

Since the introduction of biomedicines in human therapy, a number of systemic reactions have been more frequently reported as important adverse events following treatment. Some monoclonal antibodies, interleukins, receptor inhibitors, and growth factors may preferably induce acute, violent, early events with an overall low frequency, but with serious and life-threatening capacity. In fact, these reactions represent one of the major limitations to therapeutic efficacy of this new set of drugs. Different mechanisms of action, only partially known, are implicated in the various syndromes, although most of them may be related to highly specific receptor targeting causing immediate massive release of specific factors, such as in the cytokine release syndrome, or of intracellular active components of neoplastic cells, such as in the tumor lysis syndrome.

However, these syndromes are not exclusive of bio-therapeutic interventions, and may occur during the development of various pathologies and as complications unrelated to drug administration. Moreover, the therapeutic intervention may enhance the expression of underlying, low/asymptomatic conditions rather than inducing per se the evoked systemic manifestations. Therefore, among the adverse events of biomedicines, the syndromes reported in Table 3.1 should be particularly taken into account, and be carefully considered in terms of etiopathogenesis as well.

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### 3.1 Capillary/Vascular Leak Syndrome (CLS/VLS)

The capillary leak syndrome (CLS) was first described in 1960 as sudden episodes of collapse due to a massive, albeit reversible, transfer of plasma into extravascular compartments causing shock, and edema [1]. Later on, it has been related to cytokines' action on vascular permeability and identified also as vascular leak syndrome (VLS) [2]. In its acute phase (leak phase), up to 70 % of plasma is extravasated. *Prodromic signs* such as malaise, weight gain, fatigue, weakness and myalgia may occur; pyrexia, abdominal pain, diarrhea and vomiting may follow.

**Table 3.1** Systemic syndromes

Denomination	Acronym	Mechanisms of action/ expression	Manifestations	Bio-inducers (*)
<i>Capillary (vascular) leak syndrome</i>	CLS	Endothelial damage/ apoptosis Endothelial and leukocyte activation Cytokine release	<i>Leak phase</i> : hypotension, peripheral edema, hemoconcentration, hypoalbuminemia, oliguria Complications: ischemia, stroke, DVT, renal failure, rhabdomyolysis <i>Post-leak phase</i> : visceral edema Complications: pulmonary and cardiopulmonary edema	Interleukins (IL-1, IL-2, IL-3, IL-4) Interferons (IFN- $\alpha$ , IFN- $\beta$ /1b) Monoclonal antibodies (alemtuzumab, basiliximab, bevacizumab, catumaxomab, daclizumab) Growth Factors (oprelvekin) Immunotoxins (denileukin-diftitox)
<i>Reversible posterior leukoencephalopathy syndrome</i>	RPLS	Local (brain) CLS	Cerebral edema, cephalaea, visual loss, seizures, hypertension	Monoclonal antibodies (bevacizumab, certolizumab, Rituximab, ustekinumab)

(continued)

Table 3.1 (continued)

Denomination	Acronym	Mechanisms of action/ expression	Manifestations	Bio-inducers (*)
<i>Cytokine release syndrome</i>	CRS	Cytokine storm; T cells (mainly CD28+) B-cells and monocytes massive activation	<i>Early phase:</i> cephalaea, nausea, vomiting, diarrhea, chills, pyrexia, hypotension <i>Secondary/late phase:</i> cardiorespiratory and renal disorders, DIC cytopenia, ARDS, cardiovascular shock, pulmonary edema, renal/hepatic disorders, neuro-psychiatric events <i>Flu-like syndrome:</i> cephalaea, pyrexia, chills, muscular pain/weakness	Interleukins (IL-1, IL-2, IL-3, IL-6, TNF- $\alpha$ ) Monoclonal antibodies (muromomab, tositumomab, rituximab, alemtuzumab, catumaxomab)
<i>Infusion reaction syndrome</i>	IRS	CRS, hypersensitivity, anaphylaxis (IgE), intolerance, direct toxicity, anaphylactoid reactions	Hypotension, pyrexia, chills, bronchospasm, dyspnea, tachycardia, nausea/vomiting, rash/urticaria, angioedema, other cardiovascular disorders, ARDS	Most infused biomedicines, IgE-mediated (muromomab, cetuximab, panitumumab)
<i>Tumor lysis syndrome</i>	TLS	Massive tumoral cell lysis and consequent, release of K, P, nucleic acids	Oliguric renal failure, arrhythmias, hypotension, cardiac failure, neuro-muscular disorders, hyperkalemia, hyperphosphatemia, hyperuricemia elevated LDH, pyrexia, secondary hypocalcemia	Monoclonal antibodies (alemtuzumab, brentuximab gemtuzumab, ipilimumab, ofatumumab, rituximab)
				“Double TLS storm” (muromomab, ibritumomab, ofatumumab, rituximab, tositumomab) CLS-CRS-TLS “Shock waves” (alemtuzumab)

(continued)

Table 3.1 (continued)

Denomination	Acronym	Mechanisms of action/ expression	Manifestations	Bio-inducers (*)
<i>Systemic inflammatory response syndrome</i>	SIRS	Activation/release of proinflammatory cytokines	Pyrexia/hypothermia, leukocytosis/leukopenia, tachycardia/tachypnea	Pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF- $\alpha$ , IL-8) Integrins (ICAM) Monoclonal antibodies (catumaxomab)
<i>Macrophage activating syndrome</i>	MAS	Unknown. genetic defects of T and NK cells High levels of macrophage stimulating factors (M-CSF, MCP-1, IFN $\gamma$ , interleukins (IL-6, IL-12) IL-18, TNF- $\alpha$ , IL-2), receptors (IL-2R)	Hepatosplenomegaly, encephalopathy, pancytopenia, coagulative, disorders, increased ferritin, elevated non remitting pyrexia, hemaphagocytosis, LDH elevation, hyponatremia, hypertriglyceridemia, hypoalbuminemia	Monoclonal antibodies (alemtuzumab) Cytokine receptor analogues (anakinra)

(continued)

Table 3.1 (continued)

Denomination	Acronym	Mechanisms of action/ expression	Manifestations	Bio-inducers (*)
<i>Immune reconstitution inflammatory syndrome</i>	IRIS	Therapy discontinuation. immune response Dysregulation/rebound after drug-induced, immunosuppression. T memory/naive imbalance Hyperproduction of interleukins (IFN $\gamma$ , IL-2, IL-6, IL-12)	<i>Infectious</i> : worsening/unmasking, neutrophil rebound <i>Non infectious</i> : inflammatory and autoimmune exacerbation, cutaneous reactions (papular urticaria, SLE), GBS, acute porphyria	Monoclonal antibodies (natalizumab, infliximab, adalimumab)
<i>Progressive multifocal leucoencephalopathy</i>	PML	JC virus reactivation Local (brain) IRIS-PML T cells, B cells and plasma cells increase	Leukoencephalitis signs: vision loss, paralysis, cognitive disorders Alien hand syndrome	Monoclonal antibodies (efalizumab, infliximab, rituximab, natalizumab) Fusion proteins (belatacept)

\* Examples of direct and indirect events related to biomedicines administration; DIC: disseminated intravascular coagulation; ARDS: acute respiratory distress syndrome. See also list of acronyms.

The *Leak phase* is characterized by prolonged hypotension, edema (face, trunk, extremities) hemoconcentration, hypoalbuminemia, oliguria, thirst, and cool skin. Complications such as ischemia, renal failure, stroke, deep vein thrombosis, and rhabdomyolysis may also occur at this stage.

During the *postleak phase*, symptoms revert rapidly; fluids are recruited into circulation and diuresis increases; the massive fluid rebound induces diffuse visceral edema, usually not present in the leak phase. Therefore, pulmonary edema and cardiopulmonary failure are the consequent complications during the postleak phase. Their severity and frequency may be influenced by the usual high volumes of fluids administered during the leak phase to compensate extravasation.

CLS is a rare, acute, unpredictable cyclic event with intervals from days to decades, albeit stereotyped in each patient. The diagnosis is based on the simultaneous occurrence, regardless of severity, of at least two of the following signs: edema, hypoalbuminemia, and/or hypotension occurring at the beginning of a cycle of treatment, associated to signs of hemoconcentration in the absence of apparent cardiac dysfunction. However, this diagnostic approach may tend to overestimate the incidence of CLS, since these signs are common to underlying diseases and to other associated complications, such as hypersensitivity reactions.

*Reversible Posterior Leukoencephalopathy Syndrome (RPLS)* is at present considered as a localized rare brain-capillary leak syndrome associated with hypertension, fluid retention, and cytotoxic damage on the vascular endothelium.

A very rare *chronic CLS* has also been postulated, characterized by noncyclic peripheral edema and hypoalbuminemia, in the absence of hypotensive acute crisis.

The pathogenesis of these syndromes is substantially unknown. Endothelial injury and apoptosis or cell retraction have been suggested on the basis of morphological and functional studies, although not conclusive. The vascular damage may involve activation of endothelial cells and leukocytes, intercellular adhesion, and most importantly the massive release of cytokines and inflammatory mediators. Their effect greatly increases vascular permeability allowing fluids, proteins, and electrolytes to flow into interstitial spaces, producing edema, hypoxia, and multiple organ failures (mainly pulmonary, cardiac, and renal). Therefore, multifactorial mechanisms have been postulated as: (1) initial toxic effects on vascular endothelium integrity; (2) activation of endothelial cells and leukocytes; (3) additional secretion of cytokines and inflammatory mediators consequent to cell activation; (4) increased damage by activated leukocytes and secondary reaction of newly formed mediators [3–5].

CLS has been observed in various human pathologies, such as sepsis, trauma, lymphoma, monoclonal gammopathy, burns, pancreatitis, and as a consequence of bone marrow or stem cell transplantation, as well as subsequent to nonbiological anti-neoplastic drugs (cyclosporine, cyclophosphamide, mitomycin C, cytosine arabinoside, gemcitabine, and docetaxel) and dermatological (acitretin) treatments.

Since the introduction of biomedicines in human therapy, CLS has been more frequently reported as an important AE following treatment. Some monoclonal antibodies, interleukins, receptor inhibitors, and growth factors may induce CLS with low frequency but at serious/severe levels.

As for *CLS induced by biomedicines*, three aspects appear more relevant in understanding the pathogenesis: (a) the endothelial cell retraction with released cells interconnections; (b) the observed association of IgG monoclonal gammopathy with CLS, not related to therapy; and (c) the direct effect of biomolecules (cytokines, antibodies, and inflammatory mediators) exerted *in vitro* and *in vivo* on vascular endothelial cells [2, 5]. These mechanistic factors may be differently represented in specific clinical conditions, but indicate the common basic pathogenetic conditions, namely the capillary physical leakage induced by apoptosis and oxidation injury, the structural characteristics of the inducer agent, and the effectors of CLS [6].

Among cytokines, interleukins (IL-2, IL-3, IL-4) and interferons (IFN- $\alpha$ , IFN- $\beta$ 1b) were first identified as potential CLS inducers. Among monoclonals, after a mouse antiGD3 ganglioside IgG3 antibody (B24) preliminary tested against melanoma, the murine muromonab stimulated a strong cytokine production *in vitro* and induced relevant CLS reactions *in vivo* [7–9]. Among the most recent biomedicines, alemtuzumab, basiliximab, bevacizumab, catumaxomab, and daclizumab can induce CLS with different degrees of gravity. Similarly, cases of CLS have been observed with early IL-1, IL-2, and IL-4 experiences in human therapy, with stimulatory and growth factors, such as oprelvekin, filgrastim, pegfilgrastim, sargramostim, even at low doses and with immunotoxins, such as denileukin diftitox [10; see also this volume, at respective drug descriptions].

Overall, CLS represents one of the major limitations to therapeutic efficacy of cytokines and of monoclonal antibodies, together with the related cytokine release syndrome [9]. Notably, these reactions were also found to be strictly related to the respective drug-specific therapeutic actions and therefore have been indicated as possible predictor markers for efficacy (catumaxomab) [11].

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## 3.2 Cytokine Release Syndrome (CRS)

In principle, any action determining a massive T lymphocyte/Monocyte activation may produce a “Cytokine Storm”, better defined as cytokine release syndrome (CRS) consisting of an immediate immission into circulation of proinflammatory and cytotoxic cytokines which rapidly elicit systemic and dramatic signs. Although initially observed after mouse-derived mAbs infusions, more frequently as mild to moderate reactions, subsequent and prolonged experimentation encountered dramatic consequences, even with fully humanized mAbs [9, 12, 13].

Candidate targets able to induce CRS are those widely diffused on T cells (CD3, CD52), CD20, activated T cells (CD25), B cells (CD20), and monocytes (CD52). However, not all biomedicines are associated with CRS. For example, basiliximab

is considered as a low inducer of CRS because it targets the IL-2R $\alpha$  chain lacking the capacity of intracellular signaling and therefore being not able to burst violent cytokine releases, such as those causing CRS. Alternatively, some biomedicines may induce less typical reactions reported in anecdotal episodes and in the post-marketing settings yet not identified as CRS.

After early experience with muromonab (mouse-anti human CD3), licensed in 1986/87, CRS was observed with another murine mAb (anti human CD20, tositumomab), but also with chimeric (anti-CD20, rituximab), humanized (anti-CD52, alemtuzumab), and with hybrid rat/mouse tri-functional bispecific (anti-EpCAM and anti-CD3, catumaxomab) mAbs. Finally, an anti-CD28 fully humanized mAb (TGN1412), rapidly and almost simultaneously injected in six volunteers in a Phase I trial, caused an even more dramatic cascade of immediate, long lasting, and life-threatening events. The initial response was characterized by cephalaea, nausea, vomiting, diarrhea, chills, pyrexia, and hypotension accompanied by high levels of cytokines into circulation. A second phase showed increasing cardio-respiratory and renal dysfunctions, associated with disseminated intravascular coagulation. A profound lympho/mono-cytopenia followed. Finally, a prolonged cardiovascular shock and severe clinical signs of acute respiratory distress syndrome (ARDS) completed the complex dramatic feature of the syndrome.

On this basis, the etiopathogenesis and the clinical expressions of drug-induced CRS became more evident, and great concern was raised against biomedicines and their preclinical testing procedures. The CD28 positive T lymphocytes were the major targets and releasers of the pathogenetic cytokines. Moreover, the timing of infusion was a critical factor, and it became clear that even fully humanized mAbs could not avoid CRS at the most severe grades. Later on, the reason of failure to predict the cytokine storm in these subjects was ascribed to the lack of CD28 antigen on the surface of CD4+ effector memory T cells in animal species employed in preclinical investigations [14].

In the clinical experience, CRS signs usually appear after the first infusions as mild/moderate malaise, with a cohort of milder symptoms now recognized also as *Flu-like syndrome* (FLS), characterized by pyrexia (non-infective, sometimes hyperthermia), cephalaea, tremor/chills, nausea/vomiting, diarrhea, abdominal pain, muscle/joint aches, and generalized weakness. Less frequently, FLS may evolve into more serious (occasionally fatal) with additional signs including cardio-respiratory events (dyspnea, bronchospasm/wheezing, tachypnea, respiratory arrest/failure/distress, cardiovascular collapse, cardiac arrest, angina/myocardial infarction, chest pain/tightness, tachycardia, hypertension, hemodynamic instability, hypotension, shock, heart failure, pulmonary edema, ARDS, hypoxia, apnea and arrhythmias, and hypertension), transient renal and renal allograft dysfunction (oliguria, creatinemia), transient hepatic abnormalities (transaminases increase), and neuropsychiatric events (dizziness, confusion, depression, seizures, paresis/plegia, deliria, somnolence/lethargy/coma, deliria, hallucinations, and hypotonia).

Not all signs are present in every patient, even when expressing highest degrees of severity, neither they appear with all involved biomedicines. FLS is also observed in patients treated with IFNs, IL-1, IL-2, IL-3, and TNF- $\alpha$ .



Nonetheless, all forms of CRS are usually reversible and can be mitigated/controlled by slow drug infusion and appropriate therapies, according to the grading of severity.

In a number of studies, CRS has been clearly associated to specific mechanisms of action of some mAbs [9, 15]. In particular, the anti-CD3 activity initially leads to massive activation of the T cell compartment, with consequent abundant release of proinflammatory and cytotoxic cytokines initiated by the binding on immune and tumor cells, before expressing toxic and apoptotic effects on the same cells. In the case of alemtuzumab, *in vitro* testing showed that CRS is IgG isotype dependent and that IgG1—the most used isotype in mAbs production—induces the highest levels of cytokine release. Pyrexia and hyperthermia are mostly related to IL-1, IL-6, and TNF production. In particular, hyperthermia seems to be more related to IL-6 release, but independent from PGE2 production, e.g., from the usual inducer pathway of pyrexia [16]. However, CRS expression, even at moderate levels, seems also to correlate with efficacy of treatment, giving to this syndrome a potential predictive value, which can be assessed *in vitro* only on human cells [15, 17].

The potential stimulatory effect of single biomedicines can be now selectively tested in some assays, and their capacity to induce CRS seems to correlate with the response *in vitro*. However, in the case of the trifunctional antibody catumaxomab, this activity was only observed in significant amounts when the antibody was incubated *in vitro* with blood cells in the presence of the target (EpCAM positive colon tumor cells) [18]. Therefore, intercellular binding and/or additional releases of other CRS-inducing factors from tumor cells might play additional roles in CRS manifestation, particularly when a high burden of specific tumor targets are involved. Major effects were seen in releasing TNF- $\alpha$  and IL-6 in the presence of EpCAM-positive tumor cells, with a smaller activity on IL-2 and a nonsignificant action on IL-12 and IL-1. In this case, no histamine release or complement activation was observed during experiments, thus indicating the exclusive role of cytokines in the development of typical CRS. Altogether, the *in vitro* cytokine release stimulation on effector cells and the protective effect exerted by some corticosteroids in the same *in vitro* assay are a further proof-of-concept of mAb-mediated CRS pathogenesis and of the efficacy of steroid (pre) medication in mitigating its effects *in vivo*.

Therefore, the possibility of preventive checking by *in vitro* methods should be taken into consideration when CRS is expected to occur due to the underlying pathology or to the specific administered drug, becoming crucial in preventing from the dramatic “Cytokine Storms” [15, 17, 18].

### 3.3 Infusion Reaction Syndrome (IRS)

IRS is mostly related to CRS, but also involves other reactions such as hypersensitivity, direct toxicity, drug intolerance, and anaphylactoid reactivity. The reaction occurs with most systemic cancer treatments and usually appears rapidly. Hypotension, pyrexia, chills/rigors, bronchospasm, dyspnea, tachycardia, nausea, vomiting, urticaria, and/or rash are the most common signs. Serious events such as cardiac dysfunctions/insufficiency, myocardial infarction, cardiac and respiratory arrest, syncope, pulmonary infiltrates, ARDS, angioedema, and anaphylactoid shock may be associated at lower frequencies. Obviously, not all signs appear simultaneously and are of the same severity. Usually, they appear shortly after the first intravenous drug infusions, and have a mild to moderate intensity, with tendency to decrease with subsequent doses. Less frequently IRS are serious and fatal.

In the experience with biomedicines, these reactions are frequent and ultimately they appear as cytokine-mediated reactions of different intensity. However, they can be prevented by appropriate prophylactic and symptomatic therapy, and by dose grading of the drug. In a minority of cases, Type-I hypersensitivity reactions (IgE-mediated) were observed, such as after muromonab (29 %), cetuximab (3–13 %), and less frequently after panitumumab and basiliximab administrations. Interestingly, antidrug IgE antibodies were preferably directed to oligosaccharides and in some cases were present as preformed antibodies directed to the same antigens.

The subcutaneous administration significantly reduces signs and severity of IRS, but not their overall frequency. In particular, pyrexia elevation and incidence are not appreciably reduced.

Local reactions at site of injection are common, albeit mild/moderate, and tend to disappear in days or weeks. They are generated by a series of mechanisms, including local cytokine release, immune-mediated reactions, immediate or delayed, and by irritative reactions to various drug components [19].

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### 3.4 Tumor Lysis Syndrome (TLS)

The syndrome was described in 1929 in chronic leukemia, as an acute oliguric renal failure associated with hyperkalemia, followed by hyperuricemia, hyperphosphatemia, secondary hypocalcemia, elevated LDH and pyrexia, in adult and pediatric patients with high load tumors at elevated cell turnover. Usually these types of tumors, either hematologic or solid, undergo rapid spontaneous and massive cell lysis, which liberates ions and toxic metabolites affecting at first the renal function, followed by a life-threatening multisystem organ failure. Clinical consequences, due to electrolytes' abnormalities and acute toxic overload, progressively affect cardiac, muscular, hepatic, and neurological conditions. The syndrome can be fatal although in most cases is reversible and preventable [20–22].

*Spontaneous TLS* may occur mainly in high-grade lymphomas (Burkitt's, NHL), AML/ALL, and CLL. Interestingly, spontaneous TLS can be triggered by local events, such as infiltration of leukemic T-ALL cells in the renal parenchyma producing acute kidney failure, even in an aleukemic phase of the disease [23].

Cytotoxic chemotherapy, radiation therapy, occasionally glucocorticoid therapy, and biomedicines have further enlarged the category of solid tumors undergoing *secondary TLS* (hepatoblastoma, neuroblastoma grade IV, renal cell cancer, gastro-intestinal stromal tumors, pancreatic neuroendocrine tumors, and melanoma) and in particular to those combining a high rate of turnover with high sensitivity to specific treatments. In fact, cancer cells have an abnormally high amount of potassium, phosphorus, and nucleic acids. The breakdown of the latter in the liver produces hyperuricemia, mainly affecting the renal function, while secondary hypocalcemia occurs because of serum calcium binding to the elevated amounts of phosphates in the bloodstream. The subsequent calcium/phosphate unbalance produces arrhythmias, hypotension, and cardiac failure; hyperkalemia increases renal injury and impairs cardiac and neuromuscular functions.

The main *difference between spontaneous and posttreatment TLS* is that the former are also associated with particular high levels of hyperphosphatemia and related consequences. A possible explanation has been related to re-usage of released phosphates during spontaneous TLS by newly growing tumor cells, which is avoided in secondary TLS because of the prolonged action of administered cytotoxic drugs. Therefore, an acute renal failure with hyperkalemia and hyperphosphatemia and oligo/anuria in patients with a large tumor burden during therapy is highly indicative of secondary TLS.

In 1960, a "*prodromic TLS*" was identified, with 25 % increase of electrolytes and uric acid associated with signs of renal injury. This phase may occur from 3 days before to 7 days after cytotherapy initiation, showing creatinine increase, cardiac (arrhythmia, sudden death) and neurological signs (seizures), which can be controlled by appropriate therapy (anti-uric, hemodialysis). Importantly, adequate surveillance and therapy can prevent the evolution of the prodromic phase into clinical TLS.

The experience with biomedicines and other recent drug classes, such as protein kinase inhibitors and a proteasome inhibitor, confirmed that the potential susceptibility to TLS is particularly linked to tumor/patient bio-specificities, more than to drug class characteristics or specific mechanisms of action. Among mAbs, alemtuzumab (CD52), brentuximab (CD30), gemtuzumab (CD33), ipilimumab (CTLA-4), ofatumumab, and rituximab (CD20) have induced TLC or have alerted for possible potentiality of induction, due to their high efficiency in massive tumor cell destruction. Clearly, being their targets quite different, a specific pathway of destruction has been excluded. However, some of these agents, such as IL-2 and anti-CD3 (muromonab) or CD20 (ibritumomab, ofatumumab, rituximab, and tositumomab), have the capacity of activating their target cells soon after therapy initiation and before destroying them. Therefore, in the presence of relevant tumor burdens with high cell turnover, such as T cell lymphomas and acute leukemia, they may cause, although infrequently, a "*double storm*" in sequence, first through

massive *cytokine release (CRS)* and then by vast *tumor cell lysis (TLS)*. Very rarely, as documented for example during antiCD52 (alemtuzumab) therapy, *CLS*, *CRS*, and *TLS* can follow like *incoming shock waves*.

Since these episodes are rare, they can remain a mere potential risk at clinical level, provided that timing prevention occurs.

Understanding TLS at theoretical level remains important for identifying biomedicines' combined mechanisms of actions that induce violent AEs, such as T cell activation causing high endothelial toxicity (widely cytokine-dependent), and massive destructive capacity of tumor burden.

Taken together, these aspects are currently a major limitation to the therapeutic utility of most active biomedicines, yet they also represent a master lesson and a crucial point for future development.

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### 3.5 Systemic Inflammatory Response Syndrome (SIRS)

SIRS is an acute progressive reaction resulting from the activation of proinflammatory cytokines caused by infectious and other noninfectious stimuli such as ischemia, major trauma, surgical trauma, and therapy. According to a largely accepted official definition (ACCP) pyrexia ( $>38\text{ }^{\circ}\text{C}$ ) or hypothermia ( $<36\text{ }^{\circ}\text{C}$ ), leukocytosis ( $>12\times 10^9/l$ ) or leukopenia ( $<4\times 12\times 10^9/l$ ), increased heart rate ( $>90$ ) and respiratory rate ( $>20$  or  $\text{PaCO}_2 <32$ ) are the cardinal signs, and at least two of them must support the diagnosis. *Infectious SIRS* may proceed to sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS), as defined by ACCP since 1992.

*Nonseptic SIRS* evolves into a multiorgan dysfunction and eventually failure. Among them, renal failure, gastrointestinal bleeding, anemia, deep vein thrombosis, disseminated intravascular coagulation (DIC), electrolyte abnormalities, and hyperglycemia are the most relevant signs. Overall, SIRS occurs frequently (35 %) in acute hospitalized medical patients, is moderately related to initial infection, and highly related to mortality [24, 25]

Initiators of SIRS include a number of factors, such as bacterial endotoxins, immune (anaphylaxis) and complement-mediated systemic disorders (DIC), hypoxia, endothelial vascular injury, and cytokine releasing agents including biomedicines with a peculiar capacity of induction of CLS/CRS manifestations.

In principle, all cytokine releasers may induce the syndrome; the most relevant involved in the syndromic progression are  $\text{TNF}\alpha$ , IL-1, IL-6, IL-8, and possibly IL-8, and IL-17. However, other molecules may be involved, such as integrins. Interestingly, an anti-integrin monoclonal antibody blocking the CD11d receptor for ICAM3 (CD50) and ICAM1 (CD106) reduces multiorgan signs of SIRS [26, 27].

SIRS has been observed within 24 h after catumaxomab infusion, showing severe tachycardia, pyrexia, leukocytosis, and dyspnea, that resolved with symptomatic therapy. Overall, SIRS is rarely diagnosed during treatments with biomedicines, including those actively inducing cytokine storms, presumably because

of the difficulty to distinguish SIRS from CLS/CRS events, bacterial-induced sepsis, and septic shock frequently encountered among AEs, all sharing various mechanistic routes [18].

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### 3.6 Macrophage Activating Syndrome (MAS)

MAS acronym was proposed in 1993 and identifies a serious, life-threatening complication of rheumatic diseases, more frequently observed in the *Systemic juvenile idiopathic arthritic forms (SJIA)*, also known as acquired hemophagocytic lymphohistiocytosis (HLH), included in the group of hemophagocytic syndromes (HPS). Rare primary *inherited forms* of the disease are also known (Chédiak-Higashi Syndrome). MAS is also a complication of lymphoma (mainly NHL), SLE, Kawasaki disease, and of autoinflammatory inherited periodic fever disorders. The syndrome also occurs after EBV and CMV *acute infections* and is characterized by an impaired or absent function of NK cells, and of cytotoxic T lymphocytes. This unbalanced situation seems to induce a persistent antigen-driven activation, leading to a consistent production of cytokines that stimulate macrophage proliferation and activity.

The clinical features of MAS include an intense macrophage hemophagic activity, mostly evident in the bone marrow, developing into pancytopenia, coagulative disorders, hepatosplenomegaly, encephalopathy, rapidly increasing ferritin levels, and elevated nonremitting pyrexia. Additional laboratory abnormalities include high levels of LDH and triglycerides, hyponatremia, and hypoalbuminemia. Frequently, the clinical evolution is acute and dramatic, with a high rate of mortality.

At present, the syndrome is not considered rare as it used to be, since sub-clinical forms have been more recently detected with a frequency of up to 40 % of cases in SJIA. The etiology of noninfectious forms is unknown. Genetic defects in T and NK cells cytotoxicity, the latter related to perforin deficiency encountered especially in SJIA, have been identified. High levels of macrophage stimulating (M-CSF, IFN $\gamma$ , and MCP-1), or macrophage-derived (IL-6, IL-12, IL-18, and TNF $\alpha$ ) cytokines, and of T-derived products (IL-2 and IL-2R) are usually present, while IL-1 is not always elevated, although its role in developing the syndrome is revealed by beneficial effects of IL-1 antagonist, such as anakinra. However, a number of iatrogenic inducers/boosters have been suspected, such as acetylsalicylic acid and other NSAIDs, gold salts, sulfasalazine, and biomedicines with high capacity of cytokine release, including TNF- $\alpha$  releasers. Interestingly, the latter seems to play an additional role in dyscoagulative disorders [28–31]. Cases of MAS or exacerbation of underlying states of HPS, including cytopathic histiocytic panniculitis (CHP) have been reported after treatment with etanercept, rilonacept, tocilizumab, anakinra, and alemtuzumab [32, 33]. However, a direct relation between treatment and MAS induction is not always evident. For example, in cases where MAS was associated to alemtuzumab a reactivation of EBV and CMV

viruses occurred, thus indicating a possible immunosuppressive effect of the biomedicine as an indirect cause of MAS activation. In other clinical situations, such as after anakinra treatment, the agents seemed to ameliorate MAS, but in other occasions they acted as inducers of macrophage activation. In one case of CHP evolving into a severe HLH with elevated circulating  $\text{IFN}\gamma$ , IL-12, IL-4, and IL-18, but also of the antiinflammatory IL-10, etanercept was partially effective, yet produced aphasia and hemiparalysis that resolved after treatment discontinuation [34]. The subsequent treatment with anakinra was very effective in controlling the syndrome. Such biomedicine was equally effective in Still's disease and SJIA, but in other cases of JIA failed or led to induction of MAS [35–37]. It must be stated that anecdotal reported cases of similar conditions are difficult to compare per se. Observations during controlled studies are rare and often refer to different clinical situations.

Overall, the cytokine cascade defined as CRS appears as the common denominator of all syndromes associated with treatment, and in particular with biomedicines administration.

According to the induced agent typology and the individual clinical situation, CRS may be differently modulated from a mild FLS to the impressive cytokine storms (CRS, SIRS), or associated with toxic endothelial-directed events (CLS), with hypersensitivity reactions (IRS), with systemic toxicity generated by massive neoplastic destruction (TLS), or with prevalent macrophage activation (MAS).

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### 3.7 Immune Reconstitution Inflammatory Syndrome (IRIS)

While the previously mentioned syndromes are a direct consequence of therapy with some biomedicines, IRIS is the consequence of therapy discontinuation. This syndrome is defined as a dysregulated inflammatory response to noninfectious and infectious agents occurring during immune recovery, after an induced state of immunodeficiency. The syndrome is characterized by a new-onset of worsening symptoms in a phase of immune function restoration, showing aggravated or new infection, and inflammation signs.

*Unmasking IRIS* defines an occult undiagnosed infection(s), which appears after immunologic recovery. This feature is usually observed in patients recovering from drug-induced neutropenia.

*Paradoxical IRIS* defines a worsening of a known infection (opportunistic), already receiving treatment, which deteriorates during immune system recovery, in spite of appropriate concurrent therapy.

*Infectious IRIS*—initially observed in HIV patients undergoing multiple highly active antiretroviral therapy (HAART)—can also develop during other infectious (mycobacterial, herpetic infections, HBV, HCV, CMV, JCV and parvovirus infections, opportunistic infections) or noninfectious conditions (rheumatic diseases, SLE, GBS, AIDS-related lymphoma, autoimmune thyroiditis, sarcoidosis, and other granulomatous reactions).

The pathogenesis of IRIS consists in rapid and exuberant immune-inflammatory response of the host directed to resident microbial agents, or in an aspecific noninfective homeostatic rebound, causing a consistent increase of CD8 + T cells, macrophage infiltration, and necrosis.

Among the clinical manifestations there are signs of infective reactivation, such as mycobacterial lymphadenitis, recurrence of opportunistic pulmonary infection, and viral hepatitis reactivation, as well as noninfectious inflammatory and autoimmune exacerbations of underlying diseases [31, 38].

*Noninfectious IRIS* may cause cutaneous manifestations (papular urticaria, eosinophilic folliculitis, Sweet syndrome, Reiter's syndrome, and SLE), and noncutaneous disorders (GBS, radiculopathy, acute porphyria, Castleman disease, and NHL) [39].

The pathogenetic framework of IRIS consists in a rapid recovery of multiple immune functions, but the specific mechanisms involved are less clear. The syndrome may occur during antiretroviral treatment when the CD4 + cell burden rapidly increases, or after immunosuppressive treatment discontinuation. During reconstitution of the immune system, not only the number of these cells is increased, but their subtypes recover with different kinetics and peripheral redistribution; memory CD4+ cell appear to anticipate the recovery of naive T lymphocytes (of months), regulatory T cells (Treg) appear compromised by previous therapies, and an exuberant production of interleukins (IFN $\gamma$ , IL-2, IL-6, IL-12 primarily) follows, with the known activation inflammatory signs caused by the cytokine storming. However, other factors may be related to IRIS insurgence, such as VEGF signals. In one case report of TB-IRIS granulomatous infection causing retinal detachment, bevacizumab (an anti-VEGF mAb) successfully controlled the complication [40].

Overall, IRIS pathogenesis implies a complex interaction between an underlying antigen precipitant (infectious or endogenous)—the entity of immune reconstitution rebuilding a strong reactivity against the antigen—and possible host genetic yet unknown factors [41].

The immune response is predominantly of the granulomatous type, but the cell components may vary, being predominantly of the CD4+ type, with a variable association of CD8+ cells, such as in HIV-associated sarcoidosis. An additional characteristic during the immune reconstitution phase results in localized inflammation (where disseminated is typical) or in an exaggerated intensity of the inflammatory response, when the recovery of circulating T cell level has not reached normal values yet [39].

As for the rare association of IRIS to biomedicines administration, a peculiar localized IRIS form has been observed in the CNS, showing features of *Progressive Multifocal Leukoencephalopathy* (PML), soon after therapy cessation with natalizumab in MS patients.

Brain histology showed an extensive infiltration of T cells, particularly CD8+ T cells, and plasma cells. This feature, together with a low number of JCV-positive cells within the same areas, is considered as specific of "*IRIS-PML*". In fact, the number of T cells in this form was 8–9 times higher than in PML cases



observed in MS patients, as well as for plasma cells and B cells, which were practically absent in PML not related to natalizumab administration. Notably, these parameters were inversely correlated with JCV-infected cells [42].

A number of TB-IRIS were observed after TNF- $\alpha$  antagonists (infliximab, adalimumab) discontinuation. In one of these patients the reaction was associated to the recovery of cell-mediated reactivity to tuberculin, and to the capacity of organizing granulomatous lesions at pulmonary level. All patients recovered, and in one case with life-threatening manifestation; the monoclonal therapy was reintroduced with beneficial effects. The amelioration was related to inhibition of granulomatous organization allowing a better antibiotic diffusion in pulmonary lesions [43, 44].

Another and intriguing systemic syndrome has recently been observed after ipilimumab administration, related to the induction of **immune-related (mediated) adverse events (IrAES, or IMAE)** as a consequence of therapy exerting an enhanced activity on immune effector mechanisms. In this case the inhibition of a natural inhibiting signal mediated by CTLA-4, triggers a number of multiorgan serious and fatal inflammatory processes (hepatitis, enterocolitis, dermatitis etc.), driven by the massive activation of T cells (see Chap. 25). IrAEs are highly concerning, yet to be fully investigated and understood before attempting to locate them in a precise AEs framework.

The accumulated knowledge of these syndromes has offered great opportunities to put in action solid steps for their prevention. In fact, they are all infrequent adverse events related to the administration of biomedicines, but most of them can be serious and life threatening. However, their occurrence has become a mere rarity due to effective prevention and the experience of oncotherapists.

It is not easy to differentiate some of these events from hypersensitivity reactions and anaphylactoid reactions, as well as from underlying disease-related disorders. Although showing a variety of differential expressions, *the common denominator of these systemic syndromes* appears so far based on *cytokine release, cytokine dysregulation, and cytokine rebound*. They also represent a master lesson for the development of future biomedicines, having faced some failures and dramatic experiences [14]. Most of all, they have confirmed that experimentation on animal models is not sufficient to predict even frequent and life-threatening events, while in vitro efforts in finding the minimal anticipated biological level (MABEL) seems now more relevant in order to determine the initial dose for first attempts of in vivo administration [45].

More attention should be given to avoid preactivation of cytotoxic targets before their destruction, especially when rich of biologically active molecules or toxic metabolites. Finally, highest affinity bindings and highest concentrations of biomedicine/cell may not be the real goal, when targets overexpress antigens shared by normal cells at lower concentration. Lower concentration may still kill the neoplastic cells and spare a higher number of normal cells [46].

Table 3.2 reports biomedicines showing inducer capacity of one or more of the mentioned systemic syndromes.



**Table 3.2** Biomedicines as inducers of systemic syndromes and related local syndromes

Syndrome	Systemic						Local				Comparators	
	Type	CLS	CRS°	TLS	IRS	MAS	SIRS ^	IRIS	PML	RPLS	Anaphylaxis	PM reports <sup>a</sup>
<i>Subtype</i>												
<i>Monoclonals</i>												
Abciximab	-	-	-	-	4	-	4	22	-	-	<1 %	4400
Adalimumab	5	-	2	62	X, 101	1	57	1195	X, 13	X, 9	<0.01 %	130505
Alemtuzumab	X, 11	X, 11	X, 38	≥10 %	X	X	8	109	-	X, 30	<1 %, 11	3590
Basiliximab	X, 7	X, 10	-	-	-	-	20	94	-	1	32	2106
Belimumab	-	-	-	≥10	-	-	-	1	-	-	<1 %, 5	659
Bevacizumab	16	37	26	X, 101	-	2	398	-	14	105	116	21880
Brentuximab	-	-	X, 3	≥10 %, 2	-	-	-	8	-	X, 11	-	122
Canakinumab	-	1	-	-	-	-	-	7	-	-	-	403
Catumaxomab	-	X	-	-	-	-	X	-	-	-	-	-
Certolizumab	-	-	-	2	-	-	-	60	-	1	44	12087
Cetuximab	-	-	8	≥10 %, 509	-	3	141	-	2, 19	9	X, 219	7983
Daclizumab	X	-	-	-	-	-	1	30	-	-	X, 12	1141
Denosumab	-	-	-	1	-	-	-	7	-	-	3	1150
Eculizumab	-	-	-	X, 30	-	-	1	-	7	-	7	7407
Efalizumab	1	-	2	-	-	-	-	20	-	X, 26	10	3318
Gemtuzumab	3	X, 1	X, 67	≥10 %, 191	-	-	-	276	-	-	X, 30	3106

(continued)

Table 3.2 (continued)

Syndrome	Systemic						Local			Comparators			
	Type	CLS	CRS <sup>o</sup>	TLS	IRS	MAS	SIRS <sup>^</sup>	IRIS	PML	RPLS	Anaphylaxis	PM reports <sup>a</sup>	
<i>Subtype</i>							NI	I					
<i>Monoclonals</i>													
Golimumab	-	-	-	-	1	-	-	27	-	3	-	<1 %, 3	2259
Ibritumomab	-	2	5	5	<1 %, 5	-	-	74	-	X, 23	1	X, 4	1504
Infliximab	10	2	-	-	≥10 %, 5373	-	34	1065	X, 7	X, 84	33	≤1, 685	79722
Ipilimumab	-	X	X <sup>^^</sup>	X <sup>^^</sup>	10	-	-	5	-	-	-	-	938
Natalizumab	-	-	-	-	≥10 %, 610	-	10	527	X, 834	X, 258	X	<1 %, 395	90168
Ofatumumab	-	X	X, 1	X, 1	≥10 %, 11	-	-	8	-	X, 3	-	<1 %	261
Omalizumab	-	1	-	-	2	-	-	30	-	-	-	<0.1 %	10189
Palivizumab	2	-	-	-	-	-	-	66	-	-	-	<0.01 %, 21	7221
Panitumumab	-	-	-	-	≥10 %, 47	-	-	12	-	-	-	X, 7	1279
Pertuzumab	-	-	-	-	-	-	-	-	-	-	-	-	-
Ranibizumab	-	-	-	-	1	-	1	33	-	-	-	7	-
Rituximab	5	X, 25	X, 122	X, 122	≥10 %, 226	-	11	222	-	279	15	99	9758
Tocilizumab	-	-	-	-	≥10 %, 35	X	3	84	-	1	-	<1 %	3437
Tositumomab	-	-	-	-	≥10 %, 8	-	-	2	-	-	-	X	182
Trastuzumab	31	3	12	12	≥10 %, 99	-	4	119	-	-	10	X	9576
Ustekinumab	-	-	-	-	3	-	-	31	-	-	5	<0.1 %	3130

(continued)

Table 3.2 (continued)

Syndrome	Systemic						Local			Comparators			
	Type	CLS	CRS <sup>o</sup>	TLS	IRS	MAS	SIRS <sup>^</sup>	IRIS	PML	RPLS	Anaphylaxis	PM reports <sup>a</sup>	
<i>Subtype</i>						NI	I						
-	-	-	-	-	-	-	-	-	-	-	-	-	
<i>Fusion proteins</i>													
Abatacept	-	-	-	1	< 10 %, 43	-	2	55	-	X, 6	X	< 0.1 %, 57	5327
Aflibercept	-	-	-	-	-	-	-	-	-	-	X	-	104
Alefacept	3	-	-	-	-	-	-	22	-	1	-	X?	3561
Belatacept	-	-	-	-	-	-	-	-	-	X	-	-	39
Etanercept	5	2	2	7	35	X, 8	-	-	-	X, 40	-	169	166330
Rilonacept	-	-	-	-	-	X	10	679	-	-	-	-	15
Romiplostim (TPO)	2	-	-	-	4	-	8	224	-	-	-	12	10346
<i>Cytokines</i>													
Aldesleukin (IL-2)	30	1	1	X	10	-	-	-	1	-	5	10	1562
Denileukin-DT (IL-2)	≥10 %	48	3	9	7	-	1	8	-	-	-	2	404
Anakinra (IL-2R)	-	-	-	-	X, 2	X	2	33	-	-	-	18	1968
IFN- $\alpha$	15	-	-	X	1	-	-	24	2	5	-	15	8129
IFN- $\beta$	6	-	-	-	3	-	2	91	-	5	6	35	14298

(continued)

Table 3.2 (continued)

Syndrome	Systemic							Local			Comparators	
	CLS	CRS <sup>o</sup>	TLS	IRS	MAS	SIRS <sup>^</sup>	IRIS	PML	RPLS	Anaphylaxis	PM reports <sup>a</sup>	
<i>Subtype</i>						NI	I					
IFN- $\gamma$	-	-	-	-	-	-	7	-	1	-	-	779
<i>Growth factors</i>												
Darbepoetin( epoetin- $\alpha$ )	6	1	-	27	-	11	340	-	3	19	61	12714
Filgrastim (rG-CSF)	X, 45	37	51	17	1	-	-	8	21	19	57	12759
Sargramostim (rGM-CSF)	-	1	-	4	-	-	-	-	1	-	15	927
Oprelvekin (IL-11)	15	-	-	1	-	-	10	-	-	-	3	781

<sup>o</sup>: as severe reactions, excluding mild FLS. <sup>^NI</sup>: noninfectious; I: infectious; <sup>^</sup>: in ulcerative colitis. <sup>a</sup>: number of postmarketing consulted reports

%: refer to data in trials, and absolute numbers refer to postmarketing reported cases. X: not quantified, reported in controlled studies

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