Sepsis in head and neck cancer patients treated with chemotherapy and radiation: Literature review and consensus

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Abstract

The reporting of infection/sepsis in chemo/radiation-treated head and neck cancer patients is sparse and the problem is underestimated. A multidisciplinary group of head and neck cancer specialists from Italy met with the aim of reaching a consensus on a clinical definition and management of infections and sepsis. The Delphi appropriateness method was used for this consensus. External expert reviewers then evaluated the conclusions carefully according to their area of expertise. The paper contains seven clusters of statements about the clinical definition and management of infections and sepsis in head and neck cancer patients, which had a consensus. Furthermore, it offers a review of recent literature in these topics.

1. Introduction

Chemo-radiotherapy (CRT) has increased the curability of locally advanced head and neck cancer patients (HNCPs) [1] and has allowed organ and function preservation in laryngeal and hypo-pharyngeal cancer patients [2]. However, competing causes of mortality (e.g. acute and late toxicities) are increased and substantially reduce the overall survival benefit [3,4].

In CRT trials the acute mortality is described in the range from 2% [5] to 9.3% [6]. Infection is one of the main causes of acute mortality [6,7].

Unfortunately, the reporting of infection is sparse even in randomized trials and the problem is likely underestimated.

There are three main limitations in interpreting data from CRT trials:

(1) Infection-related mortality can be confounded with other potential causes of death or categorized as "due to an unknown cause" [6], as the recognition of sepsis requires an active search and finite criteria. Most importantly unexplained organ failure (renal, respiratory, cardiovascular, coagulation, multi-organ etc.) is often reported as the cause of death while the probable relationship with underlying sepsis syndrome is not recognized.

(2) Organ damage due to the systemic inflammatory response is often misinterpreted as being related to the individual toxicities of the treatment. In a retrospective

analysis of 394 patients enrolled in consecutive CRT phase II trials at the University of Chicago, 14 deaths were attributed to infection and eight cases of pneumonia were considered "comorbidities" [6]. In total, 22 deaths (5.6%) were certainly due to infectious complications. Another 10 deaths were classified as due to "unknown reasons" or due to factors that could possibly be related to sepsis (small bowel necrosis, cardiac causes, "other respiratory disease" etc.). In addition, only recently have the abscopal effects of local inflammation toxicity been described [8–10]. Treatments enhancing local toxicity seem to be related to a higher degree of severe complications and deaths [11].

(3) Finally, the infectious-related mortality is not limited to the time of CRT administration but can occur several weeks after treatment [12]. Post-treatment infections and deaths are usually not considered treatment-related.

We feel that the lack of recognition of the connection between the single toxicities and the systemic consequences is due to insufficient knowledge about infection, sepsis and its sequelae. The definitions of these conditions have been evolving over the last 20 years. Consequently, the various specialists, such as medical oncologists (MOs), radiation oncologists (ROs), infectious disease physicians (IDPs) and critical care physicians (CCPs) treating HNCPs, use the terminology with different meanings. In fact, while years ago (before 1989) the term sepsis referred solely to a severe bacterial infection and was often confused with the infection itself, more recently sepsis has been defined as a systemic syndrome [13,14] that encompasses multiple signs and symptoms resulting from the body's reaction to infectious systemic immune responses [15,16]. Helpful to the understanding of sepsis is the definition of the Systemic Inflammatory Response Syndrome (SIRS), indicating the unique, highly preserved systemic response to tissue damage (either infectious or non-infectious) [14,17].

For all these reasons MOs, ROs, CCPs and IDPs from Italy met in Milan from February 17–18, 2013 with the aim of reaching a consensus on a clinical definition and management of infections and sepsis in CRT-treated HNCPs.

The results of the literature review and the statements that obtained consensus are reported and discussed in this paper.

2. Material and methods

The Delphi appropriateness method was used for this Consensus [18].

The panel, a group of 37 multidisciplinary experts (MOs, ROs, IDPs, CCPs, nutritionists and nurses), met in Milan from February 17–18, 2013 and appointed a facilitator board of 12 expert members, from different clinical settings (6 MOs, 4 ROs and 1 IDP and 1 CCP). The facilitator board performed a systematic review of the literature on infection in CRT-treated HNCPs.

The MEDLINE database was searched for English-language studies published from 1992 to March 2013 containing the terms sepsis, head and neck cancer, nosocomial, healthcare-acquired, infections, chemotherapy (CT), and radiotherapy (RT).

Potentially relevant abstracts presented at annual meetings of the American Society of Clinical Oncology and of the European Society of Medical Oncology were examined. The study selection included the following: (a) observational and prospective studies about assessment and treatment; (b) randomized, double-blind, placebo-controlled, or uncontrolled studies; (c) retrospective and uncontrolled studies; (d) systematic reviews and meta-analyses; (e) consensus guidelines. Furthermore, the electronic search results were supplemented by manual examination of reference lists from selected articles.

On the basis of this literature review, the facilitators identified a number of key statements.

All the experts rated these statements through a two-round process. A 4-grade scale was used, where 1 was defined as high consensus, 2 was defined as low consensus, 3 was defined as no consensus, and 4 was chosen by panelists when they felt unable to express an opinion.

A web meeting was held before the second rating, where statements were discussed. The statements that received a weak approval (<75/100) were redefined according to the observations of panelists. The second ratings were analyzed to identify the statement that reached a consensus.

Each expert (including facilitators) was equally weighted in scoring the statements.

External MOs (JBV, BM), RO (JB), IDP (AC), supportive cancer care specialist (JR-D), and CCPs (MVR and RPD) reviewed the statements.

The panelists had a second meeting in Milan on May 5, 2014 in order to approve the final version of the statements.

3. Results

Consensus-reached statements are listed in Table 1.

4. Comments

4.1. General statements

4.1.1. Epidemiology
The rate of infection during CRT is around 19%, the acute mortality of CRT is between 2% and 9.3% and the majority of deaths occurring within 30 days from the end of treatment is infection-related.

4.1.2. Definition of Sepsis syndrome
The panel adopted the nomenclature and definitions for terms used by 2001 International Sepsis Definitions

Table 1
Consensus-reached statements.

Cluster Phase	Descritpion	Whom is it in charge of?	The degree of consensus
1 Before CRT	General statements		
	.1.1 Epidemiology: The rate of infection during CRT is around 19% [5,151–156], the acute mortality of CRT is between 2% [5] to 9.3% [6], and the majority of deaths occurring within 30 days from the end of treatment is infection-related	Clinical Oncologist and nurse	Not rated[a]
	.1.2 Definition of Sepsis syndrome: The panel adopted the nomenclature and definitions for terms used by 2001 International Sepsis Definitions Conference (i.e. SIRS, sepsis, severe sepsis, and septic shock) (see Table 2) [23]	Clinical Oncologist and nurse	82%
	.1.3 Etiology and pathogenesis of systemic inflammatory response syndrome (SIRS) and Sepsis in HNCPs: any kind of tissue damage can induce a SIRS through circulating mediators. When this response is prolonged and associated with infection it can result in severe sepsis and its complications [19,44].	Clinical Oncologist and nurse	Not rated[a]
	.1.4 Predisposing Factors. HNCPs with habits such as smoking [46,47] and alcohol [48] consumption, malnutrition [82,157], swallowing impairment with aspiration [45], chemotherapy-induced neutropenia [39,158,159], disruption of physiological barriers as a consequence of radiodermitis and mucositis [40,160], gingival pockets and dental caries [161–164], age [12,165,166], co-morbidities such as diabetes and chronic obstructive pulmonary disease (COPD) [166], and the presence of central venous catheters, gastrostomy and tracheostomy are at a higher risk of infections.	Clinical Oncologist, nurse and patient	80%
2 during CRT	Statements about Monitoring and Diagnosis of Sepsis.		
	.2.1. The diagnosis and monitoring of SIRS:		
	.2.1.1 SIRS should be assessed at least weekly in all HNCPs undergoing CRT through vital parameter monitoring (blood pressure, heart rate, respiratory rate, and digital oxymetry etc.), and white blood cell count.	Clinical Oncologist and nurse	85%
	.2.2. The diagnosis of Sepsis		
	.2.2.1 In the case of SIRS, the search for an associated infection should be rapidly performed through clinical examination, radiological imaging, blood cultures, and culture from the suspected sites of infection (urine, sputum, stools, needle aspirate or swabs of skin lesions). Unfortunately, positive cultures are obtained only in one third of cases and their negativity does not rule out the presence of infection (mainly due to concomitant antibiotic use, inadequacy of samples sent to the microbiology laboratory).	Clinical Oncologist and nurse	95%
	.2.2.2 Mandatory cultures of all suspected sites of infection and radiological imaging should be performed before the start of antibiotic treatment in order to improve the rate of etiologic diagnosis.	Clinical Oncologist and nurse	100%
	.2.2.3 C-Reactive Protein (CRP) and/or procalcitonin and plasma lactate can add useful information about infection diagnosis, hence these blood levels may be considerd in case of suspected infection.	Clinical Oncologist and nurse	78%
	.2.3. The evaluation of organ dysfunction or tissue hypoperfusion		
	.2.3.1 The evidence for organ dysfunction or tissue hypoperfusion should be accomplished with urine input/output evaluation, serum lactate, full biochemistry (with renal and liver function tests, coagulation), and arterial blood gas analysis.	Clinical Oncologist and nurse	95%
3 during CRT	Statements about Hospitalization and antineoplastic treatment interruption		
	.3.1. Hospitalization: HNCPs with sepsis should be promptly hospitalized as this condition can progress rapidly	Clinical Oncologist	98%
	.3.2. CT interruption: For suspected or confirmed severe sepsis during CRT, CT should be the first treatment to be interrupted.	Clinical Oncologist	95%
	.3.3. RT interruption: For suspected or confirmed sepsis during CRT, RT should be stopped only in particularly compromised patients or in the presence of severe sepsis.	Clinical Oncologist	78%
4 during CRT	Statements about the Early Empirical Antimicrobial treatment		
	.4.1. Empirical antibiotic therapy should be started within 3 h of clinical presentation [70]	Clinical Oncologist and nurse	100%
	.4.2. For suspected or confirmed sepsis (systemic inflammatory response to infection; see Table 2) empirical antibiotic therapy should be started, considering both anti Gram+ and anti Gram- antibiotics [108,109]. It should attempt to provide antimicrobial activity against the most likely pathogens based upon the potential source of infection searched on the basis of each HNCP's presenting illness	Clinical Oncologist, Infectious Disease Physician and nurse	95%
	.4.3. Empirical antibiotic therapy has to be based on local surveillance, antibiotic sensitivity and infection rate/prevalence; otherwise a rational use of antibiotics in accordance with international guidelines is advisable (e.g. Centers for Disease Control and Prevention CDC)	Clinical Oncologist, Infectious Disease Physician and nurse	80%

Table 1 (*Continued*)

Cluster Phase	Descritpion	Whom is it in charge of?	The degree of consensus
	.4.4. Considering the very high rate of infection sustained by multi- and pan- resistant microorganisms in the HNCPs as well as in the general population, when local guidelines are not available, it is suggested that treatment with broad spectrum, potent antibiotics active against enterobacteriaceae and methicillin-resistant Staphylococcus aureus be started [108].	Clinical Oncologist and Infectious Disease Physician	94%
	.4.5. In the presence of sepsis following an oral cavity infection, the treatment might consider the introduction of an antifungal agent associated with an anti-Gram+ antibiotic	Clinical Oncologist, Infectious Disease Physician and nurse	82%
	.4.6. Once aspiration pneumonia is suspected, a low threshold for CT scan and diagnostic bronchoscopy should be maintained.	Clinical Oncologist, Infectious Disease Physician and nurse	95%
	.4.7. For healthcare-associated infections non-responsive to the first line of antibiotics, the IDPs' assessment is mandatory.	Clinical Oncologist, Infectious Disease Physician and nurse	100%
5 during CRT	Statement about the antibiotic de-escalation procedure: .5.1. The empirical treatment must be optimized when microbiology results are available.	Clinical Oncologist, Infectious Disease Physician	100%
6 during CRT :	Statements about Early Goal-Directed Treatment (EGDT) .6.1. In cases of severe sepsis (sepsis + organ failure) supportive therapy using the "EGDT" scheme should be applied as soon as possible: oxygen administration, hydration with crystalloids and targeting a Svo2 of 70%.	Clinical Oncologist, Infectious Desease Physician.	78%
	.6.2. Most patient with severe sepsis (see Table 4) should be rapidly referred to an intensive care unit (ICU)	Clinical Oncologist, Infectious Disease Physician and Critical Care Physician	100%
7 After CRT	Statement on the Follow up: .7.1. Monitoring for SIRS parameters should be continued after the end of CRT until the complete resolution of acute toxicities. Indeed, mortality for pneumonia is reported to occur well after 30 days from the end of treatments and there is a high risk of infection for several months	Clinical Oncologist and nurse	95%

[a] Statements that do not need to be rated.

Conference (i.e. SIRS, sepsis, severe sepsis, and septic shock) (Table 2).

Before 1989 [13,14], "sepsis" was considered to be a systemic infection, often described as "blood poisoning" and assumed to be the result of the host's invasion by pathogenic organisms that then spread within the bloodstream. After the advent of modern antibiotics, germ theory could not fully explain the pathogenesis of sepsis: researchers suggested that it is the host, not the germ, that drives the pathogenesis of sepsis [19].

Recently a "Consensus conference" attempted to "provide a conceptual and practical framework to define the systemic inflammatory response to infection" [17]. The acronym SIRS (Systemic Inflammatory Response Syndrome) was used in order to provide a reference for the complex findings that result from a systemic activation of the immune response, triggered by a variety of infectious and noninfectious conditions. Yet, the identification of sepsis through the 1992-consensus SIRS criteria had a high sensitivity but a low specificity. Indeed, the same criteria can be found in non-infectious conditions [20] and may represent an appropriate physiological reaction [21,22]. In 2001 an International

Sepsis Definitions conference revisited the SIRS criteria (see Table 2) [23] by expanding the list of possible signs of systemic inflammation in response to infection to the physical and laboratory findings indicative of early organ dysfunction, altered tissue perfusion, and hemodynamic failure, as well.

Thus, even though the 1991 four criteria for sepsis continue to be used because they are easily measurable [24,25], in presence of suspected sepsis, the other items included in the 2001-consensus list in order that the presence of some degree of organ dysfunction, altered tissue perfusion, and/or hemodynamic failure have to be actively searched.

4.1.3. Etiology and pathogenesis of systemic inflammatory response syndrome (SIRS) and Sepsis in HNCPs

Any kind of tissue damage can induce a SIRS through circulating mediators. When this response is prolonged and associated with infection it can result in severe sepsis and related complications.

Recently the definition of immunity reactions has been revisited [26,27]: either endogenous danger signals (danger/damage-associated molecular patterns – DAMPs)

Table 2
Nomenclature and definitions for terms used in critical illness.

Nomenclature	Note	Clinical disease	Clinical signs
Infection	A microbial phenomenon characterized by a local inflammatory response to the presence of microrganisms or the invasion of normally sterile host tissue by those organisms (or by their products)	Localized inflammation	Tumor, rubor, calor, dolor and function laesa
Bacteraemia	The presence of viable bacteria in the blood. The presence of viruses, fungi, parasites should be described in a similar manner (viremia, fungemia, parasitemia)	Could be silent	Could be silent [167] (6)
SIRS	Symptoms and signs related to panoply of non-specific inflammatory response.	Systemic Inflammatory Response Syndrome: Bone version 1991 [14] 11	Two or more: • Temperature >38 °C or core temperature <36 °C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or $PaCO_2 < 37$ mmHg or mechanically ventilated • Leukocyte count > 12,000/μl or <4000/μl
Sepsis[a]	Systemic inflammatory response to infection. Recently, some Authors [168] 28 have defined sepsis when organ failures are documented	Diagnostic criteria for sepsis [23] [b])	General parameters – Fever (core temperature >38.3 °C) – Hypothermia (core temperature <36 °C – Heart rate >90 bpm or >2 SD above the normal value for age – Tachypnea: >30 bpm – Altered mental status – Significant edema or positive fluid balance (>20 ml/kg over 24 h) – Hyperglycemia (plasma glucose >140 mg/dl or 7.7 mM/l) in the absence of diabetes *Inflammatory parameters* – Leukocytosis (white blood cell count >12,000/μl) – Leukopenia (white blood cell count <4000/μl) – Normal white blood cell count with >10% immature forms – Plasma C reactive protein >2 SD above the normal value – Plasma procalcitonin >2 SD above the normal value *Hemodynamic parameters* – Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70 mmHg, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age) – Mixed venous oxygen saturation >70% – Cardiac index >3.5 l min *Organ dysfunction parameters* – Arterial hypoxemia (PaO_2/FIO_2 <300) – Acute oliguria (urine output <0.5 mL/kg/1 h or 45 mM/l for at least 2 h) – Creatinine increase ≥0.5 mg/dl – Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s) – Ileus (absent bowel sounds) – Thrombocytopenia (platelet count <100,000/μl) – Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 μmol/l) *Tissue perfusion parameters* – Hyperlactatemia (>1 μmol/l) – Decreased capillary refill or mottling
Severe Sepsis (Sepsis with organ dysfunction)[a]	Symptoms and signs related to panoply of nonspecific inflammatory response and to dysfunctions of organs and of microvasculature.	Deteriorating evolution of systemic inflammation	Sepsis + organ dysfunctions (due to abnormal organ perfusion) in acutely ill patients
Septic Shock[a]			Sepsis + refractory (unresponsive to fluid and vasopressors) hypotension+ perfusion abnormality

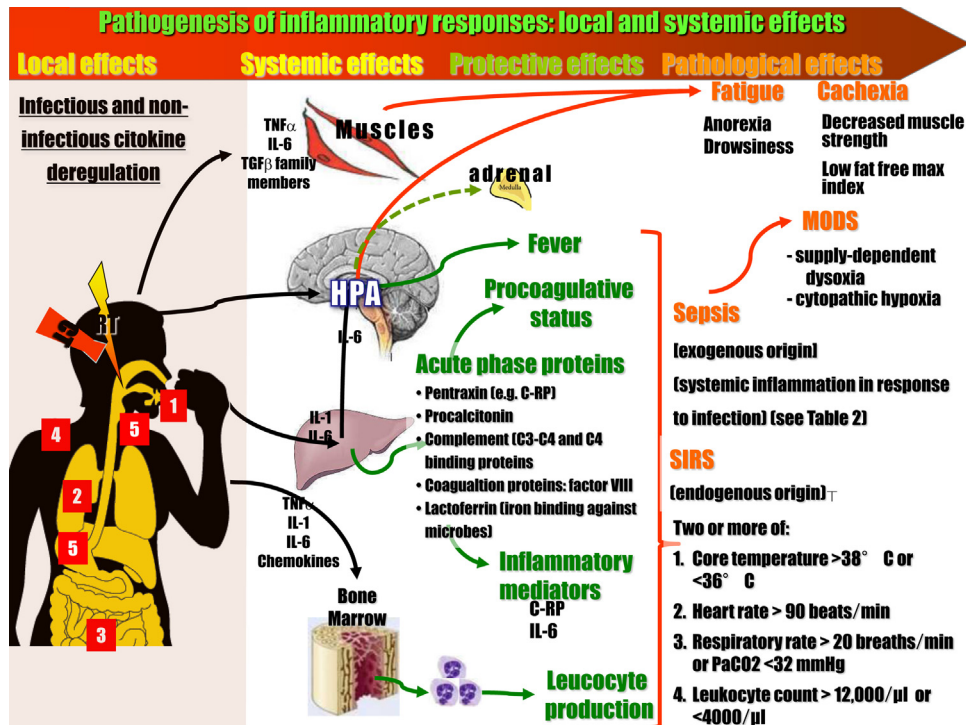[a] Septicaemia was the archaic term to identify these syndromes.

Fig. 1. Pathogenesis of inflammatory responses: local and systemic effects [20]. Legend: radiochemotherapy on the treated tissues causes damage that facilitates inflammation. Furthermore germs may more easily spread via the bloodstream after translocation through disrupted barriers: (1) mouth, (2) respiratory tract, (3) intestinal mucosa, (4) skin and (5) devices. Released cytokines act not only locally but also on other organs and tissues (Inter-organ signaling). On muscles they can alter energetic metabolism (thus favoring cachexia). On HPA (hypothalamic–pituitary–adrenal axis) they cause fever and fatigue symptoms. On the liver they provoke the synthesis of acute phase proteins that in turn act in a procoagulative and general inflammatory and anti-inflammatory sense. All these effects can lead to systemic inflammatory response syndrome (SIRS) or sepsis. Abbreviations: $PaCO_2$ = arterial carbon dioxide tension; MODS: Multi-organ Dysfunction Syndrome; Other abbreviations see the text.

[28,29], generated by stressed host cells, or exogenous pathogen-associated molecular patterns (PAMPs) [30–32] are recognized as being capable of activating the pattern recognition receptors (PRRs) [33] of the immune cells and as promoting the synthesis of inflammation mediators. Thus, any kind of tissue damage (pathogens [34,35], CRT [8,9] etc.) can induce a local [27,36] and systemic inflammatory response through circulating mediators (Fig. 1) [8,9,20]. Some Authors [37] postulated that anti-inflammatory mediators predominate within the bloodstream to avoid igniting new inflammatory foci, while their presence within tissues may not always be sufficient to prevent the initiation of a deleterious inflammatory response in various compartments [38]. Consequently, the sepsis/SIRS-patient plasma behaves as an immunosuppressive milieu [39]. A consequence of this deregulation is the fact that germs may more easily spread via the bloodstream after translocation through disrupted barriers (skin and mucosal barrier injury [40]).

Thus, it has become apparent that when prolonged or intensive host responses are provoked (infections, trauma, or CRT) [41–43] both pro-inflammatory and anti-inflammatory mechanisms (involving cytokines) can contribute to infection clearance, organ injury and secondary infections [44] (Fig. 1). During CRT, HNCPs have a number of conditions predisposing to infection [45], making them extremely at risk.

4.1.4. Predisposing factors

HNCPs with habits such as smoking [46,47] and alcohol [48] consumption, malnutrition, swallowing impairment with aspiration, chemotherapy-induced neutropenia, disruption of physiological barriers as a consequence of radiodermitis and mucositis, gingival pockets and dental caries, age, co-morbidities such as diabetes and chronic obstructive pulmonary disease (COPD), and the presence of central venous catheters, gastrostomy and tracheostomy are at a higher risk of infections.

4.2. Statements about monitoring and diagnosis of sepsis

The early identification of sepsis and implementation of early therapies have been documented to improve outcomes and decrease sepsis-related mortality [49]. Reducing the time to diagnosis of severe sepsis is thought to be a critical component of reducing mortality from sepsis-related multiple organ dysfunction [50]. As oncological patients with sepsis are logically not different from other septic patients, the panel recommends an early diagnosis of sepsis by following the three main steps:

Table 3
Infection probability score[a] (IPS) [51].

	0	1	2	3	6	8	12
Body temperature (°C)	≤37.5		≥37.5				
Heart rate (beats/min)	≤80					81–140	>140
Respiratory rate (breaths/min)	≤25	>25					
White Blood Cell ($\times 10^3/mm^3$)	5–12	>12		<5			
C-RP (mg/dL)	≤6				>6		
SOFA[b] score (see Table 4)	≤5		>5				

[a] Patients with a score <14 points have only a 10% risk of infection.
[b] Sequential organ failure assessment.

1. Diagnosis and monitoring of SIRS.
2. Diagnosis of Sepsis.
3. Evaluation for organ dysfunction or tissue hypoperfusion.

4.2.1. The diagnosis and monitoring of SIRS

4.2.1.1. SIRS should be assessed at least weekly in all HNCPs undergoing CRT through vital parameter monitoring (blood pressure, heart rate, respiratory rate, and digital oxymetry etc.), and white blood cell count. SIRS parameters need monitoring. Indeed, even if the finding of two positive SIRS parameters is not specific, it may help physicians to graduate the urgency of intervention, to promptly activate the search for infection, and to shorten the time to start antibiotic administration. In addition, it is suggested that other diagnostic parameters for sepsis, such as those suggested by the 2nd consensus conference [23], be performed as a regular procedure [22].

Another important role of the assessment of SIRS criteria can be the evaluation of patients with local tissue damage or infection. In CRT-treated HNCPs the occurrence of stomatitis, in-field skin toxicity, or device-related skin infection can be either a local limited phenomenon or a systemic evolving response [20]. The latter deserves a timely application of systemic treatment. Thus, more frequent analysis (at least daily) of SIRS criteria has the potential of capturing the systemic evolution of a local inflammation and of orienting all the following management strategies.

Recently, Peres Bota et al. [51] developed an infection probability score (IPS) which uses six variables (Table 3) to assess the likelihood of infection, resulting in a score from 0 to 26: the 14 score cut-off proved to be reliable enough (positive predictive value = 53.6%; negative predictive value = 89.5%) in distinguishing infectious (≥14) from non-infectious (<14) SIRS. In addition, changes in IPS over time may be useful in following the response to antimicrobial therapy [52].

4.2.2. The diagnosis of Sepsis

4.2.2.1 *In the case of SIRS, the search for an associated infection should be rapidly performed through clinical examination, radiological imaging, blood cultures, and culture from the suspected sites of infection (urine, sputum, stools, needle aspirate or swabs of skin lesions). Unfortunately, positive culture results are obtained only in one third of cases and their negativity does not rule out the presence of infection (mainly due to concomitant antibiotic use, inadequacy of samples sent to the microbiology laboratory)*

4.2.2.2 *Mandatory cultures of all suspected sites of infection and radiological imaging should be performed before the start of antibiotic treatment in order to improve the capability to achieve etiologic diagnosis*

4.2.2.3 *C-Reactive Protein (CRP) and/or procalcitonin and plasma lactate can add useful information about infection diagnosis, hence these blood levels may be considered in case of suspected infection*

The first step in assessing the patient with suspected sepsis is to determine the actual risk of infection and the likely source by obtaining information regarding colonizing or infecting pathogens: the nature of any localizing symptoms and signs should be noted. At any rate, the altered immune function may not present the typical sign of inflammation and may occult the localizing signs. Thus, any suspected source must be examined (skin, presence of devices, leg thrombosis, neck, mucosae and lungs.)

SIRS-positive HNCPs should undergo laboratory, microbiological, and radiological evaluation after an infection probability assessment based on history and physical examination.

- Laboratory evaluation

- Thrombocytosis, thrombocytopenia, hyperglycemia, metabolic acidosis, and changes in the inflammatory status. Even though TNF, IL-1, IL-6, IL-8, and IL-10 are all important in sepsis, they are not specific for inflammation/organ dysfunction, and do not assist in distinguishing between infectious and non-infectious causes.
- C-Reactive Protein (C-RP) and/or procalcitonin, although not always associated with infection [53–58], can add useful information about its diagnosis.
- C-RP levels > 17 mg/dl have been suggested as providing a means of separating patients with sepsis from those with non-septic inflammatory response due to other causes (e.g. trauma)[59].
- Procalcitonin has been proposed as a marker of infection [60–63]. Furthermore, it may be useful as an indicator of the severity of infection and as a guide for therapy (dose de-escalation [64]) in respiratory infections [61,62,65–68].

Thus, these markers cannot be recommended distinguishing between severe infection and other acute inflammatory

states [69], but they can be helpful adjunctive diagnostic markers to be interpreted in context with information from careful medical history, physical examination.

- Microbiological evaluation:

Obtaining cultures before antimicrobial administration is essential to confirm infection, to appropriately target antibiotic therapy and to allow antimicrobial de-escalation after receipt of the susceptibility profile [70]. Unfortunately, positive results are obtained only in one third of the cases and their negativity does not rule out the presence of infection [71]. Considering that the first antimicrobial dose can rapidly sterilize blood cultures within a few hours, obtaining those cultures before therapy is essential. Thus, at least two blood cultures, both peripherally and via indwelling catheters are recommended [70,72–74]. Although some guidelines [70] recommend that cultures should not cause significant delay (>45 min) in starting antimicrobial administration, some authors suggest that non-neutropenic and stable patients should be observed without empirical antibiotics while considering further diagnostic evaluation [75].

If fungal infection is suspected, 1-3b-D-glucan, mannan and anti-mannan antibody assays have shown positive results significantly earlier than with standard culture methods [70]. False positive reactions can occur with colonization alone [76].

Microbiological samples should also be taken from sites that are suspected of being infected.

- Radiological evaluation:

In order to identify the infection sources, imaging may help. Ultrasonography, performed at the bedside, can assist in localizing a fluid collection and may allow for percutaneous drainage and microbial cultures. CT scanning can help identify thoracic, abdominal, and deep-space infections. White Indium$_{111}$-labeled blood-cell scans and indium$_{111}$ Immunoglobulin-G have poor sensitivity and specificity, whereas Technetium scans seems to be more useful, owing to its high specificity (93–94%), but it has a poor sensitivity (40–75%) [77]. Finally, Fluorodeoxyglucose positron-emission tomography (FDG-PET) scans have a high sensitivity (95%) and a good specificity (88%) in identifying septic sources in patients with fever of unknown origin [77–79].

4.2.3. The evaluation of organ dysfunction or tissue hypoperfusion
4.2.3.1. The evidence for organ dysfunction or tissue hypoperfusion should be accomplished with urine input/output evaluation, serum lactate, full biochemistry (with renal and liver function tests, coagulation), and arterial blood gas analysis.
Sepsis and non-infectious SIRS can induce the MODS. The number of organ failures during sepsis increases the risk of mortality [80–82]. Thus, assessment of bone marrow, renal, liver, brain, coagulation, respiratory and circulatory functions through laboratory examinations and clinical monitoring should always be associated with the search for the infection site (Table 4).

The term "severe sepsis" was proposed to describe instances in which sepsis is complicated by inadequate tissue perfusion or organ dysfunction [83]. Capillary bed hypo-perfusion causes dysoxia, due to both altered microcirculation ("*supply-dependent dysoxia"*) [83,84] and the inhibition of mitochondrial respiratory enzymes caused by toxic oxygen and nitrogen intermediates ("*cytopathic hypoxia"*) [85,86].

Other causes of peripheral hypoxia are the *myocardial contractility depression*, owing to a variety of myocardial depressants found in the septic-patient plasma (such as TNF-a, IL-1, IL-6 and nitric oxide) [87,88], and the acute lung injury due to damage to the pulmonary vascular circulation and the alveolar-capillary membranes.

As a consequence of the above-mentioned causes, the circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression) and increased metabolism lead to an imbalance between systemic oxygen delivery/demand, resulting in global tissue hypoxia or even shock. As the cardiovascular system is designed to preserve arterial blood pressure to maintain cerebral and coronary perfusion during stress by reducing perfusion to peripheral tissues, the routine vital signs, central venous pressure and urinary output [89,90] may be relatively insensitive measures of early circulatory shock (also known as "cryptic shock" [90]), whereas serum lactate levels can serve as a marker of occult hypoperfusion [91,92]. Indeed, patients with cryptic hypoperfusion are often overlooked as candidates for aggressive interventions because they are hemodynamically stable [93], but they are associated with increased mortality [92,94–97]. Thus, the main endpoint in sepsis treatment is to recognize the imbalance between oxygen delivery/demand measuring serum lactate in order to start resuscitation promptly [70,93] (the so called Early Goal directed therapy (EGDT)). Current critical care guidelines recommend measuring serum lactate in hemodynamically-stable patients with sepsis to assess for occult hypoperfusion, since an elevated lactate level ($\geq$4 mmol/L) may warrant ICU transfer. Recent evidence (non-randomized trials) suggests that the serum lactate threshold used to identify patients eligible for EGDT be lowered, given the association between modestly elevated serum lactate levels ($\geq$2 mmol/L) and morbidity and mortality [70,96,97]. This transition point (lactate$\geq$2/4 mmol/L) occurs during the critical "golden hours" when treatment can provide maximum benefits in terms of outcome [93]. Thus, EGDT policy aims to restore this balance promptly by manipulating cardiac contractility, oxygenation, and tissue perfusion.

The parameters that monitor this balance between oxygen delivery/demand include mixed oxygen saturation (pulmonary-artery oxyhemoglobin saturation representing total balance of oxygen consumption and delivery assuming ability of cells to take up oxygen) (SvO$_2$) or central venous saturation (ScvO$_2$) (superior half-body oxygen saturation), lactate production, base deficit and pH [98]. Yet, one of the problems in the applicability of these guidelines is the need

Table 4
The goal of supportive treatment: restoration and maintenance of adequate tissue perfusion so as to prevent multiple organ dysfunctions.

Goal	Clinical manifestation	Monitoring		Action	Warning
Hemodinamic support (Early Goal Directed therapy)					
Tissue Oxygenation/perfusion:	Early recognition of the imbalance between oxygen delivery and oxygen demand measuring serum lactate and oxygen saturation	lactate level > 2 mmol/L. maintain O$_2$ sat > 90% or PaO$_2$ > 60 mmHg Monitor volume overload (VoL)[a].		Fluid resuscitation: Administer 30 ml/kg (0.9% sodium chloride or lactated Ringer) crystalloid for hypotension or lactate ≥2/4 mmol/L	After >4 L, if there is no improvement[b] or if there is evidence of volume overload in ICU for vasopressor therapy
Monitor and support MODS		SOFA scale [169]			
Respiratory [170]	No Dysfunction	PaO$_2$/FiO$_2$> 400 mm Hg	0		
		PaO$_2$/FiO$_2$ < 400 mm Hg	1		
	ALI or mild ARDS	PaO$_2$/FiO$_2$ < 300 mm Hg	2	CPAP >5 cm H$_2$O non invasively [171]	If non-improving ICU[*]
	Moderate ARDS	PaO$_2$/FiO$_2$< 200 mm Hg	3	PEEP (invasively)[*]	ICU[*]
	Severe ARDS	PaO$_2$/FiO$_2$< 100 mm Hg	4		
Cardio vascular	No hypotension	MAP ≥ 70 mmHg	0	Administer fluids (at least 20 ml/Kg crystalloids in 30 min) and monitor cardio-vascular and renal dysfunction.[*]	After >4 L, if there's is not improving[b] or if there is evidence of volume overload in ICU for vasopressor therapy
	Hypotension	MAP < 70 mmHg	1		
		Dobutamine any dose or Dopamine ≤ 5 μg/kg/min	2		
		Dopamine > 5 μg/kg/min or epinephrine or norepinephrine ≤0.1 μg/kg/min	3		
		Dopamine > 15 μg/kg/min or epinephrine or norepinephrine >0.1 μg/kg/min	4		
Renal dysfunction	Decreased UOP	Creatinine <1.2 mg/dl	0		
		Creatinine <2 mg/dl	1		
		Creatinine <3.5 mg/dl	2		
		Creatinine <5 mg/dl UOP< 500 ml/die	3		
		Creatinine <1.2 mg/dl UOP< 200 ml/day	4		
Coagulopathy	DIC and Bleeding	Platelet > 150.000/μl	0	Platelet transfusion in pts with DIC and bleeding (or a high risk of bleeding) with platelet <50/ml [172] or <20/ml [70]	For the diagnosis and management of DIC see the guideline of BSCH [172]
		Platelet < 150.000/μl	1		
		Platelet < 100.000/μl	2		
		Platelet < 50.000/μl	3		
		Platelet < 20.000/μl	4		
Central nervous system	GCS testing: Eye, Verbal and motor responses	GCS ≥ 15	0		

		GCS < 15	1	
		GCS ≤ 12	2	
		GCS ≤ 9	3	
		GCS < 6	4	
Hepatic	Hepatic failure	Bilirubin <1.2 mg/dl	0	
		Bilirubin <2 mg/dl	1	
		Bilirubin <6 mg/dl	2	
		Bilirubin <12 mg/dl	3	
		Bilirubin ≥1.2 mg/dl	4	
General Supportive care				
Correction of anemia		Haematocrit < 30%		If Hb levels fall <7 g/dL red blood cell is recommended to a target Hb range of 7–9 g/dL [70]
		Hemoglobin <7 g/dL		
Depressed Myocardial performance	Inadequate cardiac index	CVP > 8–12 mmHg		Restore haematocrit if <30% then use inotropic agent (dobutamine up to 20 μg/kg/min) [70]*
		MAP < 65		
		UOP > 0.5 ml/kg/h		
		ScvO$_2$ > 70% or SvO$_2$ > 65%		
Metabolism:		Maintain blood glucose levels < 150–180 mg/dL [70,173–177];		
Nutritional	Weight loss	Patient that receive less than 60% of their energy target from Enteral nutrition		Individually optimized energy supplementation with parenteral nutrition [178]
Splanchnic hypoperfusion	Stress ulceration, ileus or malabsorption	For patients with sepsis stress ulcer prophylaxis with the use of histamine H$_2$–receptor antagonists may decrease the risk of gastrointestinal hemorrhage. Proton-pump inhibitors may be effective but have not been fully evaluated for stress ulcer prophylaxis		
Deep venous thrombosis (DVT) [70]		Because sepsis increases the risk of deep venous thrombosis, prophylactic heparin is recommended for patients who do not have active bleeding or coagulopathy.		Use mechanical DVT prevention devices -low-dose unfractionated heparin (UFH; 2 or 3 times daily) or low-molecular-weight heparin (LMWH); dalteparin may be used in the case of patients with creatinine clearance < 30 mL/min

Acronyms: MODS: Multiorgan dysfunction; SOFA: Sequential Organ Failure Assessment; ALI: acute lung injury; ARDS acute respiratory distress syndrome; CPAP: Continuous Positive Airway Pressure; PEEP: Positive End Expiratory Pressure; MAP: Mean Arterial Pressure; UOP: Urine Output; DIC disseminated intravascular coagulation; BSCH: British Committee for Standards in Hematology; GCS: Glasgow Coma Scale; SCvO$_2$: Central Venous Oxygen Saturation; SvO$_2$: Mixed Venous Oxygen Saturation.

* Values or Treatment that, if not effective, indicate patient referal to the ICU.

a "VoL" clinical signs: dyspnea, elevated jugular pressure, crackles on auscultation, and pulmonary edema on chest Rx;

b improvement after fluid resuscitation of mental status, heart rate, MAP, capillary refill and UOP.

for invasive procedures such as central venous cannulation, necessary for the measurement of central venous pressure and $SvO_2/ScvO_2$ [99–102]. Recent reports suggest that early lactate [50,103,104] measurements might be equivalent to $SvO_2/ScvO_2$ monitoring in order to guide fluid resuscitation. Furthermore, lactate normalization has been shown to be non-inferior to early resuscitation based on $ScvO_2$ normalization [50,105]. Table 4 lists the parameters that need checking in order for organ dysfunctions to be monitored.

4.3. Statements about hospitalization and antineoplastic treatment interruption

4.3.1.1. Hospitalization

HNCPs with sepsis should be promptly hospitalized as this condition can progress rapidly.

4.3.1.2. CT interruption

For suspected or confirmed severe sepsis during CRT, CT should be the first treatment to be interrupted.

4.3.1.3. RT interruption

For suspected or confirmed sepsis during CRT, RT should be stopped only in particularly compromised patients or in the presence of severe sepsis.

Sepsis management requires multidisciplinary (oncologist/hematologist, IDP, CCP, nurses, pneumonologists, and dieticians), diagnostic and management actions that need to interact rapidly in order to maximize the chances of success [70]. Thus, the panel suggests that HNCPs undergoing CRT should be hospitalized when diagnostic criteria for sepsis [23] are associated with a suspected infection. This is so that HNCPs can progress more rapidly and that the specific antineoplastic treatments can continue safely by limiting interruption as much as possible.

In addition, the presence of sepsis should induce the interruption of CT administration, given its potential in worsening organ damage and in hindering immune responses. CT should be resumed when every organ failure is resolved and no sign of SIRS is present. Conversely, the radiotherapeutical systemic effects are less dangerous than chemotherapeutical ones: consequently, the panel suggests continuing RT as the advantage due to local-toxicity recovering could be annulled by the negative effects of tumor re-growth [106,107]. Of course, the symptoms of local toxicity must be monitored/controlled.

4.4. Statements about the Early empirical antimicrobial treatment

4.4.1 *Empirical antibiotic therapy should be started within 3 h of clinical presentation*

4.4.2 *For suspected or confirmed sepsis (Systemic inflammatory response to infection; see* Table 2) *empirical antibiotic therapy should be started, considering both anti Gram+ and anti Gram- antibiotics* [108,109]. *It should attempt to provide antimicrobial activity against the most likely pathogens based upon the potential source of infection searched on the basis of each HNCP's presenting illness*

4.4.3 *Empirical antibiotic therapy has to be based on local surveillance, antibiotic sensitivity and infection rate/prevalence; otherwise a rational use of antibiotics in accordance with international guidelines is advisable (e.g. Centers for Disease Control and Prevention CDC)*

4.4.4 *Considering the very high rate of infection sustained by multi- and pan- resistant microorganisms in the HNCPs as well as in the general population, when local guidelines are not available, it is suggested that treatment with broad spectrum, potent antibiotics active against enterobacteriaceae and methicillin-resistant Staphylococcus aureus be started*

4.4.5 *In the presence of sepsis following an oral cavity infection, the introduction of an antifungal agent associated with an anti-Gram+ antibiotic*

4.4.6 *Once aspiration pneumonia is suspected, a low threshold for CT scan and diagnostic bronchoscopy should be maintained*

4.4.7 *For healthcare-associated infections non-responsive to the first line of antibiotics, the IDPs' assessment is mandatory*

Initiation of therapy may be necessary for unstable or high-risk patients while the diagnostic evaluation is ongoing [75]. If an infectious cause of fever is suspected, empirical antimicrobial therapy is urgent. Indeed, delaying effective antimicrobial therapy has been associated with increased mortality [49,110–114]. Barie and associates [115] demonstrated in a prospective observational study that the delayed-antibiotic therapy increased the risk of death by 2.1% for every 30 minutes' delay (OR, 1.021; 95% CI, 1.003 to 1.038). Moreover, MacArthur et al. in a randomized trial obtained a 10% decrease in the overall crude-mortality with an adequate and early empirical antibiotic treatment [116]. Thus, antibiotics should be given before obtaining the results of cultures in any case suspected of having an infection and when one or more organ failures are manifested without other signs of infection.

The initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens [110–112,115,117,118]. Kollef et al. showed [117] that the prior administration of antibiotics (implying an increased risk of resistant pathogens) and the presence of a bloodstream infection (especially catheter-related: implying resistant gram positive cocci and failure to treat fungemia empirically) were the main causes of inappropriate therapy and increased mortality.

Initial empirical anti-infective therapy includes one or more drugs that have activity against all likely pathogens (considering both Gram+ and Gram- and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis [70] (Table 5).

Thus, the main aims that should guide the choice of anti-infective treatments are [69,70]:

Table 5
Proposals from the literature of empiric antibiotic antimicrobial choice based on suspected site of infection.

Presume Site of the source of infection	Local infection or critical colonization	Sepsis[a],[b]
Pneumonia[c]	*Early onset*, low risk for multi-drug resistant organisms: Out-patient: ceftriaxone plus azithromycin 500 mg qd or levofloxacin 500 mg bid or moxifloxacin po 400 mg qd In-patient (IV) ampicillin/sulbactam 3 g q8 h, (IV) ceftriaxone plus (IV) azithromycin 500 mg qd or levofloxacin 750 mg qd or moxifloxacin400 mg qd(IV)	*Late onset and/or risk factors for MDR organisms*: Meropenem (IV) 1 g q8 h or Piperacillin/tazobactam (IV) 4.5 g q6 h or Imipenem/cilastatin (IV) 500 mg q6 h (1 g q6-8 h if *P. aeruginosa* is suspected) *PLUS* Vancomycin (IV) 15–20 mg/kg/dose q8–12 h, or Linezolid 600 mg (IV) q12 h
Oral cavity	Topical forms of fluconazole, Itraconazole, nystatin suspension intra-orally [179].	Ampicillin/sulbactam 3 g q8 h, (IV) *PLUS* If suspected mycosis: Fluconazole 100 mg q12 h or Itraconazole oral solution 100 mg q12h [180] or Echinocandins (anidulafungin, caspofungin and micafugnin) or liposomal amphotericin B only in very severe and refractory cases [181]
Central venous device [138]	Early catheter removal (if possible) Daptomycin 6 mg/kg/dose IV once daily (in absence of pneumonia), or Vancomycin (IV) 15–20 mg/kg/dose (actual body weight) every 8–12 h *PLUS* Piperacillin/tazobactam (IV) 4.5 g every 6 h or meropenem (IV) 1 g q8 h or imipenem/cilastatin (IV) 500 mg q6 h (1 g q6-8 h if *P. aeruginosa* is suspected)	
Gastrostomy/Tracheostomy	Mupirocin 2%, gentamycin, eritrocyn or clortetracyclin topical ointment q8 h [182]	Piperacillin/tazobactam (IV) 4.5 g every 6 h or carbapenem (meropenem (IV) 1 g q8 h or imipenem/cilastatin (IV) 500 mg q6 h *PLUS* Vancomycin (IV) 15–20 mg/kg/dose (actual body weight) every 8–12 h, or Linezolid 600 mg (IV) q12 h or Daptomycin (IV) 4 mg/kg/dose once daily, or Telavancin (IV)10 mg/kg/dose IV once daily. *PLUS* If suspected invasive candidiasis/candidaemia: Caspofungin of micafungin or liposomal amphotericin B or anidulafungin [181]
Gastrointestinal Oesophageal	Moxifloxacin 400 mg intravenously (IV) qd followed by moxifloxacin 400 mg orally (PO) qd [183,184] or Amoxicillin/clavulanate and ciprofloxacin plus metronidazole [185]	In case of peritonitis: Piperacillin/tazobactam (IV) 4,5 g q6 h or Imipenem/cilastatin (IV) 2 g q8 h or Meropenem (IV) 2 g q8 h 3 or Tigecycline [185] *PLUS* Echinocandins (anidulafungin, caspofungin and micafugnin) or liposomal amphotericin B only in very severe and refractory cases [181]
Diarrhea (consider C. difficile infection)	Oral Vancomicin 125 mg q6 h for 10 days or Teicoplanin 200 mg o12 h or Fidaxomicin 200 mg q12 h for 10 days	Oral Vancomicin 125–500 mg q6 h for 10 days or Teicoplanin 200 mg o12 h or Fidaxomicin 200 mg q12 h for 10 days When oral treatment is not possible, parenteral metronidazole 500 mg tid for 10 days combined with intracolonic or nasogastric administration of vancomycin.

Table 5 (*Continued*)

Presume Site of the source of infection	Local infection or critical colonization	Sepsis[a],[b]
Sepsis [109,186] without an individuated site	In the case of non-HAI-suspected infection ampicillin/sulbactam 3 g q8 h, plus levofloxacin 500 mg qd	In patients with HAI Daptomycin (IV) 6 mg/kg/dose once daily in absence of pneumonia, or Teicoplanin (IV) 12 mg/kg/die or Vancomycin[d] (IV) 15–20 mg/kg/dose (actual body weight) every 8–12 h or Linezolid (IV) 600 mg q12 h in absence of bacteremia, *PLUS* Piperacillin/tazobactam (IV) 4.5 g every 6 h or Carbapenem[e] *PLUS* If suspected mycosis: Echinocandins (anidulafungin, caspofungin and micafugnin) or liposomal amphotericin B [181]

[a] If the patient is "antibiotic experienced" an amynoglicoside rather than a quinolone or cephalosporin for gram- is advisable. In fact certain microorganisms, chiefly Enterobacteriaceae (e.g., *E. coli* and *K. pneumoniae*), contain a beta-lactamase enzyme that inactivates penicillins and cephalosporins (Extended Spectrum Beta-Lactamase producing bacteria (ESBL) Patients presenting with ESBL-associated risk factors (intra-abdominal), tigecycline is recommended [185].

[b] The combined antibiotic therapy should consider pathogens with antibiotic resistance (such as MRSA, Pseudomonas species, and gram-negative organisms with ESBL activity) increasing the likelihood that at least one drug may be effective against that strain [187,188].

[c] Typically require dual broad-spectrum antibiotics with overlapping coverage [189–192].

[d] In patients with a history of IV drug use, those with indwelling vascular catheters or devices, or those with recent hospitalizations an agent such as daptomycin (in absence of pneumonia) or vancomycin (IF mic ≤1) or linezolid (in absence of bacteremia) should be adopted.

[e] Cephamycins (e.g., cefotetan) and carbapenems (e.g., imipenem, meropenem, and ertapenem) [193] remain effective against ESBL-producing organisms.

– The evaluation of risks for infection by multidrug-resistant pathogens.

HNCPs having been treated with CT during the previous 30 days should be considered immunocompromised [119–121] and at high risk of healthcare-associated infections.

– The evaluation of the suspected infection source

The main infection sources in HNCPs are the respiratory tract, the oral cavity, and medical devices such as central venous catheters (CVCs) [122], especially total implanted access ports [123], gastrostomy [124], and tracheostomy [47].

- Respiratory infection is the most frequent non-cancer cause of morbidity/death in HNCPs. Indeed, Soares [82] and Downey [125] reported that the main reasons for ICU admission for HNCPs were sepsis and acute respiratory failure. Other authors [126,127] showed that the most common causes of non-cancer-associated morbidities/death are respiratory diseases. Indeed, aspiration of colonized oropharyngeal contents into the lower respiratory tract can be due to HNCPs' swallowing dysfunction [45,128]. Thus, pneumonia in HNCPs should be considered and treated according to the health-care acquired pneumonia (HCAP) criteria due to the frequent involvement of multidrug resistance organisms [121].
- Regarding the oral cavity, a systematic review shows that clinical oral fungal infection/colonization rises respectively to 37.4%/72% during RT and 38%/74.5% during CT. Candida albicans (46.2%) was the prevalent colonizing fungi followed by C. tropicalis (16.6%) [129]. Furthermore, shifts in oral bacterial flora (mainly from

streptococci toward coagulase-positive staphylococci) [130]) have been attributed to CT, xerostomia, antibiotic use and associated neutropenia [130–132].
- Regarding device-related infection, it must be considered that a colonized foreign body serves as a continuing source of infection by multiple mechanisms: it impairs local host defenses and many of the organisms have the capacity to form a biofilm on invasive devices and so create a continuing focus of infection. Coagulase-negative Staphylococci species, for example, create a biofilm and therefore are a common cause of vascular catheter-related infections [133]. The infection due to these external-internal devices may be localized to entrance-site and/or tunnel (or port-pocket in the case of port-a-cath CVC) and, when associated to SIRS, is the cause of device-associated "blood systemic infection" (BSI).

Cancer patients with implantable port systems experienced a median of 0.2 infections per 1000 catheter-days (range: 0–2.7 per 1000 catheter-days) [134] versus a risk that ranges from 1.4 to 2.2 infections per 1000 catheter-days for subcutaneous tunneled CVCs [135,136]. Nevertheless, this difference may be biased by the fact that patients who receive implantable subcutaneous ports usually receive much less intensive cancer therapy [137]. Thus, the optimal device to be used during CRT is hardly advisable and needs further prospective trials.

Recommendations for culturing and treatment of catheter-related BSI are addressed by the Infectious Diseases Society of America [138,139]. In addition, ASCO guidelines [137] recommend immediate catheter removal for BSIs caused by fungi and non-tuburculous mycobacteria (e.g., *M. chelonei*, *M. fortuitum*, *M. mucogenicum*,

M. abscessus). Furthermore, BSIs caused by *Bacillus* species, *C. jeikeium*, *S. aureus*, *P. aeruginosa*, *S. maltophilia*, and vancomycin-resistant enterococci may be difficult to eradicate with antimicrobial therapy alone, and early catheter removal should be considered. Finally, catheter removal should also be considered when blood cultures remain positive 48 h after the start of antibiotic treatment if no other infection site has been identified or if bacteremia recurs shortly after the completion of a course of antibiotics.

- *Regarding the enteral nutrition*, there were significantly more infections in the PEG group (66%) compared to the NGT group (30%) *p* = 0.001 in the prospective study of Corry et al. [124], but the difference of pneumonia between the two groups (PEG = 31.3% vs. NGT = 30%) was statistically insignificant. In fact, the majority of infections in the PEG group were at the PEG site (31%: 10/32).

– Evaluation of antimicrobial sensitivity of local germ populations.

The prevalence of microorganisms differs according to the environments. Some authors [140] have observed that gram-positive bacteria prevail over the gram-negative ones as infectious pathogen in developed countries, probably because of the routine use of prophylactic oral antibiotics (such as quinolones, which can also favor bacteriaceae) [141] and the use of CVC [140]. Conversely gram-negative prevails in developing countries [142].

Consequently, most scientific guidelines [70,120] recommend recognizing the variability of bacteriology from one hospital to another over time in order to select the most appropriate antibiotic regimen.

4.5. Statement about the antibiotic de-escalation procedure

4.5.1. The empirical treatment must be optimized when microbiology results are available

The empirical combination antimicrobial therapy should not be administered for longer than 3–5 days [70]. After that period, treatment de-escalation to the most appropriate single-agent therapy should be performed as soon as the susceptibility profile is known [109]. This should minimize the risk of inducing toxicity and bacterial resistance, and of developing superinfections with other resistant organisms such as Candida species, Clostridium difficile or vancomycin-resistant Enterococcus faecium. Concern about under treatment due to de-escalation is unfounded [143]. The "Surviving sepsis campaign" [70] suggests the duration of therapy be 7–10 days if clinically indicated; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with MRSA; some fungal and viral infections, or immunological deficiencies, including neutropenia.

The use of procalcitonin [64,144,145] or similar biomarkers may facilitate discontinuance of antibiotics in a patient with clinical improvement, although one recent study failed to show any benefit of daily procalcitonin measurement [146].

4.6. Statements about early goal-directed treatment (EGDT)

4.6.1 *In cases of severe sepsis (sepsis ± organ failure) supportive therapy using the "EGDT" scheme should be applied as soon as possible: oxygen administration, hydration with crystalloids, and targeting a Svo2 of 70%*

4.6.2 *Most patients with severe sepsis (see Table 4) should be rapidly referred to an intensive care unit (ICU)*

In 2004, the "Surviving Sepsis Campaign" guidelines recommended the use of EGDT [147] based on one large randomized trial [93]. These guidelines were updated in 2008 [148], successively in 2012 [70], and were further supported by several subsequent trials that corroborated the benefit of EGDT in severe sepsis and septic shock [149].

Rivers [93] showed there was an increase in survival at 28 days through EGDT application in a randomized study in which patients with severe sepsis and septic shock received EGDT during the first 6 h after enrolment or the usual therapy. EGDT involves identifitcation of high-risk patients (see Table 4), invasive monitoring, and 6 hours of protocolled resuscitation with fluids, vasoactive agents, and packed red blood cells. Although these strategies are common in the ICU, they are not in oncology or internal medicine wards. Recently, some authors have not found any significant benefit of the mandated use of central venous catheterization and central hemodynamic monitoring in all patients [102].

The mechanisms of the benefit of EGDT are unknown but may include reversal of tissue hypoxia and a decrease in inflammation and coagulation defects.

4.7. Statement about the follow up

4.7.1. Monitoring for SIRS parameters should be continued after the end of CRT until the complete resolution of acute toxicities. Indeed, mortality for pneumonia is reported to occur well after 30 days from the end of treatments and there is a high risk of infection for several months

Mortality for pneumonia is reported to occur well beyond 30 days after the end of treatments and a high risk of infection is maintained for several months [6,12]. Indeed, it must be considered that the local damage and nutritional impairment last several months after the end of treatment [150], consequently the risk of infection remains higher well after the end of treatment.

5. Conclusions

The sepsis in CRT-treated HNCPs is a serious much-feared complication and constitutes a reason for treatment reduction, delay, or interruption. It may affect the prognosis and

cause the death of potentially curable patients. In order to better manage this adverse event, it is necessary to standardize clinical definitions, diagnosis, management, and treatment according to international guidelines. Since very little has been written concerning severe sepsis in HNCPs, our review aimed to obtain some indications for the management of septic patients from literature and tried to draw up recommendations/suggestions for HNCPs, based on the consensus among multidisciplinary health professionals. The main aim is to standardize their diagnostic and treatment behavior.

Obviously, the main limit of this study is the fact that most literature is obtained from non-HNCPs.

Conflict of interest statement

The Authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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