinical picture.

The timeliness of the diagnosis, the sharing of information about the identified focus and the selection of the procedure enable eradication.

Identification and Eradication of the Source of Infection (Source Control)

All patients with sepsis and septic shock who demonstrate the presence of a potentially eradicable focus that is responsible for the clinical picture must undergo procedures aimed at eradicating the focus (drainage, removal, removal of devices). Less invasive manoeuvres with less systemic impact are recommended, postponing the definitive treatment to the stabilisation phase of vital functions

Activity	Healthcare professionals	Instruments and Structures	Training, Procedures and Routine
Eradication of the focus	Radiologist, Interventional Radiologist, Surgeon, Anaesthesiologist, Resuscitator, Responsible Doctor (anyone in charge of the patient, including the General Practitioner), Nurses (of the various departments, it is desirable to identify individual professionals to be instructed and connected to the team to widely disseminate the "fight against sepsis" culture).	Ultrasound (even portable). CT (if prescribed, if the patient is transportable) Drainage kit + set for cultures and possible cytology.	Guidelines (one, simple, univocal). Operating manual for sepsis urgency/emergency activation. Decisional algorithm for removing devices and cultures. Decisional algorithm (general and for single pathology). Clinical report (for each patient - aimed at analysing the pathway). Bibliographic collection document (update every 6 months). IT support (database). Quick, immediate reporting/communication/consulting system to reduce operating delay.
	Healthcare professionals	**Instruments and Structures**	**Training, Procedures and Routine**
	Workgroup creation: report writing, case review, outcome analysis. The eradication of the focus may be necessary in any *setting* (the patient can come from the home or from the GP's clinic), alert level must be maximum (need for constant communication also with the ED and the Emergency Medical Service)	Dedicated operating theatre (urgency/emergency), use of video diagnostic laparoscopy is desirable (even at the patient's bedside - if in resuscitation, intubated). Graphs in the medical records with patient summary information (biochemistry, parameters, blood gas analysis, D-dimer, platelets, PT and PTT	Clinical report (for each patient - aimed at analysing the pathway). Bibliographic collection document (update every 6 months). IT support (database). Quick, immediate reporting/communication/consulting system to reduce operating delay.

Table 30 - System approach to eradicating and identifying the infectious focus

3.10 Oxygen Therapy

Sepsis is linked to the body's systemic inflammatory response to infection. Haemodynamic changes and respiratory failure can lead to poor oxygenation of the tissues. Administering O2 therapy at high flows can help prevent metabolic acidosis and maintain an aerobic metabolism. Administering supplemental O2 is an integral part of sepsis treatment (NICE and Sepsis Six Guidelines) [122] [46]. There is no evidence in the literature to support an oxygen therapy aimed at obtaining "super oxygenation" and the recommendation is as follows: "administer oxygen in order to obtain an O2sat of 94-98% in adult patients or 88-92% in patients at risk of hypercapnic respiratory failure"

Administering Oxygen			
Supplemental oxygen administration helps improve oxygen transport by correcting arterial desaturation. The goal of the treatment is to have an arterial saturation of O2 >94%. The administration of O2 can cause respiratory depression in particular conditions.			
Activity	Healthcare professionals	Instruments and Structures	Training, Procedures and Routine
Administer Oxygen Therapy	Identify the operators responsible for the administration of O2 Local Emergency Medical Service staff DEU [Emergency-Urgency Department] nurses and doctors	Prepare a sepsis panel of actions to be carried out upon arrival in DEU that provides for the administration of O2 after performing blood gas analysis	Create a specific protocol with a defined responsibility matrix

Table 31 - System approach to oxygen administration

3.11 Culture tests

Microbiological tests are essential to know the microbial aetiology of the sepsis and the characteristics of susceptibility to the antimicrobial drugs of the germ involved. In order to be effective, they must be performed on samples taken correctly. The number of samples to be taken varies from a minimum of two pairs of bottles (one bottle for aerobes and one for anaerobes for each pair) taken from different sites, to three, to optimise the sensitivity of the investigation [123] (which increases by about 30% for each pair of bottles), or to even more than three, if there are multiple vascular accesses (one pair of bottles from each access). In fact, changing the sampling site increases the possibility of collecting the germ from circulating blood, and also makes it possible to establish whether the source of the infection is a catheter. Sampling should be performed immediately when there is a suspicion of sepsis, prior to the administration of empirical antibiotic therapy, and prioritising blood culture bottles over tubes for other tests. The box below provides the 7 steps with precautions for performing the sampling [124] [125].

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The method of performing a blood culture can significantly influence the sensitivity of the examination and its result, both in terms of false-positives caused by sample contamination and false-negatives due to an insufficient blood sample. The whole procedure MUST be carefully standardised and recorded. The quality of the result is guaranteed by compliance with the 7 elements listed below.

1. **Timing of the sampling**

   Blood cultures must be performed immediately, upon recognition or suspicion of sepsis, without waiting for the feverish peak or the appearance of chills and, in any case, before starting antibiotic therapy. Venipuncture from a peripheral vein remains the preferred choice to reduce contamination.

2. **Quantity of bottles to be collected**

   The volume of blood cultured is the most important variable to improve sample sensitivity. The recommendations indicate 2-3 sets of blood cultures. The taking of a single set is not recommended for adults because the interpretation of the only positive result could be debatable: is it infection or contamination at the time of sampling? In case of suspected CVC bacteraemia, also take a central vein set together with sampling from the peripheral vein.

3. **Volume of blood to be sampled**

   In general it is recommended to fill 8 mL of blood per bottle without exceeding 10 mL. In case of problems with the venous system, the quantity of blood should not be less than 5 mL. Quantities greater than 10 mL are not recommended due to the increased risk of false positive results. Maintaining the bottles in the vertical position is a useful method of ensuring that the right amount of blood is inoculated.

4. **Bottle filling sequence**

   If a vacutainer® system is used, first the bottle for aerobes must be filled and then the bottle for anaerobes to prevent the air present in the fitting being introduced into the sample.

5. **Time between one sample collection and another**

   The custom of allowing 30 minutes to elapse between one sampling and the next is arbitrary: if empirical therapy has to be started, samples can also be taken 5-10 minutes apart or sample the entire volume of blood to fill 4-6 bottles in a single collection (*single-sampling strategy).* This technique allows to reduce the number of sample collections, limit the workload, reduce the biological risk for healthcare professionals and discomfort for patients. Only in the case of endocarditis is it preferable to take samples at a distance of 30-60 minutes (to document continuous bacteraemia) and, in the case of negativity, collect another 3 sets after 24 hours.

6. **Method of collection, antisepsis of the skin and disinfection of the bottle cap**

   The following is important when collecting specimens:
   a. perform careful hand hygiene;
   b. wear clean gloves (sterile, if necessary palpate the collection site after antisepsis) and barrier devices as indicated by standard precautions;
   c. carry out the antisepsis with 2% chlorhexidine in 70% isopropyl alcohol (alternatively, 10% iodiopovidone in alcoholic solution);
   d. comply with contact times (generally 30 seconds for chlorhexidine and more than 2 minutes for iodiopovidone), and with drying times of the product on the skin;
   e. apply antiseptic with *"back and forth, side to side"* technique, preferably using a sterile disposable applicator;
   f. perform the sampling according to the aseptic technique;
   g. disinfect the rubber diaphragm of the bottles with 70% ethanol or isopropyl alcohol and allow it to dry before inoculating the blood.

7. **Storage and transportation**

   Bottles must be sent to the laboratory as soon as possible. Alternatively, keep the bottles at room temperature until dispatch. For further details on specimen storage, ask the Microbiology Unit to which they are to be sent.

More extensive documentation on blood culture sampling can be found in the document "Infections of the blood stream" edited by GLIPaC [124]. If there is a suspicion of what the origin of the infection may be, it is advisable to take a specimen from this site immediately before the administration of antibiotics, thus shortening the time of laboratory diagnosis and eradication of the focus. In the case of catheter-related sepsis, the positivity times of blood cultures taken from the catheter, at least two hours earlier than those from the peripheral vein, will be indicative.

Culture tests

Specific operating instructions must be provided to carry out the culture tests, including the methods of collection, storage and dispatch by the departments accepting and processing the specimen, and communication of the result and critical values by the laboratory, which must also be guaranteed in the case of a subsequent transfer of the patient to another ward. In particular, not less than 2 complete blood culture sets must be collected; if the acceptance of the samples is not guaranteed 7 days a week, the appropriate storage methods must be defined. The use of technologies that reduce response times should be evaluated.

Activity	Healthcare professionals	Instruments and Structures	Training, Procedures and Routine
Sampling for culture tests	Identify the healthcare professionals responsible for the three stages of the culture tests (pre-analytical, analytical, post-analytical phase). Activate a multidisciplinary team representative of the individuals responsible for the three stages of the culture test to define the standards for collecting, storing and transporting the culture specimens. Involve the outsourced services when they intervene in the transport and/or storage process of the culture specimens	Make the protocol and specific operating instructions for carrying out the culture tests available through IT and/or paper systems. A sepsis panel for the simplified request of all the blood chemistry tests suggested by the diagnostic process. Availability of rapid microbiological diagnosis technologies (rapid identification, with molecular systems or MALDI-TOF mass spectrometry, rapid phenotypic antibiograms, molecular tests for the search for resistance genes, such as Verigene, Cepheid, Biofire, Pheno)	Create a specific protocol with a defined responsibility matrix. Produce a simple graphical representation of the individual operating instructions for each culture test. Draw up a diagram that identifies, based on the suspected infectious focus, the corresponding culture tests to be carried out. Prepare a training project for the implementation of the operating instructions. Define the objectives of the training project based on the degree of involvement of the professional categories. Identify indicators to monitor the quality of all stages of the microbiological investigation

Table 32 - System approach to culture sampling

3.11.1 Communication of the results of microbiological tests

This aspect is crucial for the timely therapeutic intervention, and yet it is subsequent to two generating events: the first is the *concise* communication between clinician and microbiologist, indispensable on the one hand to inform the microbiology laboratory of the priority needs of information and actions pertinent to the critical patient and, on the other hand, based on the laboratory diagnostic findings, to draw attention to patients who could become critical, if they are not so already. The second event is the possibility of performing rapid and reliable diagnostic tests, chosen on the basis of the clinical information and of the results already ascertained. Those who are treating the patient must know what they can ask for. Where necessary, they can resort to adequate training and information, but they must also know how to use the data received and adapt the treatment measures effectively. Dialogue can contribute to locate specimens other than blood cultures with already demonstrated positivity, which also assist in ascertaining the source of infection. There cannot be previously established rules on rapid microbiological tests, since the optimal diagnostic strategy must be established on a case-by-case basis; hence the need for diagnostic *stewardship*. Some general information on the types of tests that can be performed and performance times are summarised in the following table:

Type of test	Waiting time for the result
Rapid microscopic-identification test of species	30-60 minutes
Research on genetic determinants of antibiotic resistance	60 minutes
Phenotypic antibiogram (results in SIR and/or MIC)	3-5-6-8 hours, depending on the method
Culture identification (reference method)	12-24 hours (*)
Culture antibiogram (reference method)	36-48 hours (*)
The positivity time varies according to different parameters; in the case of samples collected correctly and from patients not treated with antibiotic therapy, the positivity time mainly depends on the generation time of the microorganism present, and varies from 2-3 to 24 hours for germs most commonly responsible for bacteraemia.	
Tests that can be performed starting from the positive blood culture (*)	

Table 33 - Waiting times by type of test

In the table above the times reported for culture identification and for the antibiogram performed according to the reference methods are marked with the sign (*); the variability indicated in this case does not refer to the method used in a certain laboratory, but to laboratory opening hourse. Indeed, specialised Microbiology laboratories do not operate in our region on a 24-hour basis or on holidays. This impairs their effectiveness in cases of sepsis and septic shock, causing an increase in patient mortality [126]. It should be stressed that even rapid tests, although obtainable in extremely short times, are not performed in non-operational periods. As regards the methods of communication, these should be excessive: the telephone notification must be confirmed by the recipient, repeating what was communicated by the laboratory. The laboratory must be able to produce partial reports (for example, with the sole identification of the microorganism, or with the sole result of the microscopic examination); send *alert* messages, in the event of isolation of sentinel germs or the detection of particular mechanisms of antibiotic resistance, to the contact persons of departments, infection control, clinical risk, etc. The above are tools that enhance safety in the delivery of information that is potentially crucial for the patient's health.

3.12 Urine Output

Urine Output			
Diuresis should be monitored in all patients with sepsis, including placement of a bladder catheter (CV), if the patient is unable to urinate spontaneously.			
Activity	**Healthcare professionals**	**Instruments and Structures**	**Training, Procedures and Routine**
Placement of the bladder catheter (CV)	The staff who insert and manage the CV and who perform diuresis monitoring must be qualified, adequately trained and periodically updated	Kit for insertion of sterile bladder catheter Sterile bladder catheter Identify the instruments to ensure hourly monitoring of diuresis. Define a tool (paper or IT) to record the monitoring of diuresis	Define a 'bundle'[4] for the prevention of CV infections Arrange a procedure for hourly monitoring of diuresis

Table 34 - System approach to monitoring diuresis

3.13 Serial procalcitonin (PCT) measurements and assay of lactates

For more in-depth information about the role of PCT as part of the three *stewardships* and the bioscore, refer to sections 2.4 and 2.5. PCT reveals the production of calcitonin (of which it is the pre-hormone) and is widely produced by organs and tissues in case of sepsis. The characteristics presented below make PCT a bacterial sepsis marker. During the acute phase of sepsis, PCT production is massive. Furthermore, there is a correlation between the PCT production peaks following a bacterial insult and the intensity of the stimulation. PCT has a short half-life (24 hours) and levels drop rapidly after the end of the stimulus. This makes PCT an indicator of bacterial infections also useful in the decision-making phase regarding the decrease in antibiotic therapy. In the different clinical *settings* the use of PCT can be described as follows [127]:

DEA-ED	PCT should be used to differentiate between bacterial and non-bacterial infections. PCT should be among the tests available at the urgency/emergency clinical biochemistry laboratory.
Department (medical area, infectious diseases)	In non-critical patients admitted to medicine or infectious diseases departments, PCT should be applied in the diagnosis of bacterial infections that may require timely antibiotic treatment. In patients with community pneumonia that does not meet the sepsis or septic shock criteria, PCT can be used as an indicator of an unfavourable outcome.

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[4] The *bundle* is a collection of *evidence-based* practices which, when applied jointly and appropriately, improve the quality and outcome of processes with a greater effect than if they had been implemented separately.

Intensive care or critical patient	In critical area medicine, PCT should be used to identify patients who need immediate antibiotic therapy. In addition, PCT should be used to identify patients with an unfavourable diagnosis. In this case, the PCT trend must be considered in its temporal trajectory. The time interval between two consecutive samples should be adjusted to different clinical scenarios.
Surgical patient with intra-abdominal infection	In patients with intra-abdominal infection, PCT should be used to manage the duration of antibiotic treatment even in the presence of a suspicion of postoperative peritonitis. In contrast, in post-surgical patients with intra-abdominal infection, a worsening (i.e., increasing) PCT trend should be used to consider the need for re-intervention.

In patients with suspected or ascertained infection and positive screening for high risk (i.e., qSOFA ≥ 2 or NEWS ≥ 5-7), or with organ dysfunction (SOFA score ≥2), a blood lactate concentration evaluation is suggested, even if fluid-refractory hypotension is not present to identify the possible presence of a hypoperfusion condition.

The measurement of lactates is recommended as this allows early identification of a condition of tissue hypoperfusion, characterised by the activation of anaerobic glycolysis, even in patients who are not yet hypotensive. Although high lactataemia cannot be considered a specific marker of cell dysfunction during sepsis/septic shock, it is still an important and independent negative prognostic factor for patients, and intermediate or elevated initial serum lactate levels are independently associated with the mortality of patients with sepsis.

Serial measurement of blood lactate is recommended in patients with fluid-refractory hypotension to identify a shock condition and to evaluate its evolution. An increase in lactate concentration during treatment of the patient with shock indicates a high risk of death and the need for an immediate review of the therapeutic strategies in place.

The current criteria for defining a condition of septic shock are, as already mentioned, hypotension refractory to fluids with the need to administer vasopressors to maintain an average pressure ≥ 65 mmHg and the detection of serum lactate levels > 2 mmol/L. This cut-off was chosen because it represents the lowest level of lactate to be associated with an increased risk of death in patients with sepsis or septic shock. Given the correlation between lactate levels and the risk of patient death in hospital, serial measurement of this parameter is recommended in order to monitor the patient, evaluate the response to therapy and indicate possible changes. Jansen et al. showed that a treatment protocol aimed at reducing lactate levels by 20% within 2 hours of admission to the ICU made it possible to significantly reduce hospital mortality, despite lactate clearance in patients treated with this protocol not being faster than in the control group. The evaluation of lactate clearance during treatment also seems to be a useful predictor of patient survival: rapid clearance appears to be strongly associated with patient survival. Conversely, persistently high values of lactate and, therefore, low clearance, are associated with an unfavourable outcome. Since lactate clearance is closely linked to capillary perfusion, it can be considered a biomarker to roughly assess the microcirculation, which is typically impaired in the patient with septic shock.

3.14 Bioimaging

The use of bedside ultrasound in the management of the patient with sepsis. In recent decades, point-of-care ultrasound (PoCUS) has become a diagnostic tool widely used in the Emergency Department because it can be quickly performed at the patient's bedside by the emergency-urgency doctor. It is now unambiguously considered an extension of the physical examination, adding an anatomical-functional evaluation to the clinical data. There is extensive evidence in the literature that ultrasound is essential both for the diagnosis of septic shock and for the research and treatment of the infection site, as well as for haemodynamic monitoring during treatment [128] [129] [130].

Use of Bioimaging			
Diagnostic courses of action (bioimaging) suitable for the formulation of the correct diagnosis and treatment interventions should be developed. The actual operational possibilities available over 24 hours should be verified, and the alternative possibilities defined. Possible critical issues with corrective actions must be identified. Patient care procedures must be defined during the various diagnostic stages.			
Activity	Healthcare professionals	Instruments and Structures	Training, Procedures and Routine
Ultrasound performance	Emergency Medicine Doctors, Radiologists To search for the focus, to guide invasive procedures and haemodynamic monitoring	Portable ultrasound system in the ED and in Sub-Intensive care	Guidelines (e.g., SIMEU [Italian Society of Emergency-Urgency Medicine]) to search for and treat the focus, the haemodynamic management of the patient with septic shock Provide training courses for ED medical staff and regular *re-training* Decisional algorithm to search for the focus and possible drainage Ultrasound-guided haemodynamic patient *management* algorithm in the initial stages in the ED

Table 35 - System approach to ultrasound performance

Gruppo Tecnico Programma Regionale Lotta alla Sepsi – Regione Toscana

Indicators: monitoring the pathway

SDO [hospital discharge form] coding criteria for Sepsis and Septic Shock

The terms Septicaemia and Sepsis are NOT synonymous. The following is thus specified:

Septicaemia (038): systemic pathology due to the presence in the blood of pathogenic microorganisms or toxins. For septicaemia supported by microorganisms (e.g., virus or cryptococcus) for which specific codes are not expected, the code 038.8 - Other forms of septicaemia - should be used. The coding of Sepsis or Septic Shock is complex in that it is implemented by using the ICD-9-CM codes, and should be adjusted to the new sepsis-3 definition [131]. It is essential that the clinical documentation reported in the record is clear and can show evidence of this pathology during hospitalisation. We shall refer to the definition of Sepsis below.

SEPSIS-3 DEFINITION (2016): sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

ICD9 CM CODES to be reported in the SDO
Use code 995.92 for SEPSIS (previously "SEVERE SEPSIS") or code 785.52 for SEPTIC SHOCK. In addition, specify the underlying aetiology and indicate any organ failure with the following codes:
the underlying systemic infection with codes 038.XX;
any localised infection (e.g., 5695 intestinal abscess, 041 SHIGELLA FLEXNERI);
one or more organ failures, for example 5845 for acute renal failure. Give precedence to what is most related to the main diagnosis or procedure (see surgery).
CODES **NOT** TO BE USED AS ASPECIFIC OR CONFUSING: code 7907 BACTERAEMIA, UNSPECIFIED, code 99590 SYSTEMIC INFLAMMATORY RESPONSE SYNDROME, UNSPECIFIED, code 99591 SEPSIS.

Monitoring of the sepsis treatment pathway: methodological aspects

The proposal is developed on the assumption that it is necessary to provide methods and tools applicable in hospitals to monitor the treatment pathway of patients with suspected sepsis and to evaluate the quality of care.

> in October 2015, the US *Centre for Medicare and Medicaid Service* introduced the assessment of "compliance" in the sepsis bundle after years of testing. Starting from a sample of hospital discharge forms with sepsis diagnosis, the facilities participating in the programme are required to verify the adequacy of the patient's treatment pathway based on the information available in the medical records. This measurement system was effective, valid and feasible, although its transferability to another context, such as the Italian one, has yet to be assessed.
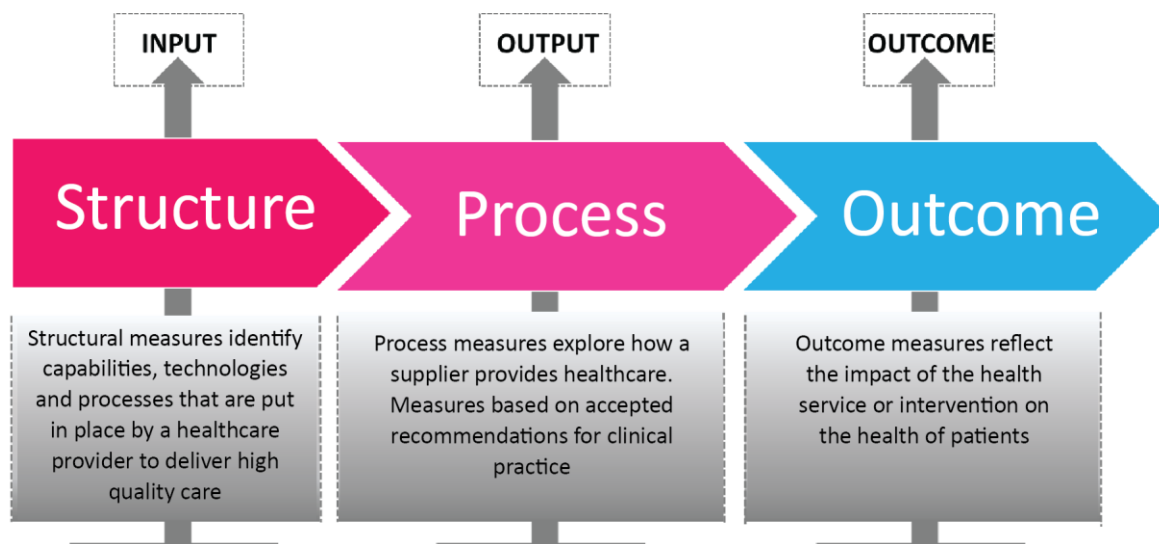
The prerequisite for monitoring is to use, as far as possible, the already available **administrative information flows**; in particular, the first aid data flows and the hospital discharge form (SDO). Therefore, the first objective is to improve the coding of this pathology in these flows, in order to obtain valid and precise estimates of the incidence. The SDO is to be considered an indispensable basis for the evaluation of *trends*, for the identification of different subpopulations and for a measurement of fatality. The interventions aimed at improving and standardising the coding of sepsis, and thus reducing the variability of the coding profiles between hospitals, are essential to increase the value of administrative sources as epidemiological surveillance and initial *screening* tools. It is not appropriate to use these data to make comparative assessments of hospitals both in terms of incidence and mortality, but only to evaluate, over time, the *performance* of each individual hospital.

Another aim to pursue is to promote **integration with other information sources** (structured data obtained with *record linkage* techniques from microbiology and from the analysis laboratory, and textual data obtained with *text mining* techniques from the electronic health record), which could allow implementation of an effective and timely epidemiological surveillance system with extremely limited costs. The goal of this monitoring is not to produce rankings or comparisons.

Lastly, it is considered appropriate to promote **audits** and **feedback** with information on selected cases using the system information sources, in order both to verify the quality of the coding and to monitor the diagnostic and treatment courses of action.

Proposal of monitoring indicators

Treatment pathway monitoring is entrusted to the hospitals. It must be planned at the time of implementation of the pathway, and must be carried out with shared methods and tools. The measurements to be arranged should concern the structure, process and outcome, according to the outline proposed below.

INPUT	OUTPUT	OUTCOME
Structure	**Process**	**Outcome**
Structural measures identify capabilities, technologies and processes that are put in place by a healthcare provider to deliver high quality care	Process measures explore how a supplier provides healthcare. Measures based on accepted recommendations for clinical practice	Outcome measures reflect the impact of the health service or intervention on the health of patients

Structure indicators

The formal act of joining the regional fight against sepsis plan consists in:
- defining a PDTA (Diagnostic Therapeutic Treatment Pathway) that is consistent with the guidelines of this document
- training on operational protocols and coding of sepsis in the SDO
- definition of appropriate care *settings* for the patient with sepsis and septic shock
- accessibility to a dedicated clinical microbiology service

Process indicators

- % sampling of blood cultures, procalcitonin, lactate, administration of antibiotics and fluid infusion in hospitalisations with sepsis in the diagnosis (Source: First Aid record)
- % of *compliance* with 6+1 bundle (Source: audit & feedback)
- % of appropriate empirical antibiotic therapy (regimens proposed in this document) (Source: medical record)
- % targeted antibiotic therapy modulated on the basis of the result of the microbiological test (Source: microbiological report - medical record)

Outcome indicators

- Risk of death at 30 days after sepsis or septic shock
- Only for intensive care: risk of death at 30 days *Risk adjusted* (Source: Prosafe)
- Risk of readmission at 30 days, 6 months and 1 year from sepsis or septic shock episode
- One year survival from sepsis or septic shock episode

Conclusions and next steps

In the Tuscan Regional Administration, for many years now, at least since 2004 when the first edition of the *Surviving Sepsis Campaign* "International Guidelines for the diagnosis and treatment of Sepsis and Septic Shock" was published, a process of raising awareness of this pathology and organisational structuring of the "Sepsis Pathway" have been underway, involving clinicians from various disciplines. In the early period, from 2004 to 2012, in which three editions of the *Surviving Sepsis Campaign* Guidelines were published, the spokespersons for this awareness raising were the Tuscan Anaesthesiologists Resuscitators, members of SIAARTI [Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Care and GIVITI [Italian group for the evaluation of Intensive Care interventions] (Margherita and then PROSAFE project). In 2013, the Tuscan Regional Centre for Clinical Risk and Patient Safety (GRC) and the Tuscan Regional Health Agency (ARS Tuscany) began to identify the characteristics the "Sepsis Pathway" should present from the Local Emergency Medical Service to the hospital. In fact, this was the first noteworthy innovation from the "Tuscan Sepsis Pathway": *wanting to intercept sepsis everywhere*. In the community, with the involvement of Family Doctors and of Emergency Medical Service outside the hospital and in the hospital, with the involvement of the healthcare staff of each *setting* (ED, Medical and Surgical Area, Obstetrics). In this pathway, the life-threatening time-dependent pathology sepsis is no longer the exclusive competence of the intensivists, but of all healthcare staff. Sepsis and Septic Shock are a Health Emergency and, therefore, concern everyone: suffice to think that sepsis alone can invalidate the impressive progress achieved by medicine in recent years, such as in transplants or advanced surgical medical treatments in the onco-haematology setting. In 2016, together with the publication of the 4th edition of the *Surviving Sepsis Campaign* International Guidelines, and the publication of the new definition of Sepsis and Septic Shock (*Sepsis-3*), GRC and ARS published the first PDTA (Diagnostic Therapeutic Treatment Pathway), basic training for all healthcare professionals in the Tuscan Health Service. In 2017 there was a real leap forward, with Tuscan Regional Council Resolution No. 752 and its annex of 10/07/2017 "Three-Year Plan to Fight Sepsis (2018-2020)". During 2018, the Regional Sepsis Multidisciplinary Group worked on this document, which presents the "Integrated Tuscan Model of the Fight against Infections and Sepsis", whose conceptual focus is represented by the integration of the three *stewardships*: Diagnostic, Antimicrobial and Sepsis. This marked, the sharing of tangible actions with the decision-makers of the Tuscan Regional Administration, the University Hospitals and the Health Authorities. This model underscores the importance of awareness of the risk factors, which are further amplified by the involvement of General Practitioners and of Medical Emergency Service operators, the programmes of sepsis *stewardship*, the programmes of antimicrobial *stewardship* and the programmes of diagnostic *stewardship*, mutually integrated, and the improvement in sepsis and septic shock coding in SDOs through the application of Resolution 773 of 9/07/2018. The foundations are laid to uphold the minimum levels of care suggested for management of the patient with sepsis and, in particular, the patient with septic shock, and consequent reorganisation of the Intensive and HDU (Sub-Intensive) Care Units, considered as the appropriate locations of hospitalisation of sepsis and septic shock patients. In fact, these pathologies necessitate the availability of specialised skills and structural equipment, which should be either present or readily made available, depending on the severity of the patient. The reorganisation in the logistical network of microbiology departments established as Autonomous Clinical Microbiology departments open 24/7 in *HUB* hospitals and

12 hours daily, 6 days out of 7 in *SPOKE* hospitals is envisaged. In short, this model sets up a fight against sepsis throughout the Tuscan Healthcare System. Other highlights of the model include: Citizen empowerment, advanced training and simulation, creation of the intra-hospital Emergency Team with activation of the M(N)EWS in the departments at each change of shift, the integration of the PNCAR [National Antimicrobial-Resistance Contrast Plan], and strengthening of the IPC and surveillance (*Infection Prevention, Control and Surveillance*), with a critical review of the control of healthcare-associated infections.

For 2019, the construction of a Regional Neonatal and Paediatric Sepsis PDTA was part of the working group's activities. In 2020, the Model plans for checks to be carried out on the process and outcomes of sepsis and septic shock management by means of indicators that can also become tools to assess *performance* and *budget* objectives, and that a sepsis - also understood as an adverse event - prevention programme can be constructed. The Integrated Tuscan Hospital Model has been designed currently to act on the three *settings*: the ED/DEU, the Medical, Surgical and Obstetrics Department, and the Intensive Care/HDU. The Integrated Tuscan Model is, therefore, characterised by an expanded vision, no longer limited to the individual operating frameworks, and by an integrated action, which makes use of the sharing of **"risk stratification"** of the patient through use of the BIOSCORE (logical fusion of heuristics and biomarkers in order to operate in conditions of uncertainty and time constraints), of the differentiated clinical microbiological pathways with rapid and molecular technology, of standardised communication, of *team working*, of *Information Technology*, and of all the cultural instruments offered by *Human Factors and Ergonomics* (HF\E). The Integrated Tuscan Model never separates the fight against infection - both concerning the community and related to care in the places where it is provided (hospitals, RSA, [elderly care homes], rehabilitation facilities, etc.) - from the fight against sepsis and septic shock, but rather combines them in both the technical and non-technical aspects. This Model has also been proposed internationally, through participation in the *Global Sepsis Alliance*. The objectives, in common with the various Scientific Societies involved in the diagnosis and treatment of Sepsis and Septic Shock, were to reduce the present excessive variability of clinical interventions across Italian Regions and, among the same Scientific Societies with different disciplinary specialisations, and to cooperate and share experiences, basic and clinical research, reorganisations and innovations with the goal of coming together - and building together - the Fight Against Sepsis National Plan - to be proposed to the attention of the Italian Government and its operational federalhealth articulations.

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