Fièvre

Contenu

- Hyperthermie
- Fièvre : abord initial
- Fièvre aiguë
- Pneumonie
- Fièvres très graves

Problème de fièvre : abord initial

- Faire la différence fièvre – hyperthermie
- Voir mode d'installation : aiguë ou persistante
- Voir l'évolution: analyse de la courbe thermique (de valeur assez limitée)
- Apprécier les conséquences cliniques de la fièvre et notamment la tolérance du patient
- Identifier un éventuel contexte particulier

Hyperthermie

Fièvre versus hyperthermie

FIEVRE

- Induite par le déplacement vers des niveaux supérieurs des températures de référence vers le chaud et le froid
- Causée par des cytokines circulantes
- **Cliniquement indifférenciable de l'hyperthermie**

HYPERTHERMIE

Survient lorsque la thermorégulation est défaillante:

- défaut de thermolyse
- excès de production de chaleur
- anomalie du thermostat

Principales causes d'hyperthermie sévère

TABLEAU 1

Principales causes d'hyperthermie

Par production excessive de chaleur

- hyperthermie d'effort
- coup de chaleur d'effort
- hyperthermie maligne (suite à une anesthésie, des neuroleptiques)
- *delirium tremens*, état de mal épileptique, tétanos généralisé
- hyperthermie hormonale (crise thyréotoxique, phéochromocytome…)
- déshydratation
- intoxication aux salicylés
- traitement anticholinergique
- stupéfiants : cocaïne, amphétamine

Par évacuation insuffisante de chaleur

- coup de chaleur
- vêtements trop chauds, trop couvrants
- dysfonction dysautonomique
- syndrome malin des neuroleptiques

Par dysfonction hypothalamique

- syndrome malin des neuroleptiques
- accident vasculaire cérébral
- encéphalite
- sarcoïdose et granulomatose
- traumatisme

ΔΔ : remarque fondamentale

Toute maladie systémique avec un tableau clinique similaire de fièvre et manifestations de dysfonctionnement cérébral ne doit être envisagée qu'après qu'un coup de chaleur ait été exclu, car un retard dans le traitement du coup de chaleur augmente considérablement la morbidité et la mortalité.

Coup de chaleur

- classique : en dehors de tout exercice, lors d'un séjour prolongé dans un espace confiné exposé à la chaleur
  - facteurs favorisants : déshydratation, transpiration insuffisante, consommation d'alcool, prise de médicaments (diurétiques, antihistaminiques, psychotropes, β-bloquants), comorbidités (maladie cardiovasculaire, troubles neurologiques ou psychiatriques, obésité, sujet âgé …)
- à l'effort intense

Tableau clinique du coup de chaleur

- Sensation intense de soif
- Température atteignant 39 °C ou 40 °C voire plus
- Peau chaude et sèche
- Asthénie, pseudo-vertiges, étourdissements
- Hallucinations, somnolence voire baisse du niveau de conscience ou convulsions

Hyperthermie d'effort

Prodromes:

- Myalgies, crampes, asthénie, soif intense, troubles du comportement, état pseudo-ébrieux, nausées, vomissements et hyperthermie
- Dans une atmosphère chaude et humide.

LA REVUE DU PRATICIEN - MÉDECINE GÉNÉRALE. TOME 20. N° 738/739 DU 27 JUIN 2006

Phase d'état

- signes neurologiques : obnubilation, syndrome cérébelleux, syndrome méningé, coma pouvant tre accompagné de convulsions
- signes musculo-cutanés : contractures diffuses, muscles œdématiés, anhidrose avec peau brûlante, pli cutané (traduisant la déshydratation)
- signes cardiovasculaires : état de choc hypovolémique avec tachycardie, hypotension artérielle et polypnée.
- hyperthermie > 40 °C.

- Biologie : hémoconcentration, insuffisance rénale, acidose métabolique, rhabdomyolyse, anomalies ioniques, CIVD, perturbation des tests hépatiques.
- Évolution : se fait vers un **syndrome de défaillance multiviscérale**.

Table 1. Epidemiologic and Clinical Features of Classic and Exertional Heatstroke.

Feature*	Classic Heatstroke	Exertional Heatstroke
Age group	Prepubertal, elderly	Postpubertal and active
Occurrence	Epidemic (heat waves)	Sporadic (any time of year)
Concurrent activity	Sedentary	Strenuous
Health status	Chronically ill	Generally healthy
Medications	Often being used (prescribed medications)	Usually none being used (sometimes ergogenic aids, illicit drugs)
Mechanism	Absorption of environmental heat and poor heat dissipation	Excessive heat production, which overwhelms heat-loss mechanisms
Sweating	May be absent (dry skin)	Usually present (wet skin)
CNS dysfunction	Common	Common
Acid–base disturbance	Respiratory alkalosis	Metabolic acidosis
Rhabdomyolysis	Unusual	Frequent
Liver dysfunction	Mild	Marked to severe
Renal failure	Uncommon (<5%)	Common (25–30%)
DIC	Mild	Marked to severe
ARDS	Common	Common
Creatine kinase	Mildly elevated	Markedly elevated
Calcium	Normal	Low (hypocalcemia)
Potassium	Normal	Usually high (hyperkalemia)

* ARDS denotes acute respiratory distress syndrome, CNS central nervous system, and DIC disseminated intravascular coagulation.

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Table 2. Risk Factors Underlying Heatstroke.*

Heatstroke Type and Risk Factor	Explanation
Classic	
Weather	Heat waves, with successive hot days and nights
Physiological factors	Cardiovascular insufficiency impeding normal cardiovascular adjustments to heat stress: inability to maintain acceptable stroke volume in the heat, inadequate peripheral vasodilatation due to structural changes and compromised nitric oxide–mediated vasodilatory mechanism, reduced capillary density and quality of cutaneous microcirculation, decreased sweat rate and sweat-gland output in response to heat stress
Social factors	Social isolation, unventilated and non–air-conditioned living space, inability to care for oneself, confinement to bed
Underlying illness	Exacerbation of mental, cardiovascular, cerebrovascular, and pulmonary illnesses and multiple sclerosis by exposure to heat stress
Medications	Beta-blockers, diuretics, calcium-channel blockers, laxatives, anticholinergic drugs, salicylates, thyroid agonists, benztropine, trifluoperazine, butyrophenones, α-agonists, monoamine oxidase inhibitors, sympathomimetic medications, tricyclic antidepressants, SSRIs
Exertional	
Social factors	Overmotivation, peer and coach pressure
Functional factors	Low physical fitness (physical effort unsuited to physical fitness; "killer workouts"), lack of acclimatization (habituation) to heat, low work efficiency, overweight (reduced ratio of skin area to mass and greater heat-storage capacity in fat layers), protective clothing (reduced sweating efficiency)
Acquired factors	Viral or bacterial infection (even if subclinical), dehydration, sleep deprivation, sweat-gland dysfunction (e.g., deep burns, scarred skin on >40% of total body-surface area)
Congenital factors	Chronic idiopathic or familial anhydrosis, ectodermal dysplasia
Drug abuse	Amphetamines and amphetamine-like agents (e.g., ephedra), MDMA, cocaine, PCP and LSD, synthetic stimulants of the cathinone class (e.g., α-PHP), alcohol

* LSD denotes lysergic acid diethylamide, MDMA 3,4-methylenedioxymethamphetamine (ecstasy), PCP phencyclidine, α-PHP α-pyrrolidinohexanophenone, and SSRI selective serotonin-reuptake inhibitor.

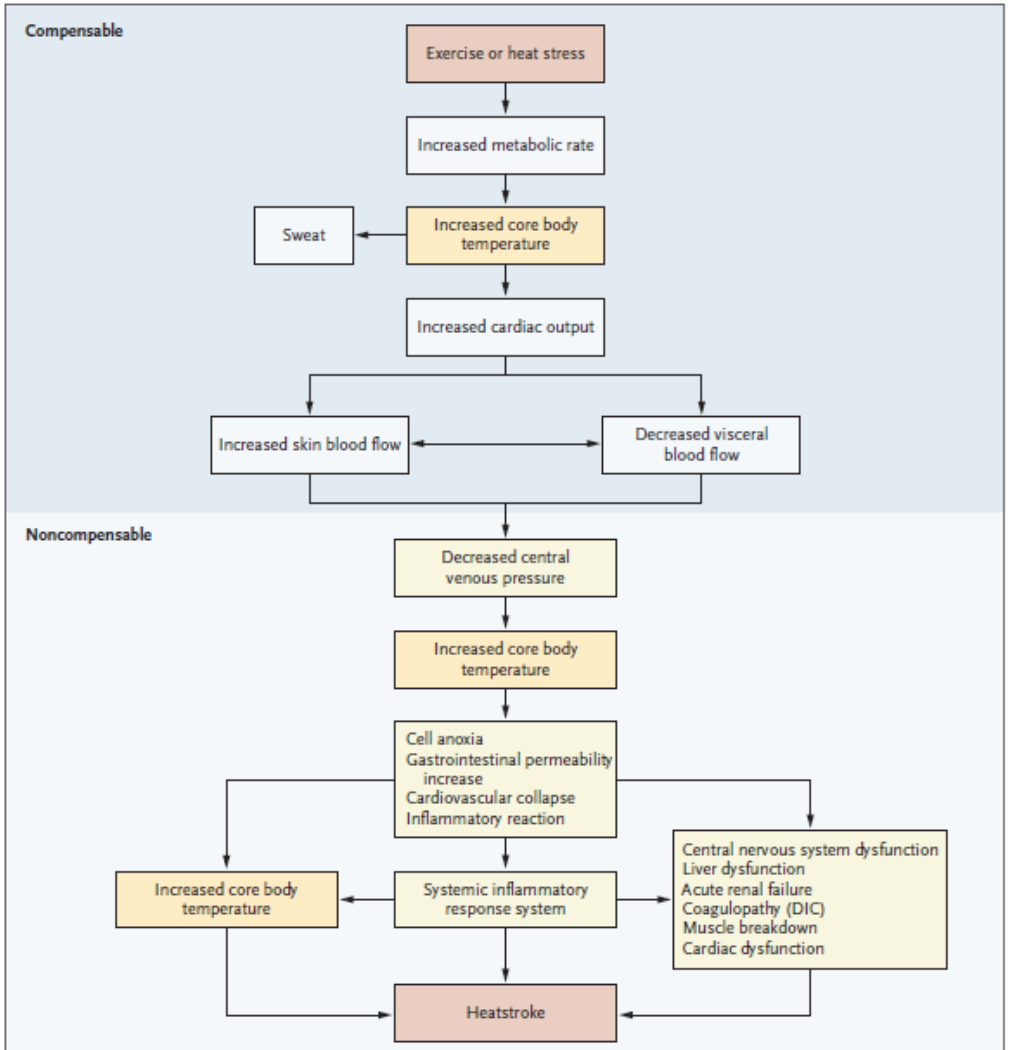

Figure 1. Pathophysiological Pathway Leading to Heat Stroke.

The sequence of events that leads to heat stroke involves a transition from a compensable thermoregulatory state to the noncompensable condition. Heat stress initiates a thermoregulatory response to increased cardiac output and redistribution of blood flow. When central venous pressure begins to decrease substantially, core temperature begins to increase rapidly and becomes noncompensable. The thermoregulatory failure aggravates pathophysiological processes at the cellular level, including an inflammatory reaction, and multiorgan failure occurs as a result of the combination of high body temperature and circulatory collapse, and ultimately is expressed as heatstroke. DIC denotes disseminated intravascular coagulation.

Table 3. Guidelines for the Treatment of Heatstroke.*

Treatment	Comments
Treatment on site	
CPR	Perform according to ACLS protocol; administer oxygen at 4 liters/min to increase oxygen saturation to >90%
Core body temperature	Monitor rectal temperature and perform cooling in cases of hyperthermia; for exertional heatstroke, cold-water immersion; for classic heatstroke, conductive or evaporative cooling
Fluids	Administer isotonic saline IV (1–2 liters/hr); dehydration is not a major issue
Seizure medication	Administer benzodiazepines IV (5 mg) until seizures cease (not more than 20 mg)
Evacuation	For classic heatstroke, transport immediately to ED; for exertional heatstroke, transport to ED after cooling to body temperature <39.0°C
Treatment in the ED	
Core body temperature	Monitor rectal or intravesical temperature and perform cooling until core temperature <38.0°C; use either a cooling suit or cold fluids (4°C, 1000 ml/30 min) infused through central catheter; antipyretics are toxic and should be avoided; dantrolene has not been proved to be effective
Seizure medication	Administer benzodiazepines IV (5 mg, repeated) or phenytoin IV (loading dose, 15–20 mg/kg in 15 min) until seizures cease
Laboratory testing	Perform CBC, urinalysis, blood cultures, kidney-function and liver-function tests (ALT, AST, ammonia, INR); test for glucose, electrolytes, arterial blood gases and acid–base balance, clotting function, CK, LDH, myoglobin, CRP

Table 3. (Continued.)

Treatment	Comments
Monitoring of circulation	For circulatory failure, administer fluids (30 ml/kg), monitor CVP or perform invasive hemodynamic monitoring, maintain mean arterial pressure at >65 mm Hg (or >75 mm Hg if patient is elderly or has hypertension), all with a goal of normal lactate level and urine output >50 ml/kg/hr; vasopressors should be considered if fluid therapy fails
Treatment in the ICU	
General	Perform CPR according to ACLS protocol; ECMO may be used as needed
	Monitor rectal, intravesical, or blood temperature; continue cooling to maintain core temperature at <38.0°C by infusing cold fluids (4°C, 1000 ml/30 min) through central catheter or use extracorporeal blood cooling for resistant hyperthermia; antipyretics are toxic and should be avoided; dantrolene has not been proved to be effective
	Perform laboratory tests: CBC, glucose, arterial blood gases and acid–base balance, clotting function, CK, LDH, liver function (ALT, AST, ammonia, INR), myoglobin, kidney function, urinalysis, CRP, blood cultures; repeat every 12 hr during the first 48 hr, then every 24 hr
Heart failure	Perform CPR according to ACLS protocol; perform invasive hemodynamic monitoring and echocardiography; for mild multiorgan failure, administer dobutamine IV (1 μg/kg/min, then 2–20 μg/kg/min as needed) or milrinone IV (loading dose, 50 μg/kg in 10 min, then 0.2–0.75 μg/kg/min) or adrenaline IV (1 μg/min); for severe multiorgan failure, ECMO may be used as needed
Acute kidney injury	Administer crystalloid solution to maintain urine output >50 ml/kg/hr; administer furosemide IV (10–20 mg in patients without previous exposure to diuretics; follow-up dose depends on urine output); provide hemodialysis or CVVH in cases of volume overload, severe acidosis, hyperkalemia, or uremia; adjust fluid infusion rate according to blood pressure and urine output; monitor electrolytes and correct as needed
Encephalopathy and brain edema	For a score of <8 on the GCS,† intubate and ventilate; for mild hyperventilation (P_{CO_2}, 34–36 mm Hg) administer hypertonic saline 3% IV (starting dose, 100 ml/30 min, then according to patient's total body water to reach sodium level increase of 12 mmol/day) or mannitol 20% IV (0.25–2 g/kg in 30 min); keep head at 45-degree angle, administer tranquilizers; patients with hyperammonemia require hemofiltration or MARS therapy; condition improves with cooling; consider monitoring ICP
Rhabdomyolysis	Administer IV fluid infusion, 1–2 liters/hr (aggressive fluid treatment in the first hour), then 300 ml/hr; furosemide IV (10–20 mg in patients without previous diuretic treatment; follow-up dose depends on urine output) in case of fluid overload; sodium bicarbonate, 30 mmol/hr (to achieve urine pH >6.5); myoglobinuria is expected; hypercalcemia and metabolic alkalosis (pH >7.5) should be avoided
DIC and other coagulation abnormalities	For bleeding and thrombosis, administer fresh-frozen plasma (bolus dose, 10–15 ml/kg, then 200–400 ml according to coagulation indexes); administer cryoprecipitate (5–10 U each time) for fibrinogen level of <180 mg/dl; administer platelet concentrates (infusion of one therapeutic dose) if platelet count <20 per mm^3 or if there is bleeding and platelet count <50 per mm^3; in patients with hepatic failure, consider PCC to achieve a target INR ≤1.5; inject PCC dose according to INR and patient's weight; avoid heparin; beware of hypothermia and metabolic acidosis
ARDS	Perform intubation and mechanical ventilation; avoid fluid overload
Liver failure	Monitor liver function and mental status for at least 4 days; provide supportive treatment: hemodynamic stability, *N*-acetylcysteine IV (bolus dose, 150 mg/kg in 200 ml of 5% glucose solution for 20 min, then 50 mg/kg in 500 ml of 5% glucose solution for 4 hr, then 100 mg/kg in 1000 ml of 5% glucose solution for 16 hr); administer hypertonic saline 3% IV or mannitol IV (0.25–2 g/kg in 30 min in 20% solution), hemofiltration, laxatives (e.g., oral lactulose, 30 ml every 2 hr until diarrhea occurs), oral rifaximin (400 mg 3 times a day) in case of fulminant liver failure; liver transplantation rarely needed, and there is no evidence that it is effective
ECG changes	Monitor continuously for possible arrhythmias; ECG changes are nonspecific
SIRS	Treat the same as sepsis; consider antibiotics

Hyperthermie maligne

- au cours d'une anesthésie générale (succinylcholine, halothane)
- parfois jusqu'à 10h après l'induction
- lié à une anomalie héréditaire au niveau des muscles striés
- Traitement : dandrolène

Tableau I. Signes cliniques de la crise d'hyperthermie maligne.

Signes précoces	*Signes tardifs*
Spasme des masséters	Contracture généralisée
Tachycardie inexpliquée	Hyperthermie (> 40 °C)
Tachypnée	Acidose mixte
Augmentation $PETCO_2$	Élévation majeure $PETCO_2$
Rigidité localisée	Troubles du rythme

Ann Fr Anesth Réanim 2001 ; 20 : 838-52

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Tableau II. Signes biologiques de la crise d'hyperthermie maligne.

Signes précoces	*Signes tardifs*
Hypercapnie	Myoglobinémie, myoglobinurie
Acidose respiratoire	Hyperlactatémie, acidose mixte
Hyperkaliémie	↗ CPK
↘ $\overline{S}vO2$	CIVD

$\overline{S}vO_2$: saturation veineuse en oxygène ; CIVD : coagulation intravasculaire disséminée.

Syndrome malin des neuroleptiques

- réaction idiosyncrasique à des agents psychotropes
- principaux agents en cause : halopéridol, tiapride, rispéridone, métoclopramide
- tableau neurologique important : rigidité musculaire (tuyau de plomb), tremblements, dystonies, dyskinésies, troubles mentaux, instabilité végétative (tachycardie, tachypnée, arythmies cardiaques, HTA, hypotension, sudations…)

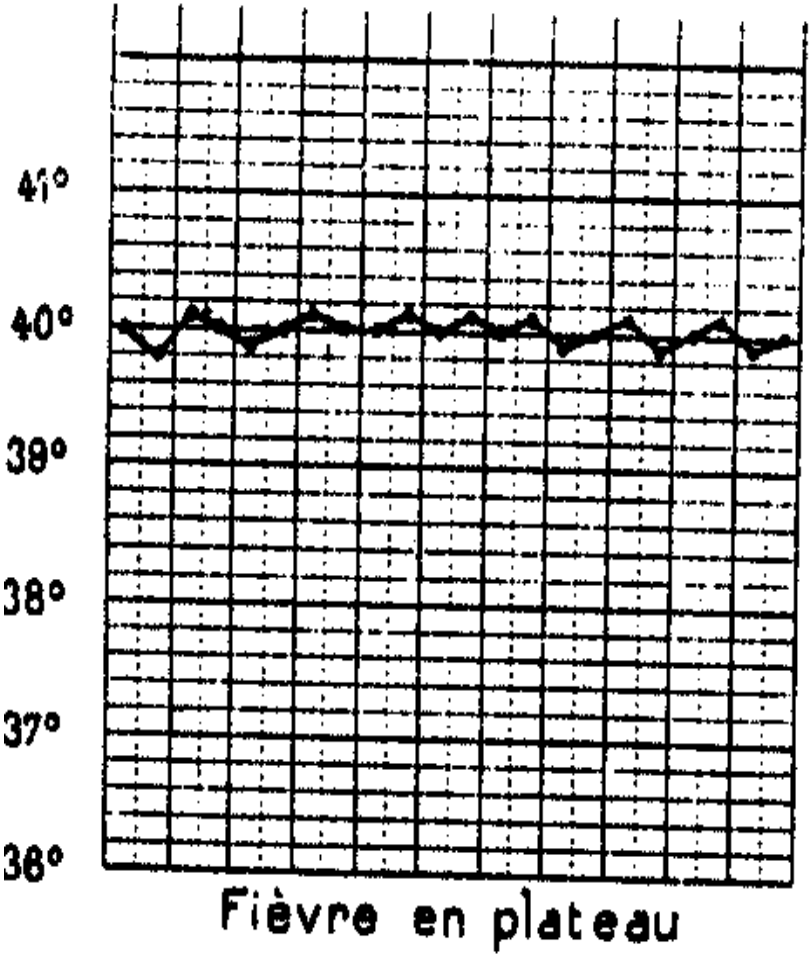
Fièvre

Mode d'installation

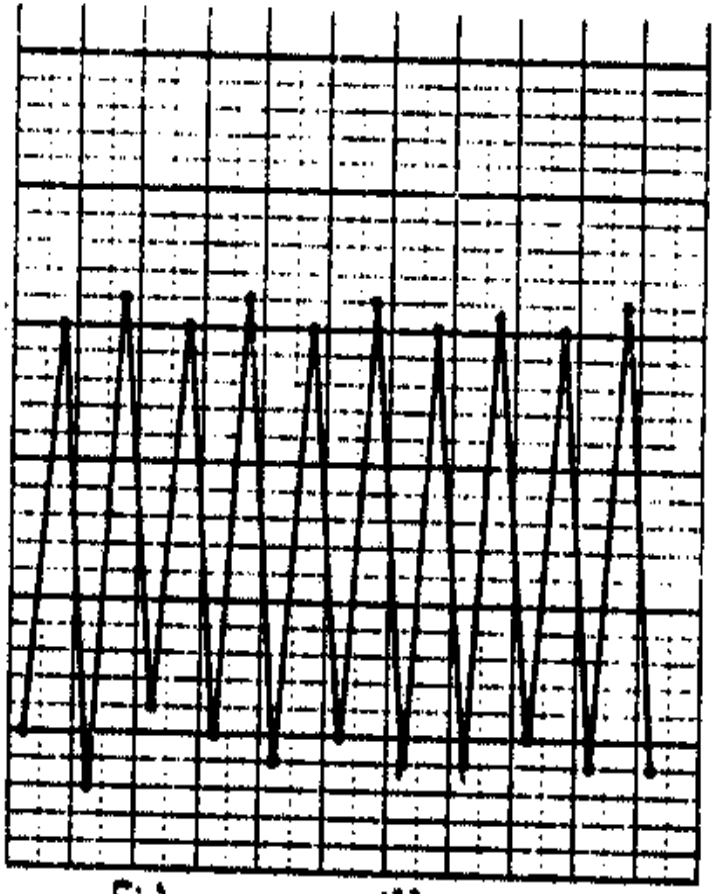
- fièvre aiguë : < 5 jours
- fièvre persistante : > 20 jours

Evolution de la fièvre : analyse de la courbe thermique

- En plateau ou continu
- Ondulante
  - fièvre de Pal Ebstein
- Intermittente (pseudopalustre)
- Rémittente
- Oscillante
- Hectique
- Fébricules (« états subfébriles »)

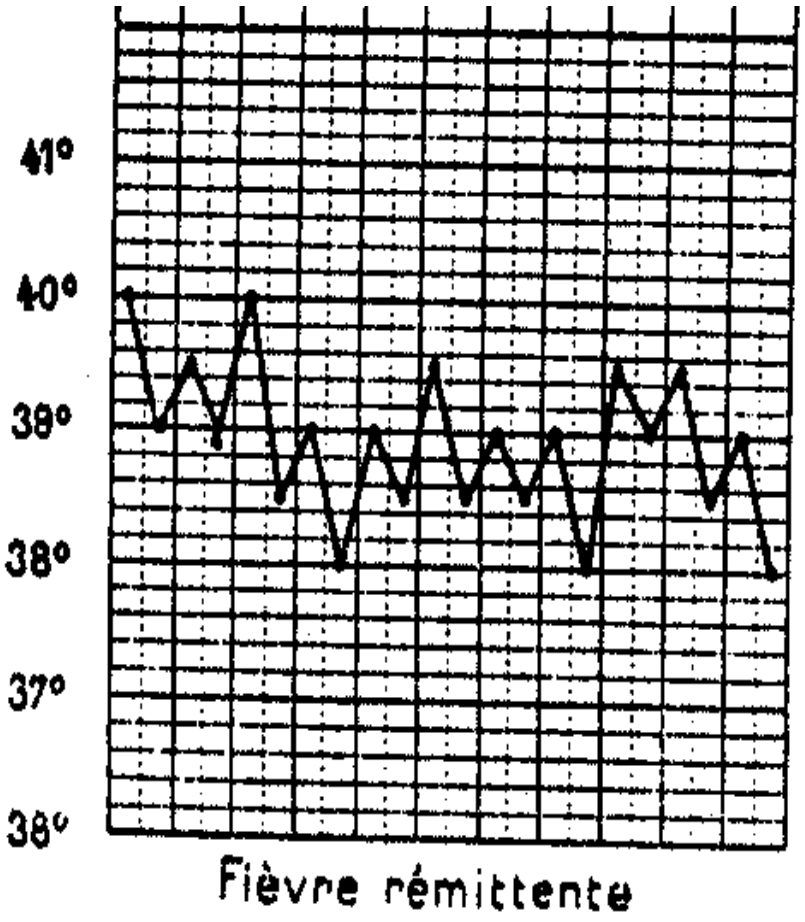


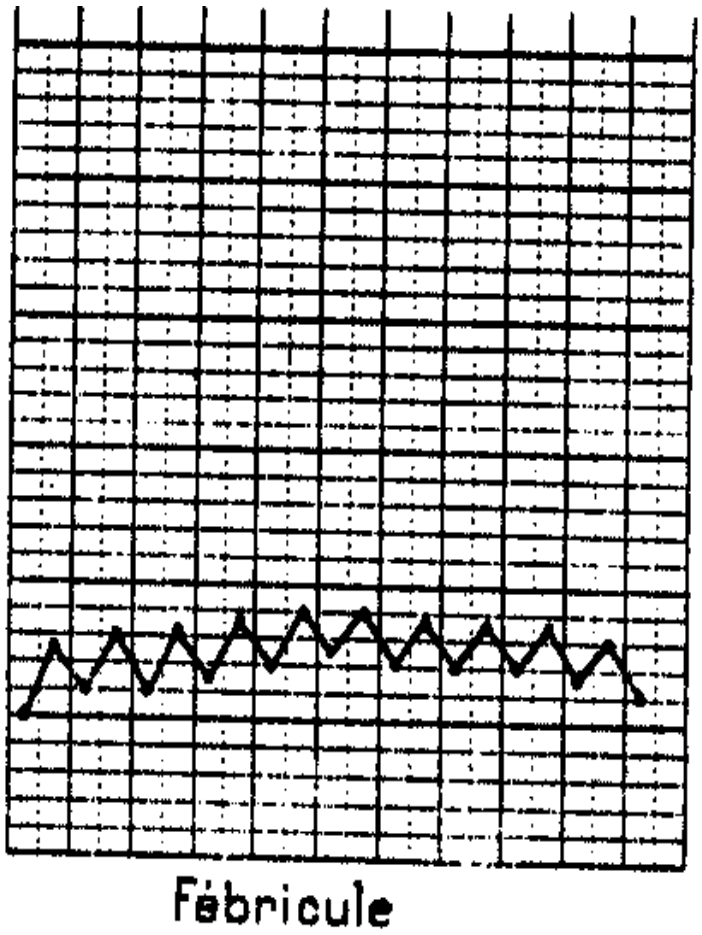
Fièvre en plateau


Fièvre oscillante

Fièvre typhoïde

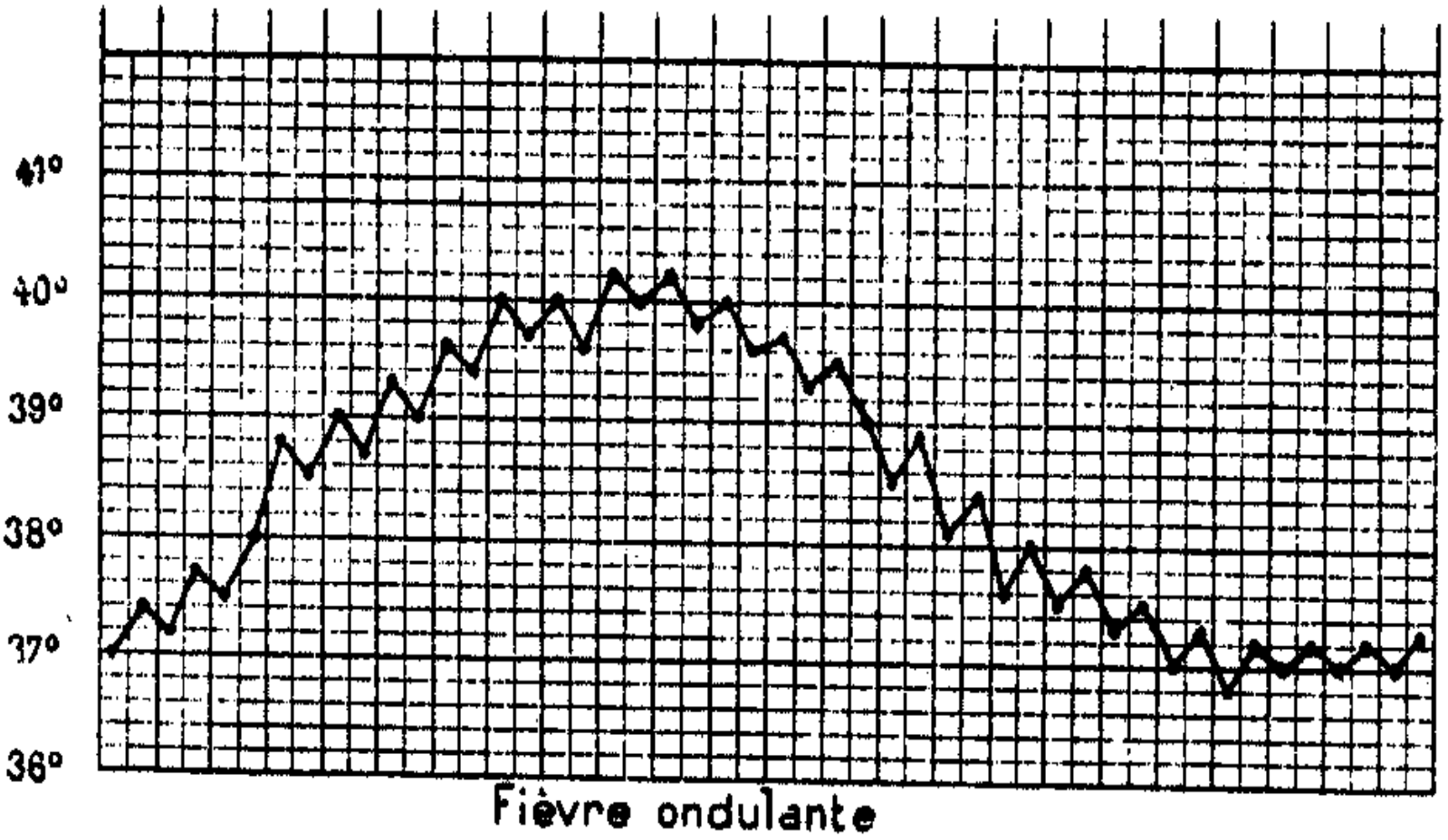
Septicémies



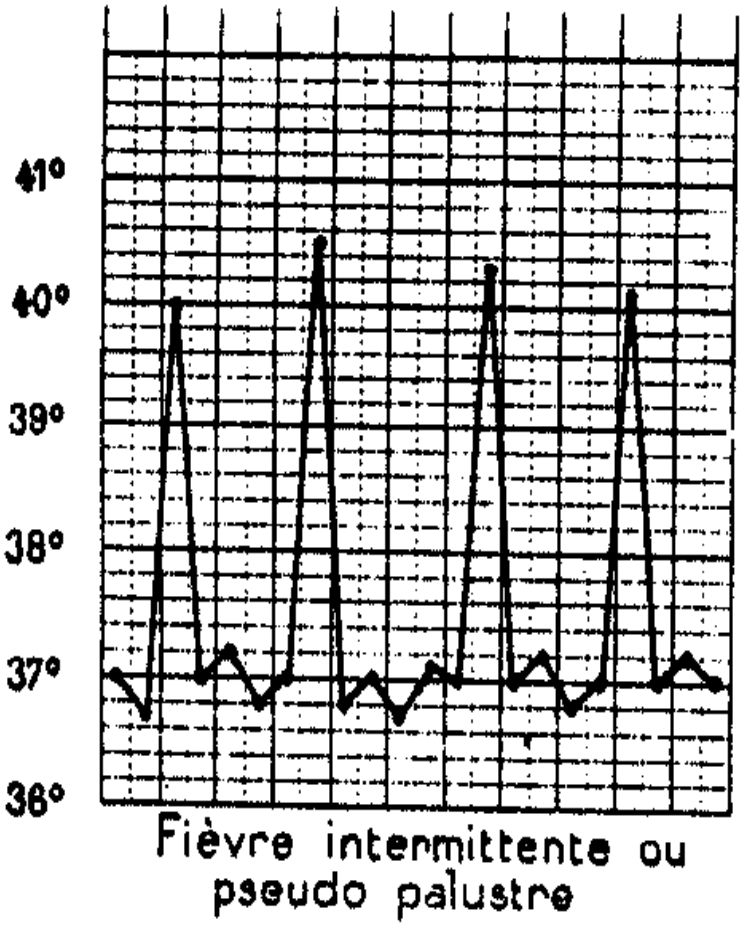


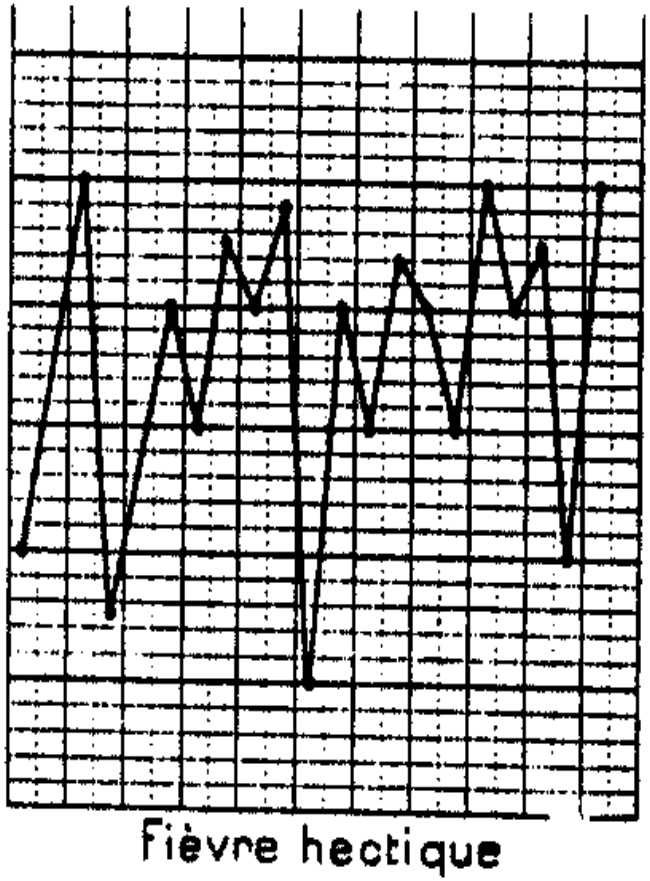
Infections localisées

Tuberculose, TVP



Brucellose, lymphome de Hodgkin
(fièvre de Pal Ebstein)

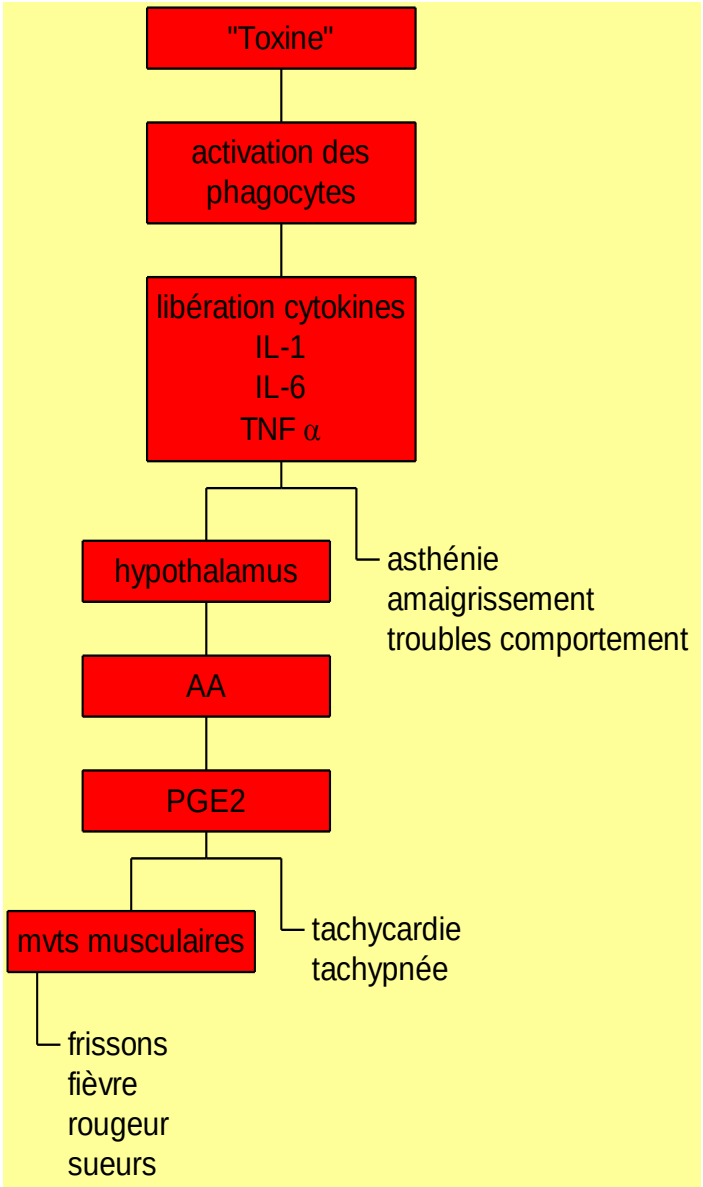




Malaria

Abcès profonds

Conséquences cliniques



Fièvre aiguë

Température normale

Sujette à des variations individuelles physiologiques: **35,8-37,1 °C**

et

- variation nycthémérale
- variation au cours du cycle menstruel
- variations liées à l'émotion, à l'exercice, à la digestion, à la T° ambiante

Évaluer les signes de mauvaise tolérance

- déshydratation
- hypotension, choc
- pouls trop rapide ou trop lent
- hyperventilation
- cyanose, marbrures, purpura
- troubles de la conscience
- chute de la diurèse
- niveau de fièvre: « maligne » si > 42°C
- se méfier de l'immunodéprimé

Fièvre aiguë à pouls

Normalement + 1°C = + 8 à 12 batt/min

Trop rapide:

- sepsis sévère
- choc toxi-infectieux
- maladie thrombo-embolique

Trop lent:

- fièvre factice
- HTIC
- fièvre typhoïde
- pneumopathies atypiques
- hépatite virale
- oreillons

Orientation diagnostique

Isolée : rare

- médicaments
- malaria
- hépatite
- abcès hépatique
- endocardite
- ...

Associée à une symptomatologie focale:

- pyélonéphrite, prostatite
- angine
- otite
- méningite
- pneumonie lobaire
- ...

TABLEAU 6

Principales causes de fièvre aiguë de cause infectieuse

Infections bactériennes	Infections virales	Infections parasitaires	Infections fongiques
Septicémie avec ou sans foyer **Foyer localisé** avec ou sans bactériémie : ▮ ORL ▮ respiratoire : pneumopathies (pneumocoque, germes intracellulaires, anaérobies) ▮ neuroméningé : méningocoque, pneumocoque, *Hæmophilus influenzæ*, *Listeria monocytogenes*) ▮ génito-urinaire : salpingite, endométrite, pyélonéphrite, prostatite ▮ digestif : diarrhée (salmonelle, shigelle, *E.coli*, *Campylobacter*) ▮ hépato-biliaire : cholécystite, angiocholite (BGN, anaérobie) ▮ peau et tissus mous : dermohypodermite, fasciite nécrosante ▮ ostéoarticulaire : arthrite, ostéite ▮ cardiovasculaire : endocardite ▮ sur prothèse	**Virus respiratoires :** *Myxovirus influenzæ* ou *parainfluenzæ*, VRS, coronavirus (SARS)… **Virus intestinaux :** norovirus, calicivirus, West-Nile… **Hépatites virales** **Arbovirus :** dengue, fièvre jaune, Chikungunya, West-Nile… **Autres :** adénovirus, HSV, VZV, rougeole, oreillons…	**Paludisme :** à évoquer devant toute fièvre au retour d'un pays en zone d'endémie **Autres parasitoses** plus rares : migrations larvaires de certaines helminthoses (bilharizoses) **Amoebose hépatique**	**Candidose systémique** **Cryptococcose** (contexte d'immunodépression)

TABLEAU 2

Principales causes de fièvre non infectieuse

Maladies thrombo-emboliques

▮ thrombose veineuse profonde ▮ embolie pulmonaire

Maladies inflammatoires systémiques

▮ maladie de Still ▮ lupus ▮ maladie de Horton
▮ maladie périodique ▮ goutte…

Affections malignes

▮ hémopathies malignes (leucémie, lymphome…) ▮ tumeurs solides (surinfection, nécrose, fièvre dite « spécifique »)

Causes endocriniennes

▮ thyréotoxicose

Médicaments

→ **cardiovasculaires :** ▮ antihypertenseurs ▮ β-bloquants ▮ quinidine ▮ α-méthyldopa ▮ antivitamine-K

→ **anti-infectieux :** ▮ pénicillines ▮ céphalosporines ▮ sulfamides, nitrofurane ▮ cycline ▮ vancomycine ▮ amphotéricine B ▮ isoniazide

→ **neurotropes :** ▮ neuroleptiques ▮ barbituriques ▮ phénytoïne ▮ carbamazépine

→ **divers :** ▮ estroprogestatifs ▮ anti-inflammatoires non stéroïdiens ▮ cimétidine ▮ allopurinol ▮ antihistaminiques ▮ antimitotiques ▮ hydroxyurée ▮ interféron

Tenir compte de la situation épidémiologique

- https://www.sciensano.be/fr

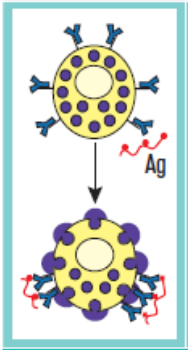
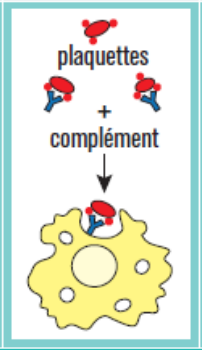
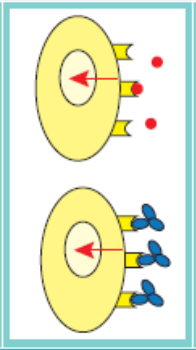
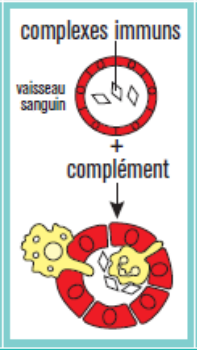
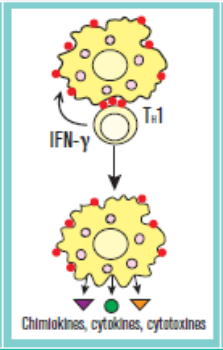
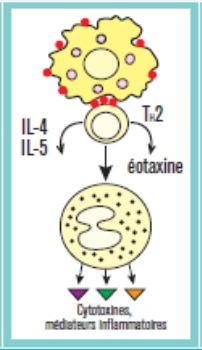
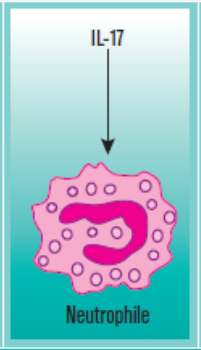
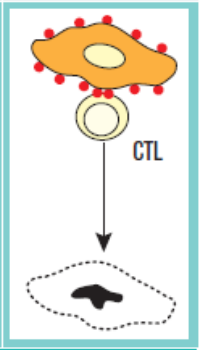
Table 4. Drug-Related Causes of Classic FUO.*

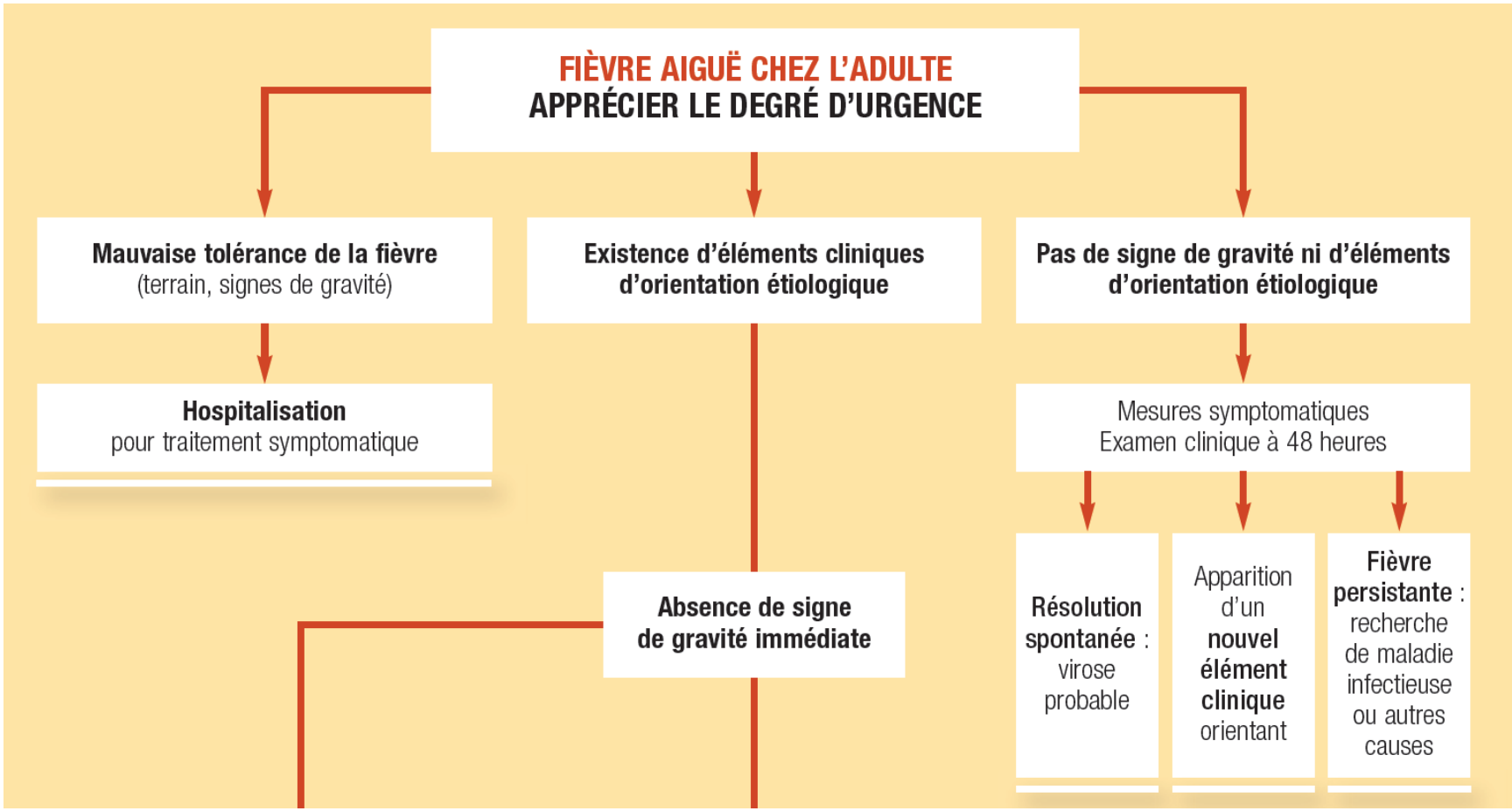
Type of Drug Reaction	Usual Time to Onset of Fever	Commonly Implicated Drugs or Other Agents
Hypersensitivity reaction	7–10 days	Antimicrobial agents (beta-lactams, sulfonamides, minocycline), allopurinol, anticonvulsants (phenytoin, carbamazepine), methyldopa, heparin, quinidine, quinine
Chemotherapy-related reaction	3–19 hr	Chemotherapeutic agents (cytosine arabinoside, bleomycin, chlorambucil, vincristine, cisplatin), molecular targeting agents for melanoma (dabrafenib, trametinib)
Infusion-related reaction	0.5–3.0 hr	Amphotericin B formulations, vancomycin, bleomycin, vaccines, monoclonal antibodies
DRESS	2–6 wk	Sulfonamides, carbamazepine, allopurinol, lamotrigine, phenytoin
Hyperthermia syndromes		
Serotonin syndrome	6 hr–several days†	Selective serotonin-reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline Serotonin–norepinephrine reuptake inhibitors: duloxetine, trazodone, desvenlafaxine, levomilnacipran, milnacipran, venlafaxine Tricyclic antidepressants: amitriptyline, nortriptyline MAO inhibitors: nonselective irreversible inhibitors (phenelzine, tranylcypromine), nonselective reversible inhibitors (linezolid), selective irreversible MAO type A inhibitor (methylene blue), selective irreversible MAO type B inhibitor (selegiline) Antiemetic agents: ondansetron, metoclopramide Serotonin receptor agonists: psychedelics (LSD), fentanyl, buspirone, triptans, lithium Herbal products: St. John's wort, Syrian rue (harmine and harmaline) Cytochrome P-450 inhibitors‡: fluoxetine, ciprofloxacin, ritonavir, fluconazole, sertraline
Malignant hyperthermia	0.5–2.0 hr	Depolarizing muscle relaxants: succinylcholine Inhalation anesthetics: halothane, sevoflurane, isoflurane, desflurane
Neuroleptic malignant syndrome	1–2 wk	Antipsychotic agents: haloperidol, quetiapine, olanzapine, risperidone Antiemetic agents: metoclopramide, prochlorperazine Parkinsonism–hyperpyrexia syndrome: abrupt withdrawal of dopamine agonists or nondopaminergic agents (amantadine)
Adrenergic fever	Variable	Sympathomimetic agents and MAO inhibitors: theophylline, cocaine, MDMA (ecstasy)
Anticholinergic fever	About 2 hr	Anticonvulsants: carbamazepine Antiemetics: scopolamine, promethazine, prochlorperazine Muscle relaxants: cyclobenzaprine, methocarbamol, carisoprodol Herbal agents: belladonna, jimsonweed (datura), lupin Antidepressants: amitriptyline, imipramine, nortriptyline
Mitochondrial uncoupling of oxidative phosphorylation	0.5–3.0 hr	Pesticides and toxins: organochlorine compounds, snake venom–derived phospholipases Salicylates: high-dose aspirin

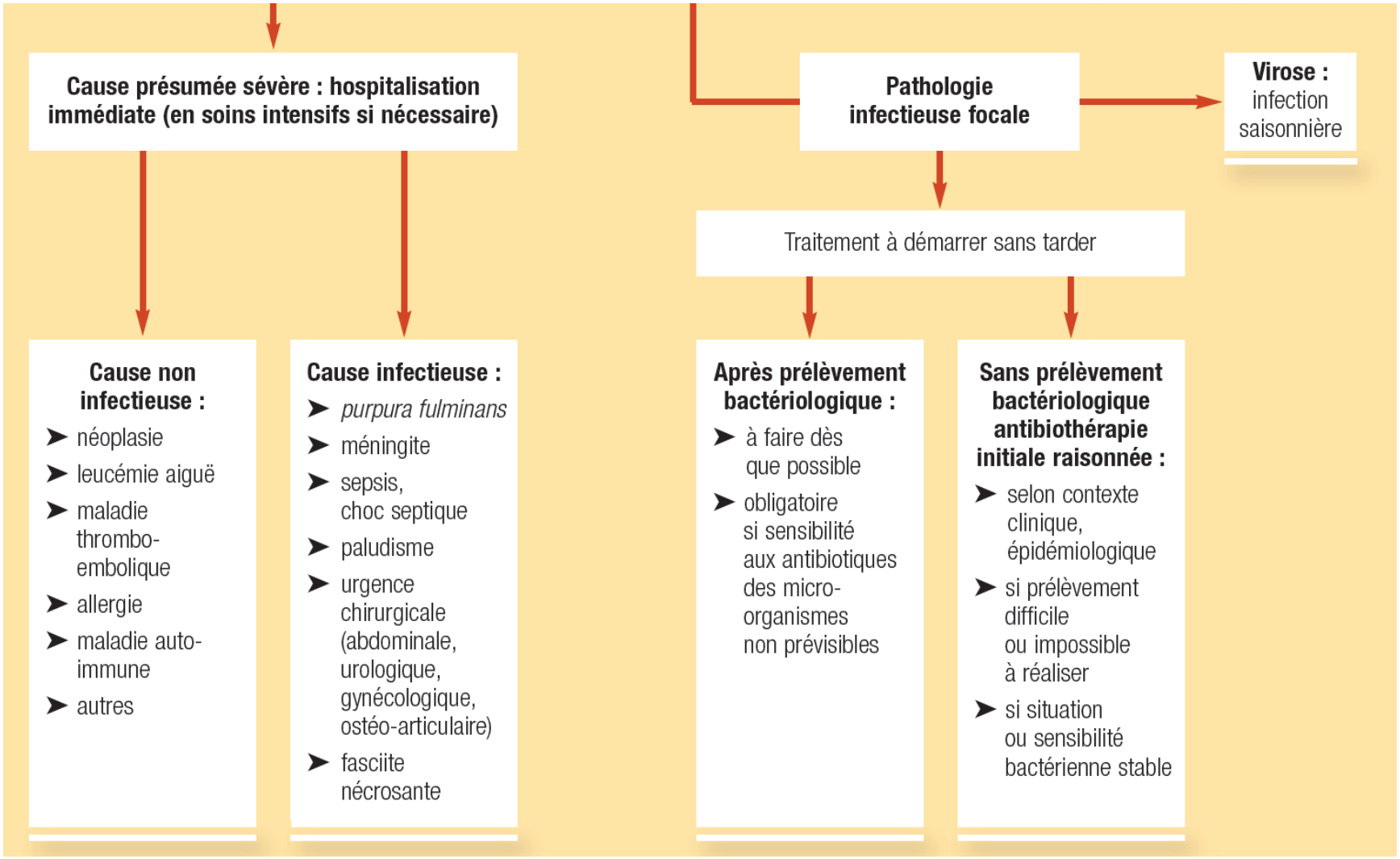
Maladie sérique

- maladie liée à un dysfonctionnement du système immunitaire, qui associe des *éruptions cutanées* et des *atteintes articulaires inflammatoires*, avec ou sans *fièvre*
- Apparaît généralement 1 à 2 semaines après une exposition au médicament
- Allergie de type III (avec dépôts de complexes immuns comme l'urticaire, les vascularites allergiques et le lupus induit)

CLASSIFICATION DES MALADIES ALLERGIQUES (ET AUTO-IMMUNES) SELON GELL & COOMBS

TYPE I	TYPE II		TYPE III	TYPE IV			
IgE	IgG		IgG	CD4 Th1	CD4 Th2	CD4 Th17	CD8 cytotoxique
Ag solubles	Ag cellulaires ou matriciels	Récepteurs cellulaires	Ag solubles	Ag solubles	Ag solubles		Ag cellulaires
Mastocyte	Complément, phagocytes, NK	Ac altèrant la signalisation	Complément, phagocytes	Macrophages	Éosinophiles	Neutrophiles	Cytotoxicité
							
EXEMPLES DE MALADIES							
Rhinite, asthme, anaphylaxie	Réaction transfusionnelle, anémie hémolytique	Thyroïdite, myasthénie	Lupus érythémateux, maladie sérique	Rejet de greffes, arthrite, diabète psoriasis (intradermoréaction à la tuberculine)	Asthme chronique, rhinite chronique, eczéma atopique	Psoriasis, polyarthrite, sclérose en plaques, maladie de Crohn	Rejet de greffes, diabète de type I, eczéma de contact, vitiligo, pelade
ALLERGIES AUX MÉDICAMENTS							
Choc anaphylactique	Cytopénie médicamenteuse		Vascularite immuno-allergique, pseudo-maladie sérique	Exanthème, DRESS	DRESS	Pustulose exanthématique	Nécrolyse épidermique, Syndrome de Lyell/syndrome de Stevens-Johnson


FIÈVRE AIGUË CHEZ L'ADULTE
APPRÉCIER LE DEGRÉ D'URGENCE
Mauvaise tolérance de la fièvre
(terrain, signes de gravité)
Existence d'éléments cliniques d'orientation étiologique
Pas de signe de gravité ni d'éléments d'orientation étiologique
Hospitalisation
pour traitement symptomatique
Mesures symptomatiques
Examen clinique à 48 heures
Absence de signe de gravité immédiate
Résolution spontanée : virose probable
Apparition d'un nouvel élément clinique orientant
Fièvre persistante : recherche de maladie infectieuse ou autres causes


Cause présumée sévère : hospitalisation immédiate (en soins intensifs si nécessaire)
Pathologie infectieuse focale
Virose : infection saisonnière
Traitement à démarrer sans tarder
Cause non infectieuse :
➤ néoplasie
➤ leucémie aiguë
➤ maladie thrombo-embolique
➤ allergie
➤ maladie auto-immune
➤ autres
Cause infectieuse :
➤ purpura fulminans
➤ méningite
➤ sepsis, choc septique
➤ paludisme
➤ urgence chirurgicale (abdominale, urologique, gynécologique, ostéo-articulaire)
➤ fasciite nécrosante
Après prélèvement bactériologique :
➤ à faire dès que possible
➤ obligatoire si sensibilité aux antibiotiques des micro-organismes non prévisibles
Sans prélèvement bactériologique antibiothérapie initiale raisonnée :
➤ selon contexte clinique, épidémiologique
➤ si prélèvement difficile ou impossible à réaliser
➤ si situation ou sensibilité bactérienne stable

Fièvres aiguës très graves

Amènent le patient aux soins intensifs.

Il faut penser à :

- Hyperthermie
- Sepsis et choc septique
- Syndrome de libération de cytokines
- Syndrome d'activation macrophagique
- DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Sepsis et choc septique

Ancienne définition du Sepsis

- **SIRS** (syndrome de réponse inflammatoire systémique) : si deux ou plus des conditions suivantes sont remplies
  - température < 36°C ou > 38°C
  - fréquence cardiaque > 90/min
  - fréquence respiratoire > 20/min ou PaCO2 < 32 mm Hg
  - leucocytose > 12.000/mm3, < 4.000/mm3 ou présence de formes immatures circulantes (> 10 % des cellules)
- **Sepsis** : si le SIRS est dû à une infection
- **Sepsis sévère** : si le sepsis est associé à une dysfonction organique, de l'hypoperfusion (acidose lactique, oligurie, troubles de conscience,...) ou de l'hypotension artérielle (TAs < 90 mm Hg ou chute de > 40 mm Hg de la valeur de base sans autre raison connue)
- **Choc septique** : sepsis avec hypotension, malgré un remplissage adéquat, avec des signes d'hypoperfusion
  - l'hypotension peut manquer si des agents vasopresseurs sont administrés

TABLEAU 5

Classification des états septiques

Syndrome de réponse inflammatoire systémique	Sepsis	Sepsis sévère	Choc septique
Deux signes ou plus parmi : ▪ température > 38 °C ou < 36 °C ▪ rythme cardiaque > 90/min ▪ rythme respiratoire > 20/min ou hyperventilation avec PCO_2 < 32 mmHg en air ambiant ▪ Leucocytes > 12 000/mm^3 ou < 4 000/mm^3 ou > 10 % de cellules immatures (sans autre cause)	**Syndrome de réponse inflammatoire systémique + infection confirmée**	**Sepsis + dysfonction d'organe** (hypoxémie, oligurie < 0,5 mL/kg/h, coagulopathie, acidose métabolique) **+ hypoperfusion** (acidose lactique, oligurie, encéphalopathie aiguë) **et/ou hypotension artérielle** (pression artérielle systolique < 90 mmHg ou < 40 mmHg des chiffres tensionnels habituels)	**Sepsis sévère + hypotension artérielle persistante malgré un remplissage vasculaire adapté**

Nouvelle définition du sepsis

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Définitions

= dysfonction d'organe secondaire à une réponse inappropriée de l'hôte envers une infection.

- sepsis : défini par un score SOFA supérieur ou égal à 2 ou une augmentation supérieure ou égale à 2 points si une dysfonction d'organe est présente avant l'infection.
  - Afin de dépister rapidement les patients ayant un sepsis : un score simplifié (quick SOFA). **Celui-ci n'a pas fait ses preuves par rapport au SIRS.**
- choc septique : défini par l'association d'un sepsis, de la nécessité de vasopresseurs pour maintenir une pression artérielle moyenne supérieure ou égale à 65 mm Hg et un taux de lactate supérieur à 2 mmol/L malgré un remplissage adéquat

Score SOFA

TABLEAU 1

Score SOFA (*Sequential Organ Failure Assessment*)

Organe/Système	Score				
	0	1	2	3	4
➥ Poumons					
PaO_2/FiO_2 mmHg (kPa)	● ⩾ 400 (53,3)	● < 400 (53,3)	● < 300 (40)	● < 200 (26,7) avec assistance respiratoire	● ⩽ 100 avec assistance respiratoire
➥ Coagulation					
Plaquettes, $\times 10^3$/uL	● ⩾ 150	● < 150	● < 100	● < 50	● < 20
➥ Foie					
Bilirubine, mg/dL (µmol/L)	● < 1,2 (20)	● 1,2-1,9 (20-32)	● 2,0-5,9 (33-101)	● 6,0-11,9 (102-204)	● > 12,0 (204)
➥ Cardiovasculaire					
	● PAM ⩾ 70 mmHg	● PAM < 70 mmHg	● Dopamine < 5 *ou* ● Dobutamine	● Dopamine 5,1-15 ● *ou* Adrénaline ⩽ 0,1 ● *ou* Noradrénaline ⩽ 0,1	● Dopamine > 15 ● *ou* Adrénaline > 0,1 ● *ou* Noradrénaline > 0,1
➥ Système nerveux central					
Score de Glasgow	● 15	● 13-14	● 10-12	● 6-9	● < 6
➥ Rein					
Créatinine, mg/dL (umol/L)	● < 1,2 (110)	● 1,2-1,9 (110-170)	● 2,0-3,4 (171-299)	● 3,5-4,9 (300-440)	● > 5,0 (440)
Diurèse, mL/j				● < 500	● < 200

PaO_2 : pression artérielle en oxygène ; FiO_2 : fraction d'oxygène inspiré ; PAM : pression artérielle moyenne. La dose de catécholamines est donnée en µg/kg/min sur au moins 1 heure.

Quick SOFA

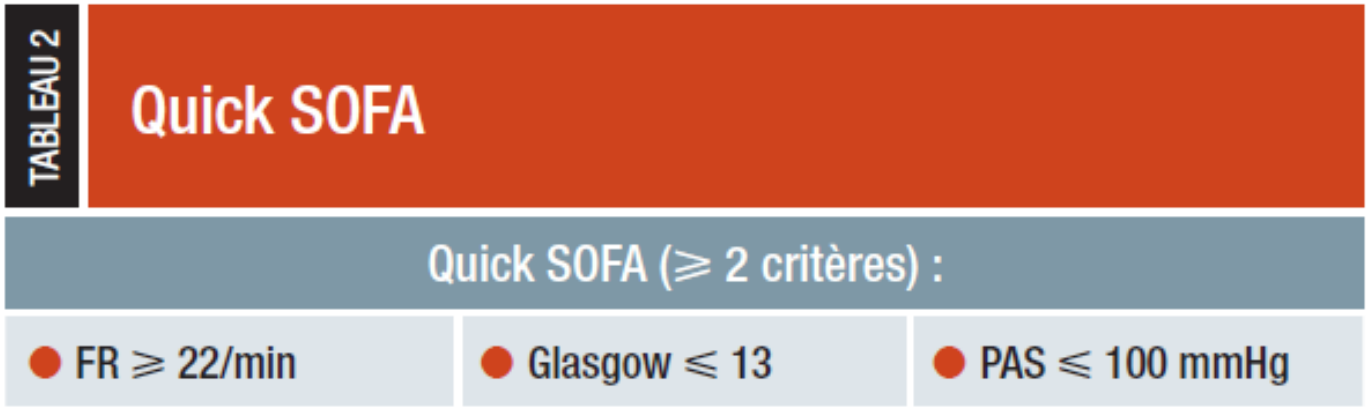


TABLEAU 2
Quick SOFA
Quick SOFA (⩾ 2 critères) :
FR ⩾ 22/min
Glasgow ⩽ 13
PAS ⩽ 100 mmHg

Le qSOFA n'est pas recommandé dans les RPC de la SSC

Recommendation
2. We **recommend against** using qSOFA compared with SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.
Strong recommendation, moderate-quality evidence.

Les études ont montré que le qSOFA est plus spécifique mais moins sensible que deux des quatre critères SIRS pour l'identification précoce d'un dysfonctionnement organique induit par une infection.

TABLEAU 2

Principaux germes communautaires et nosocomiaux chez les patients développant un choc septique en fonction de la porte d'entrée de l'infection

Sources potentielles de sepsis	Poumon	Abdomen	Peau/tissus mous	Urinaire	Système nerveux central
Principaux germes communautaires	*Streptococcus pneumoniæ* *Hæmophilus influenzæ* *Legionella sp.* *Chlamydia pneumoniæ*	*Escherichia coli* *Bacteroides fragilis*	*Streptococcus pyogenes* *Staphylococcus aureus* *Clostridium perfringens*	*Escherichia coli* *Klebsiella sp.* *Proteus sp.* *Enterobacter sp.*	*Streptococcus pneumoniæ* *Neisseria meningitidis* *Listeria monocytogenes* *Hæmophilus influenzae* *Escherichia coli*
Principaux germes nosocomiaux	*Staphylococcus aureus* *Pseudomonas æruginosa* Entérobactéries *Acinetobacter sp.*	*Pseudomonas æruginosa* Anaérobies *Candida sp.* Entérobactéries	*Staphylococcus aureus* *Pseudomonas æruginosa*	Bacilles aérobies Gram négatif *Staphylococcus aureus* *Pseudomonas æruginosa* *Enterococcus sp.*	*Staphylococcus sp.* *Pseudomonas æruginosa* *Escherichia coli* *Klebsiella sp.*

TABLEAU 4

Traitement probabiliste des principaux états septiques chez un patient communautaire

Contexte clinique	Antibiothérapie probabiliste de première intention
Sepsis communautaire sans point d'appel clinique	Céphalosporines de 3e génération IV (ceftriaxone 1 g/24 h ou céfotaxime 3 g/24 h) + amikacine 30 mg/kg/j
Méningite communautaire	Céphalosporines de 3e génération (ceftriaxone 100 mg/kg/24 h, céfotaxime 300 mg/kg/24 h)
Pneumopathie communautaire grave	Amoxicilline-acide clavulanique (2 g/8 h) ou ceftriaxone (1-2 g/24 h) **ou** céfotaxime (2 g/8 h) + spiramycine (9 MUI/24 h) ou ofloxacine (200 mg/12 h) ou lévofloxacine (500 mg/12 h)
Infections urinaires communautaires	
Formes sans signe de gravité	Céphalosporines de 3e génération IV (ceftriaxone 1 g/24 h ou cefotaxime 3 g/24 h) **ou** ofloxacine (200 mg/12 h)
Formes graves (hypotension)	Céphalosporines de 3e génération IV (ceftriaxone 1 g/24 h ou cefotaxime 3 g/24 h) + amikacine (30 mg/kg/j)
Infections intra-abdominales	
Péritonite communautaire	Amoxicilline-acide clavulanique (2 g/8 h) + gentamicine (ou céphalosporines de 3e génération IV (ceftriaxone 1 g/24 h ou cefotaxime 3 g/24 h) + métronidazole (500 mg/8 h)
Péritonites nosocomiales/postopératoires	Pipéracilline-tazobactam (4 g/6 h) + amikacine (30 mg/kg/j) **ou** imipénème (1 g/8 h) + amikacine (30 mg/kg/j)
Infection de liquide d'ascite	Amoxicilline-acide clavulanique (1 g/6 h) **ou** céphalosporines de 3e génération IV (ceftriaxone 1 g/24 h ou cefotaxime 3 g/24 h)
Angiocholites aiguës communautaires	Amoxicilline-acide clavulanique (2 g/6 h) + gentamicine (5 mg/kg/j) si forme grave **ou** céphalosporines de 3e génération IV (ceftriaxone 1 g/24 h ou céfotaxime 3 g/24 h) + métronidazole (500 mg/8 h) + gentamicine (5 mg/kg/j) si forme grave
Dermohypodermite bactérienne nécrosante Atteinte membres et région cervico-faciale Gangrène périnéale communautaire	Amoxicilline-acide clavulanique (100 mg/kg/j) + clindamycine (600 mg × 3-4/24 h) Pipéracilline-tazobactam (12 g/24 h) + clindamycine (600 mg × 3-4/24 h) + gentamicine (5 mg/kg/24 h) si forme grave
Endocardite communautaire	Amoxicilline-acide clavulanique (3 g/6 h) + gentamicine (3 mg/kg/j)

Syndrome de libération de cytokines

Responsable d'un syndrome de fuite capillaire conduisant à un syndrome de défaillance multiviscérale

Résulte d'une activation massive du système immunitaire non spécifique d'un antigène

La tempête cytokinique

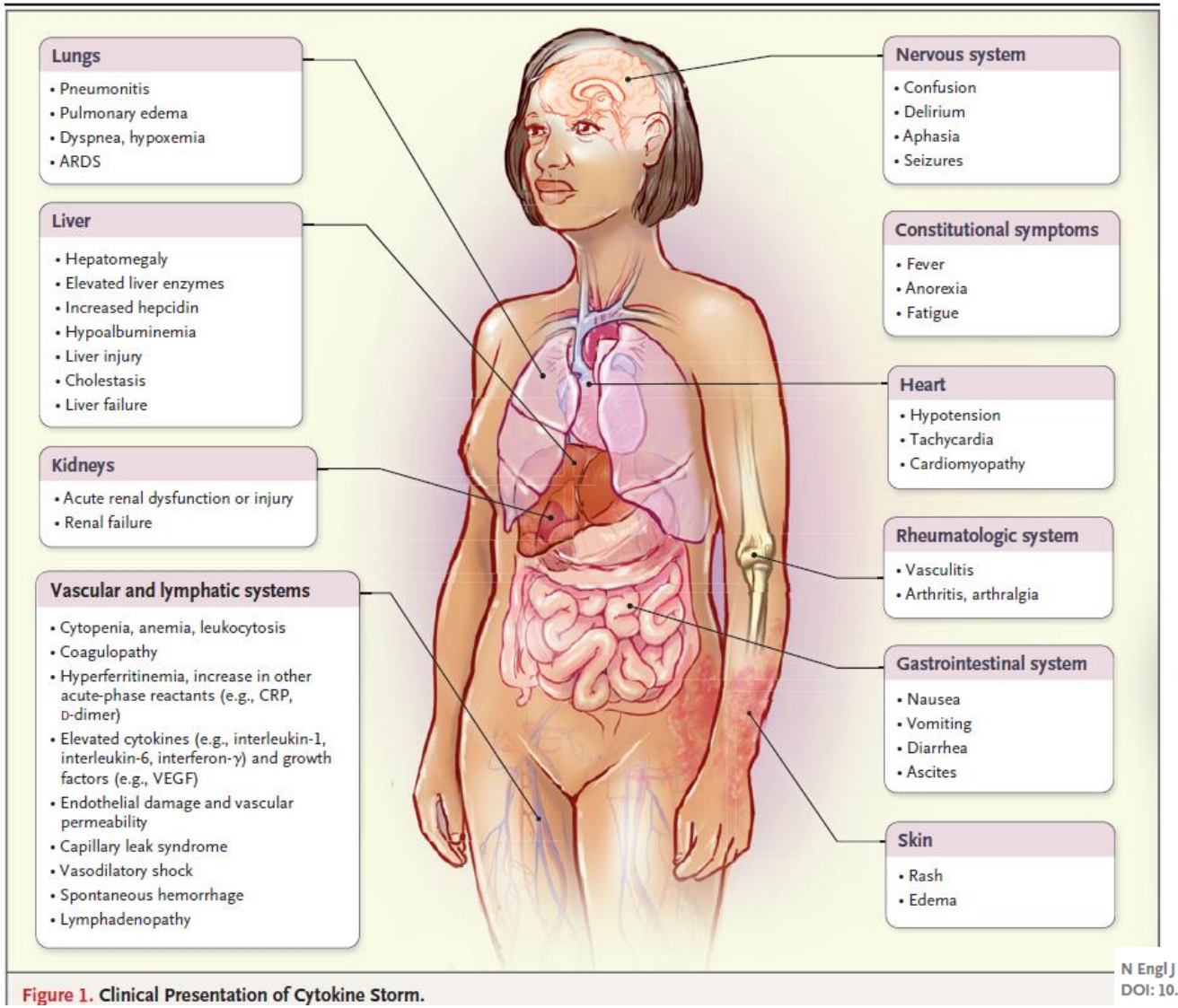
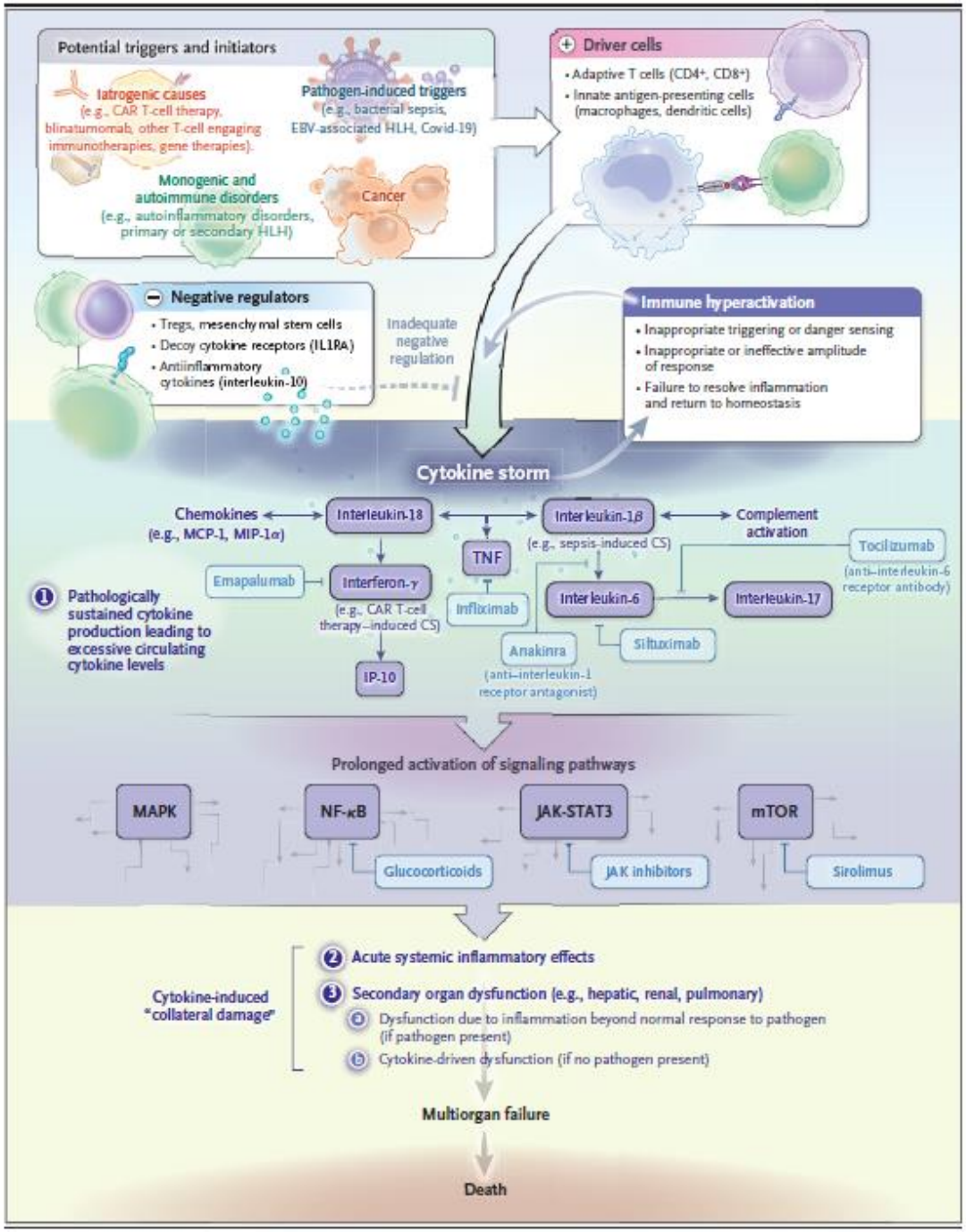


Figure 1. Clinical Presentation of Cytokine Storm.

N Engl J Med 2020;383:2255-73.
DOI: 10.1056/NEJMra2026131


Potential triggers and initiators
Iatrogenic causes
(e.g., CAR T-cell therapy, blinatumomab, other T-cell engaging immunotherapies, gene therapies)
Pathogen-induced triggers
(e.g., bacterial sepsis, EBV-associated HLH, Covid-19)
Monogenic and autoimmune disorders
(e.g., autoinflammatory disorders, primary or secondary HLH)
Cancer
Driver cells
• Adaptive T cells (CD4+, CD8+)
• Innate antigen-presenting cells (macrophages, dendritic cells)
Negative regulators
• Tregs, mesenchymal stem cells
• Decoy cytokine receptors (IL1RA)
• Antiinflammatory cytokines (interleukin-10)
Inadequate negative regulation
Immune hyperactivation
• Inappropriate triggering or danger sensing
• Inappropriate or ineffective amplitude of response
• Failure to resolve inflammation and return to homeostasis
Cytokine storm
Chemokines
(e.g., MCP-1, MIP-1α)
Interleukin-18
Interleukin-1β
(e.g., sepsis-induced CS)
Complement activation
TNF
Tocilizumab
(anti–interleukin-6 receptor antibody)
Emapalumab
Interferon-γ
(e.g., CAR T-cell therapy–induced CS)
Infliximab
Interleukin-6
Interleukin-17
Siltuximab
Anakinra
(anti–interleukin-1 receptor antagonist)
IP-10
1 Pathologically sustained cytokine production leading to excessive circulating cytokine levels
Prolonged activation of signaling pathways
MAPK
NF-κB
JAK-STAT3
mTOR
Glucocorticoids
JAK inhibitors
Sirolimus
Cytokine-induced "collateral damage"
2 Acute systemic inflammatory effects
3 Secondary organ dysfunction (e.g., hepatic, renal, pulmonary)
a Dysfunction due to inflammation beyond normal response to pathogen (if pathogen present)
b Cytokine-driven dysfunction (if no pathogen present)
Multiorgan failure
Death

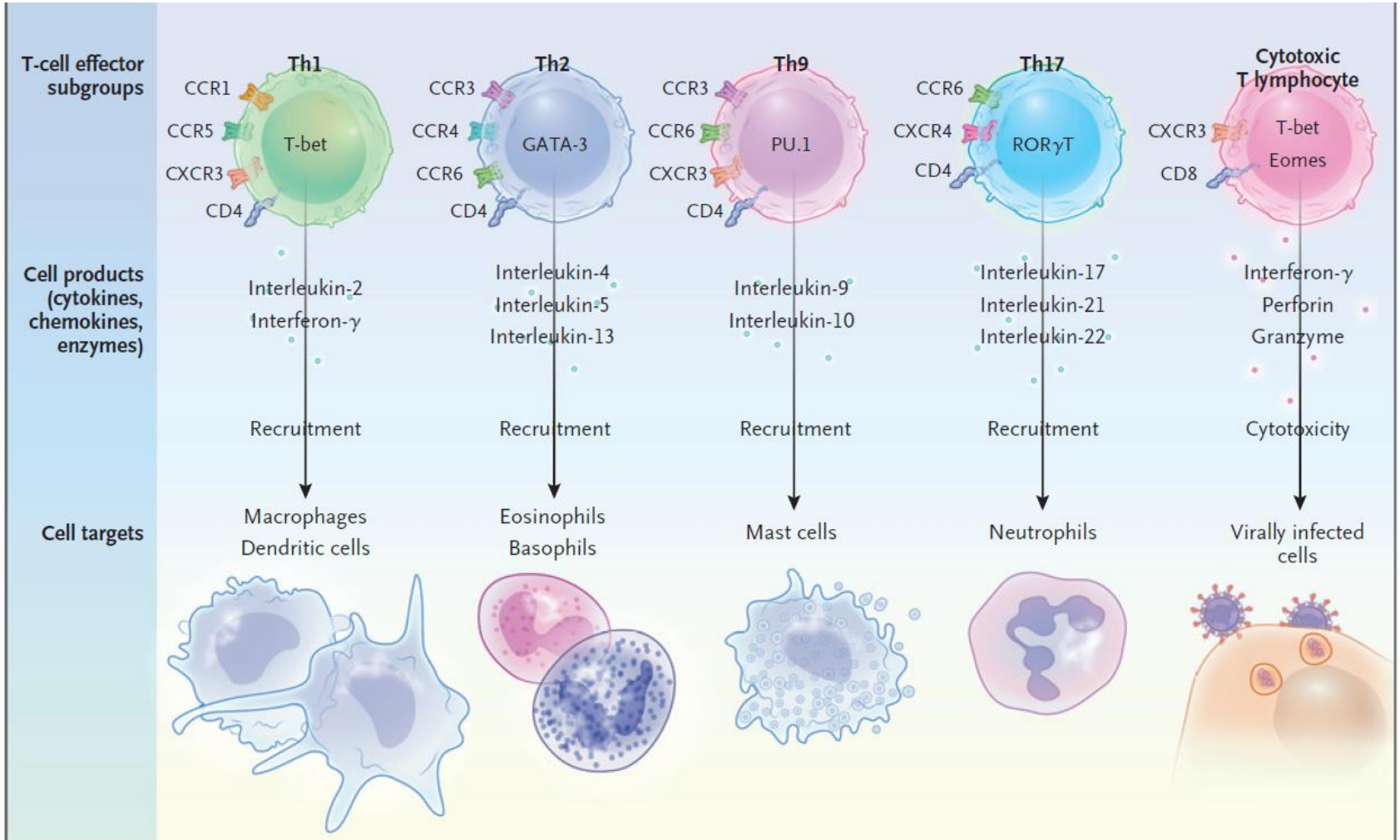


Figure 3. T-Cell Effector Subgroups Involved in Cytokine Storm.

The master transcription factors (T-bet, GATA-3, PU.1, RORγT, and eomesodermin [eomes]), effector molecules, and cell targets are shown for the following T-cell subgroups: types 1, 2, 9, and 17 helper T (Th1, Th2, Th9, and Th17, respectively) cells and cytotoxic T lymphocytes.

Table 2. Clinical Causes of Cytokine Storm, Pathologic Drivers, and Therapeutic Approaches.*

Type of Cytokine Storm and Trigger	Cause	Pathologic Cellular or Cytokine Driver	Common Therapeutic Approaches
Iatrogenic			
CAR T-cell therapy	Infusion of CAR T cells	Macrophages, CAR T cells, interleukin-6, interleukin-1β	Anti–interleukin-6 antibody, glucocorticoids
Blinatumomab	Infusion of CD19- and CD3-specific T-cell receptor–engaging antibody	Activated T cells, macrophages, interleukin-6	Anti–interleukin-6 antibody, glucocorticoids
Pathogen-induced			
Bacterial sepsis	Hematogenous bacterial infection	Heterogeneous and multifactorial drivers	Intravenous antibiotics
EBV-associated HLH	EBV infection in patient with genetic susceptibility	Interferon-γ, TNF, CD8+ T cells	B-cell–depleting therapy, glucocorticoids
HHV-8–associated MCD	HHV-8 infection in patient with HIV coinfection, genetic susceptibility, or both	Viral interleukin-6, interleukin-6	B-cell–depleting therapy
Covid-19	SARS-CoV-2 infection, potentially in a susceptible person	Unknown driver	Glucocorticoids
Monogenic and autoimmune			
Primary HLH	Germline mutation in genes regulating granule-mediated cytotoxicity	CD8+ T cells, interferon-γ	T-cell inhibition or ablation, interferon-γ inhibitor, glucocorticoids
Secondary HLH, or MAS	Viral cause (EBV or CMV), autoimmune disorder (rheumatoid arthritis or adult-onset Still's disease), or neoplastic disorder in patient with genetic susceptibility (lymphoma)	CD8+ T cells, interferon-γ, interleukin-1β, myeloid-cell autoinflammation	Treatment of the underlying cause, in addition to T-cell inhibition or ablation, interleukin-1β inhibitor, JAK1 and JAK2 inhibitors, glucocorticoids
Autoinflammatory disorders	Germline mutations in genes regulating the innate immune system and inflammasome activation	Innate cells, TNF, interleukin-1β	Anti-TNF antibody, anti–interleukin-1 antibody
Idiopathic MCD	Unknown cause	Interleukin-6, activated T cells, mTOR	Anti–interleukin-6 antibody, sirolimus, cyclosporine, cytotoxic chemotherapy, glucocorticoids

* CAR denotes chimeric antigen receptor, CMV cytomegalovirus, Covid-19 coronavirus disease 2019, EBV Epstein–Barr virus, HHV-8 human herpesvirus 8, HIV human immunodeficiency virus, HLH hemophagocytic lymphohistiocytosis, JAK1 Janus kinase 1, JAK2 Janus kinase 2, MAS macrophage activation syndrome, MCD multicentric Castleman's disease, mTOR mammalian target of rapamycin, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

Le modèle : traitements aux cytokines

- Le meilleur exemple est l'interleukine-2
- Tableau clinique: syndrome de fuite capillaire avec rétention hydrique, œdème, gain de poids; hypotension artérielle; insuffisance rénale, oligurie; œdème pulmonaire
- Peut donner des états de choc et un syndrome de défaillance multiviscérale

Intensive Care Med (1988) 14:666–667

Intensive Care Medicine

Multiple organ failure during interleukin-2 administration and LAK cells infusion

J. P. Sculier, D. Bron, N. Verboven and J. Klastersky

Service de Médecine et Laboratoire d'Investigation Clinique H. J. Tagnon, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Bruxelles, Belgium

Les médicaments en cause

- cytokines : IL2, GM-CSF à hautes doses
- certains agents chimiothérapiques : docétaxel, gemcitabine
- greffes de moelle osseuse avec conditionnement
- anticorps monoclonaux donnés iv, dont les immunothérapies par inhibiteurs de points de contact immunitaire (comme le nivolumab ou le pembrolizumab)
- CAR T cells (chimeric antigen receptor)

Anticorps monoclonaux

6 sur 8 volontaires à l'USI

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

N Engl J Med 2006;355:1018-28.

Table 1. Data for All Six Affected Patients on Transfer to the Intensive Care Unit (ICU).*

Characteristic	Patient No.					
	1	2	3	4	5	6
Age (yr)	24	34	31	19	28	20
Weight (kg)	68.9	84.3	81.8	72.1	88.5	82.4
TGN1412 dose (mg)	6.8	8.4	8.2	7.2	8.8	8.2
Transfer to critical care (hr after dose)	15.5	16.0	16.0	16.0	16.0	12.0
APACHE II score on transfer†	8	10	11	18	20	18
Bilateral pulmonary infiltrates‡	+	++	++	++	++	+++
Duration of abnormalities on chest radiography (days)	7	6	8	>5	6	7
Hemodynamics on transfer						
Blood pressure (mm Hg)	120/50	124/79	107/42	98/40	95/40	80/64
Heart rate (beats/min)	125	103	116	120	105	140
LVEF on echocardiogram (%)	50–55	70	60	50–55	60	55
PaO_2:FIO_2	395.5	195.6	329.5	321.3	201.8§	84.0§
Base deficit (mmol/liter)	–5.1	–6.5	–5.6	–5.8	–10.3	–8.2
Lactate (mmol/liter)¶	3.1	4.5	5.7	6.0	5.9	4.2
Urinary output (ml/hr)	20	30	30	45	30	0
Treatment						
Days spent in ICU	4	7	7	5	11	21
Days receiving corticosteroids (including tapering)	21	21	21	21	24	33
Epiphenomena						
Generalized desquamation‖	+	++	+	+	++++	+++
Muscle weakness‡	+	++	+	+	++	++
Late myalgia	Calf	Calf and hip adductors	Calf	—	Calf	—
Neurologic findings	Headaches and hyperalgesia	Hyperalgesia	Hyperalgesia and numbness	Headaches	Headaches and numbness	—

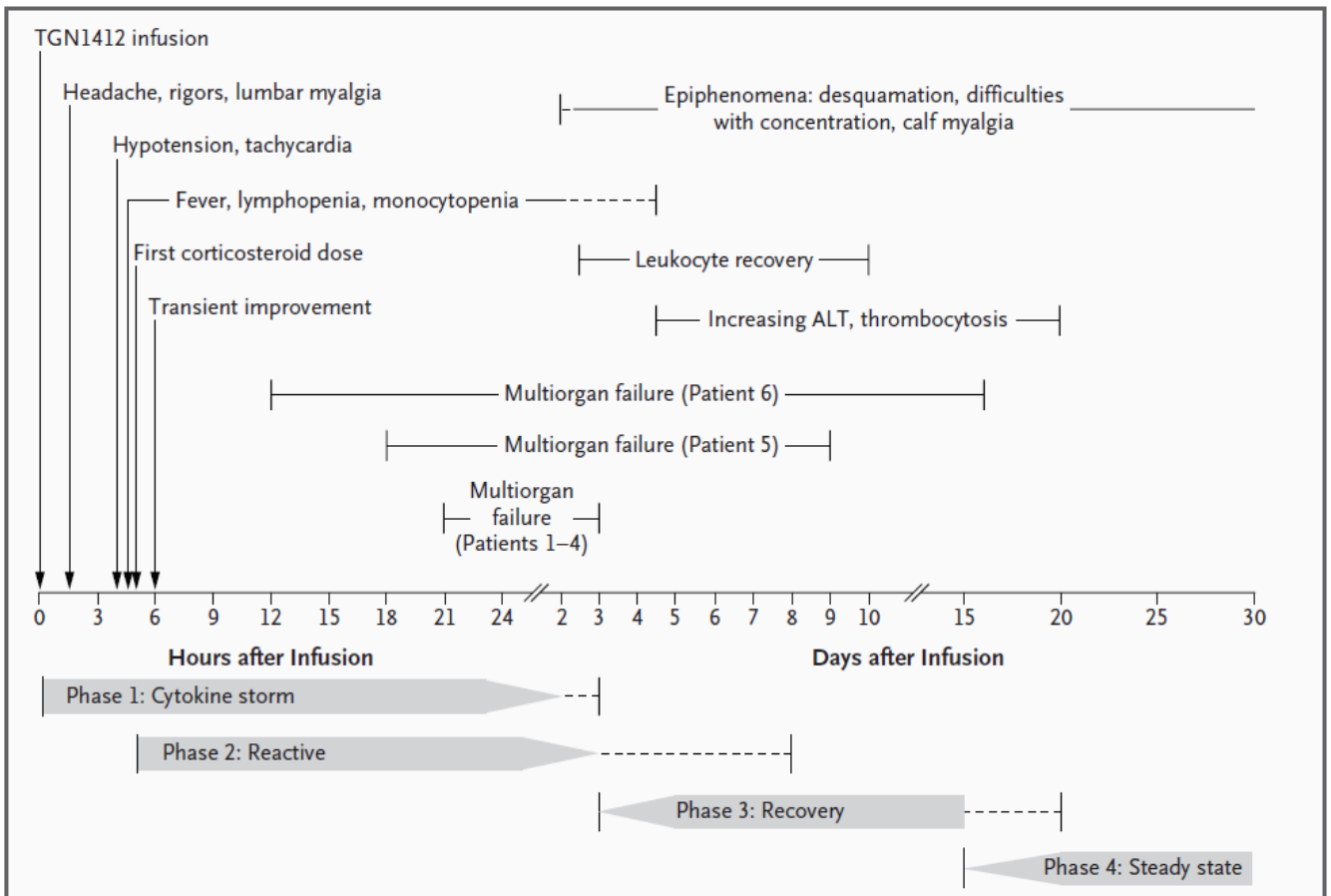
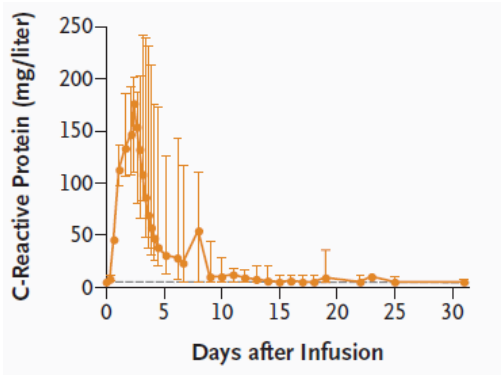


Figure 1. Summary Timeline of the Main Events after Infusion of TGN1412.

The course is divided into four phases: cytokine storm, reactive, recovery, and steady state. ALT denotes alanine aminotransferase. Dashed lines represent the responses of Patients 5 and 6 (who were the most seriously ill).


C-Reactive Protein (mg/liter)
250
200
150
100
50
0
0 5 10 15 20 25 30
Days after Infusion

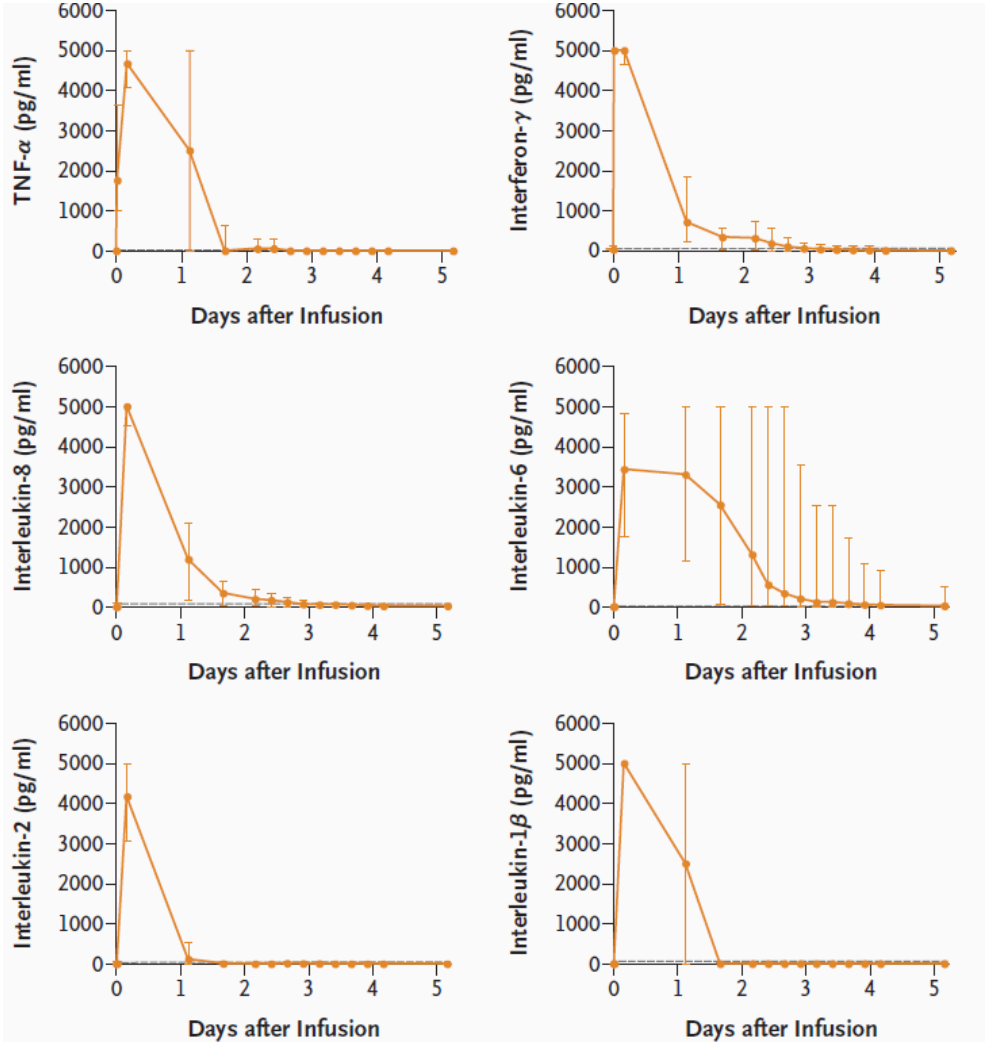

TNF-α (pg/ml)
Interferon-γ (pg/ml)
Interleukin-8 (pg/ml)
Interleukin-6 (pg/ml)
Interleukin-2 (pg/ml)
Interleukin-1β (pg/ml)
6000
5000
4000
3000
2000
1000
0
0 1 2 3 4 5
Days after Infusion

Table 3. Common Features after Infusion of TGN1412.

System	Feature
Cardiovascular	Capillary leak Hemodynamic instability Lactic acidemia
Renal	Early acute renal impairment Urinary sediment 10–100 White cells <10 Red cells Granular casts (two patients)
Pulmonary	Acute pulmonary changes (six patients) Met criteria for acute lung injury (two patients)* Met criteria for acute respiratory distress syndrome (one patient)*
Hematologic and immunologic	Cytokine storm (TNF-α; interferon-γ; interleukin-10, 6, 2) Increased C-reactive protein level and erythrocyte sedimentation rate Lymphopenia Monocytopenia Thrombocytopenia Disseminated intravascular coagulation Normochromic, normocytic anemia Dysplastic neutrophils but preserved numbers
Hepatic	Increased alanine aminotransferase and alkaline phosphatase levels
Integumentary	Diffuse erythema Late desquamation
Neurologic	Delirium Partial amnesia Paresthesia or localized numbness Difficulty concentrating (late) Headaches (early and late)
Autonomic, gastrointestinal, or both	Bowel urgency or diarrhea Nausea or vomiting
Musculoskeletal	Myalgia in lower back (early) and calves (late)

* Criteria are from the American–European Consensus Conference on ARDS.[7]

AC monoclonaux en cause

- Anti-CD20: rituximab, ocrélizumab, obinutuzumab
- Anti-CD52: alemtuzumab
- Anti-CD19 et anti-CD3: blinatumomab
- Anti-HER2: trastuzumab, pertuzumab
- Anti-EGR: cétuximab
- Anti-PCD1: nivolumab, pembrolizumab
- …

Inhibiteurs des points de contact immunitaire

Systemic Capillary Leak Syndrome (Clarkson's Disease) as a Complication of Anti-Programmed Death 1 Immunotherapy

To the Editor:

We report here the case of a 50-year-old woman treated for an advanced lung adenocarcinoma (thyroid transcription factor-1 negative, Cytokeratin 7 positive, KRAS+) with liver, bone, subcutaneous, and muscular metastases who suffered from rapidly progressing diffuse edema of unusual etiology.

secondary to profound hypoalbuminemia with no proteinuria and without cardiac or liver failure, systemic capillary leak syndrome (SCLS) (or Clarkson's disease) was suspected.[1] Known causes of secondary SCLS and hypoalbuminemia were eliminated including absence of exudative enteropathy, liver disease, or renal protein leak. There was no monoclonal gammopathy on serum electrophoresis. As hypothyroidism could not be responsible for such hypoalbuminemia, the diagnosis of idiopathic SCLS was established. Considering that only levothyroxine and nivolumab were recently introduced, and because levothyroxine had never been reported as a cause of SCLS, the hypothesis of an immunological adverse event of nivolumab was suspected. High doses of intravenous steroids were introduced but with no

CAR-T : lymphocytes T à récepteur antigénique chimérique (comme anti CD19)

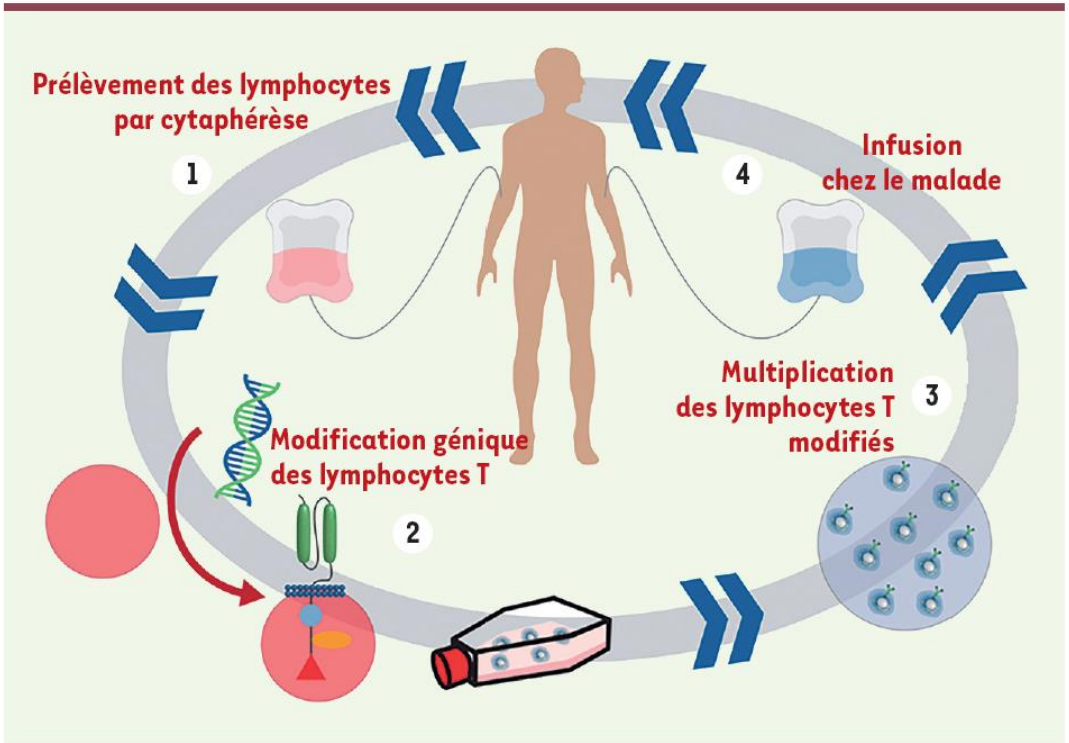


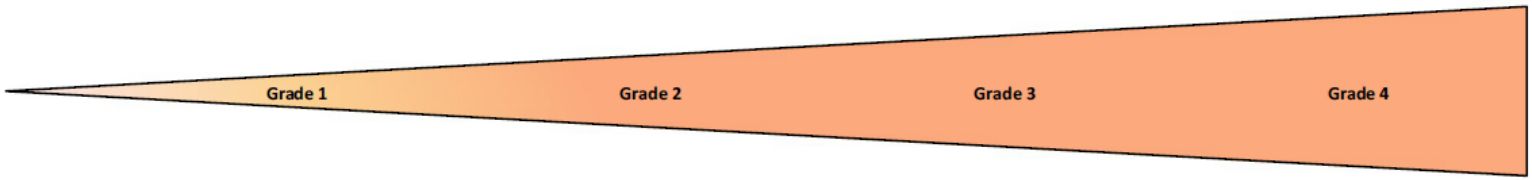
Figure 1. ***Schéma général d'une thérapie de type CAR-T.*** Le lymphocyte T modifié (en bas à gauche) exprime un récepteur antigénique chimérique comportant, en surface, deux domaines variables d'immunoglobuline et, à l'intérieur de la cellule, plusieurs domaines d'activation et de stimulation (adapté de *Rockland Immunochemicals*, https://rockland-inc.com/car-t-cell-therapy-services.aspx).

Complications

- cytokine release syndrome (CRS): lié à une libération massive de cytokines (fièvre, tachycardie, hypotension, insuffisance rénale, etc.)
- toxicités neurologiques : tremblements, aphasie, convulsions, etc.

Traitement

- arrêt du médicament
- symptomatique : réduire les apports et favoriser la diurèse en maintenant les signes vitaux
- corticothérapie : lorsque la vie du patient est en danger
- Anti IL6: Tocilizumab



CTCAE Grade

General symptoms requiring symtomatic therapy
- Fever
- malaise
- Nausea etc.

Symptoms responding to moderate intervention
- Oxygen (< 40% FiO2)
- Hypotension responsive to fluids or low dose vasopressors
- any Grade 2 organ toxicity

Symptoms requiring aggressive intervention
- Oxygen (> 40% FiO2)
- Hypotension responsive to high dose vasopressors (> 1000ug/h norepinephrine equivalent)
- any grade 3 organ toxicity or grade 4 transaminitis

Life-threatening symptoms
- Mechanical ventilation
- any grade 4 organ toxicity (excl. transaminitis)

Therapeutic approach

Symptomatic support
- Fluids
- Antipyretics

Anti-infective therapy

Oxygen supply (< 40% FiO2)

Low dose vasopressors
(< 1000ug/h norepinephrine equivalent)

Tocilizumab
- 4-8 mg/kg BW, max. 800 mg/day)
- Insufficient response: repeat once after 24-72 hrs

Methylprednisolone
- 2 mg/kg BW

If refractory consider
- TNF-α blocker, anakinra
- Siltuximab
- Cyclophosphamide
- ATG, alemtuzumab

Oxygen supply (< 40% FiO2)

High dose vasopressors
(> 1000ug/h norepinephrine equivalent)

Mechanical ventilation

Differential diagnosis

Anaphylactic Reaction
- Prior exposure?
- Response to antihistamines?

Tumor lysis syndrome (TLS)
- hyperuricemia, hyperkalemia
- hyperphosphatemia, hypocalcemia

Sepsis
- Positive blood cultures, X-ray etc.
- Response to anti-infective therapy?

MAS/HLH
- family history of MAS/HLH?
- genetic abberations associated with HLH/MAS (PRF1, STX11, STXBP2, MUNC13-4)?

ΔΔ : Syndrome de fuite capillaire idiopathique (syndrome de Clarkson)

Formes cliniques

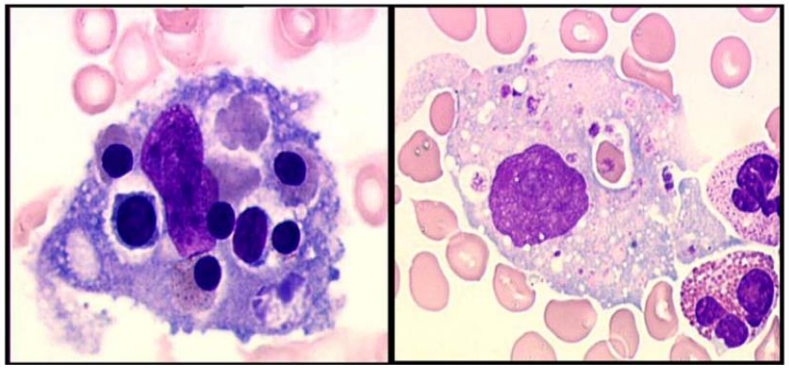
- subaiguë : cyclique avec œdème et prise de poids
- aiguë : épisodes de crises hypotensives avec œdème
  - conservation de la conscience malgré la gravité de l'hypotension
  - absence d'atteinte pulmonaire initialement
  - prodromes : irritabilité, rhinorrhée, diarrhées, douleurs …
  - facteurs précipitants : infections des voies respiratoires supérieures, cycle menstruel, exercices physiques

Biologie

- hémoconcentration paradoxale : augmentation forte de l'hématocrite, hyperleucocytose, hypoalbuminémie
- insuffisance rénale fonctionnelle
- gammopathie monoclonale (le plus souvent IgG)

Syndrome d'activation macrophagique

= SAM ou syndrome hémophagocytaire ou lymphohistiocytose hémophagocytaire



Critères diagnostiques

diagnostic retenu si au moins 5 des critères suivants présents:

1. fièvre (> 7 jours)
2. splénomégalie
3. bicytopénie : Hb <9 g/dl ; plaq < 100.000/mm³ ; PN < 1100/mm³
4. hypertriglycérédémie et/ou hypofibrinogénémie (< 150 mg/dl)
5. hémophagocytose
6. taux bas ou nul de cellules NK
7. hyperferritinémie (> 500 µg/l)
8. taux élevé de CD-25 solubles (> 2400 UI/ml)

Tableau clinique

- Fièvre élevée d'installation rapide
- Perte de poids
- Adénopathies périphériques (35%)
- Hépatosplénomégalie (50%)
- Infiltrats pulmonaires (20-30%)
- Atteinte cardiaque
- Atteinte rénale
- Atteinte cutanée (20%) : rash, érythème, purpura
- Encéphalopathie, méningite, convulsions
- Tableau d'insuffisance multi-organique

Laboratoire

- Cytopénie (bi- ou pan)
- Élévation ferritinémie
- Hypofibrinogénémie
- CIVD
- Cytolyse ou cholestase hépatique
- Hypoalbuminémie
- Insuffisance rénale
- Hyponatrémie (SIADH)
- **Histologie** : hématophagocytose (moelle osseuse, ganglions, foie, rate)

Physiopathologie

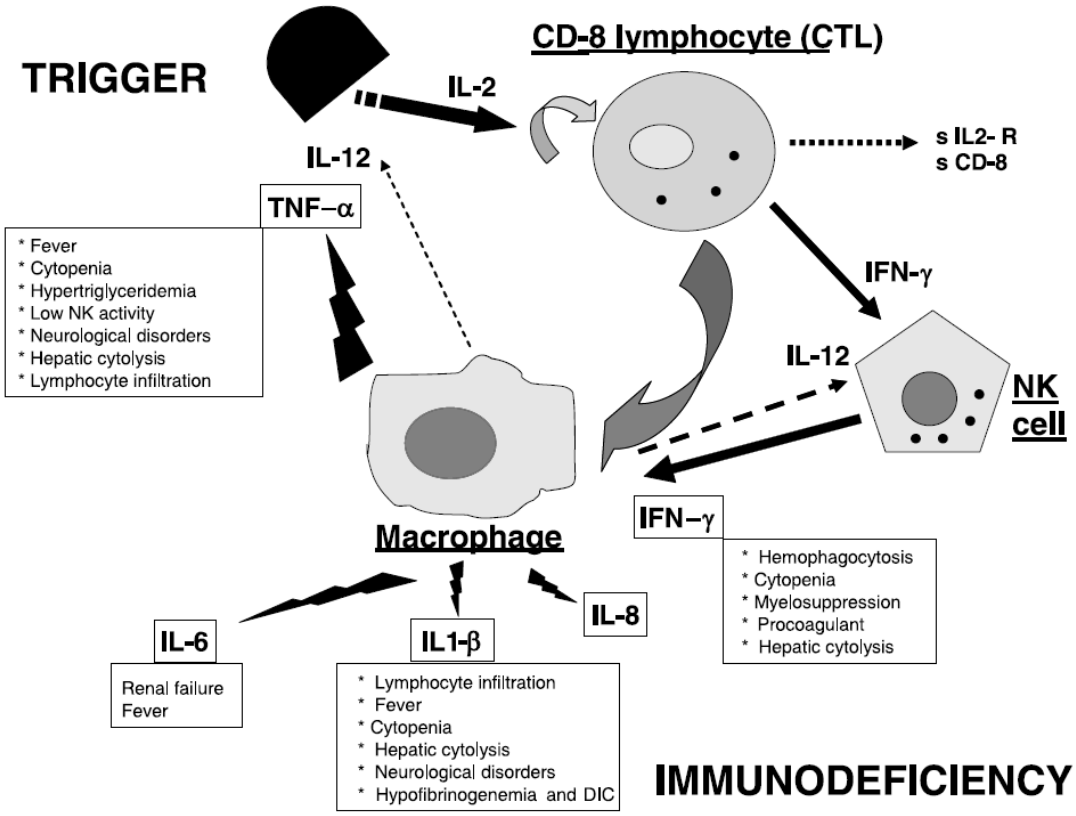


Fig. 2 Immunopathological mechanisms in hemophagocytic lymphohistiocytosis: clinical effects of Th1 activation loop and cytokines production. Activation of CD-8 T lymphocytes results in clonal proliferation and activation of NK cells, with production of high levels of activating cytokines. Elaboration of TNF-α and other cytokines causes fever and systemic illness. TNF-α and IFN-γ production contribute to macrophage activation with resulting hemophagocytosis. *TNF-α*, tumor necrosis factor alpha; *IFN-γ*, interferon-gamma; *IL1-β*, interleukin-1 beta; *IL-2*, interleukin-2; *IL-6*, interleukin-6; *IL-8*, interleukin-8; *IL-12*, interleukin-12; *sCD-8*, soluble cluster of differentiation 8; *NK cell*, natural killer cell

Intensive Care Med (2008) 34:1177–1187
DOI 10.1007/s00134-008-1111-y

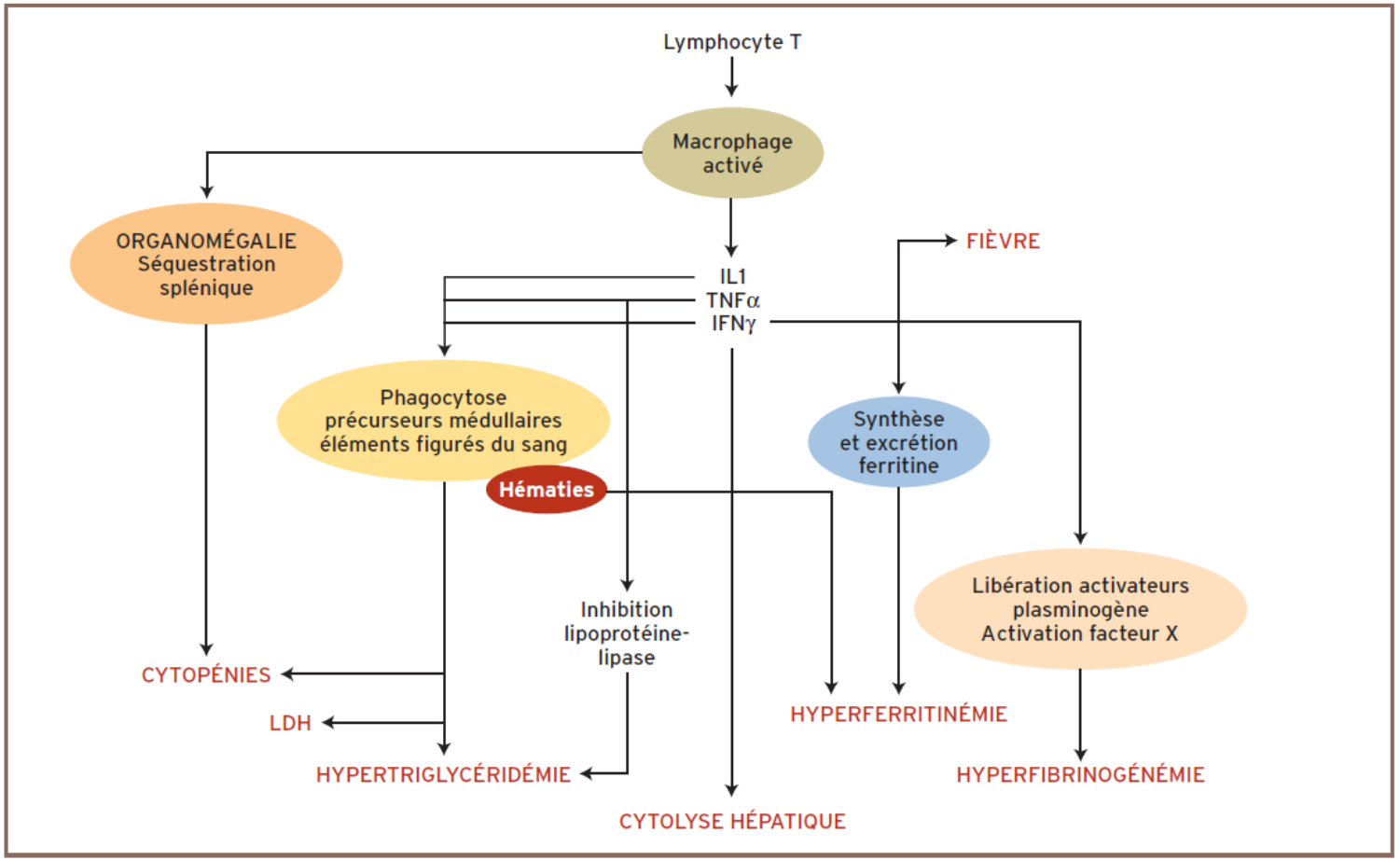


Figure 2 **Syndrome d'activation macrophagique.** Hypersécrétion de cytokines et manifestations cliniques et biologiques. LDH : lacticodéshydrogénase ; TNF : *tumour necrosis factor* ; IL : interleukine.

Etiologie

- infections virales (30%) : CMV, EBV, HSV, HIV, pv B19
- infections bactériennes (30%) : mycobactéries, mycoplasme, Legionella, Chlamydia, Brucella
- infections fongiques ou parasitaires (8%) : malaria, leishmaniose, pneumocystose, aspergillose, candidose, toxoplasmose, cryptococcose
- maladies lympho-prolifératives (28%) : lymphomes T liés à EBV, HHV-8 …
- tumeurs solides (1,5%)
- maladies systémiques (7%) : LED, maladie de Still, PCE, PAN, sarcoïdose, Sjögren …
- traitements par inhibiteurs des points de contact immunitaire
- cause non identifiée (20%)

Treatment and Mortality of Hemophagocytic Lymphohistiocytosis in Adult Critically Ill Patients: A Systematic Review With Pooled Analysis

Cornelia Knaak, MD[1]; Friederike S. Schuster[1]; Peter Nyvlt[1]; Claudia Spies, Prof[1]; Insa Feinkohl, PhD[2]; Gernot Beutel, MD[3]; Thomas Schenk, MD[4]; Paul La Rosée[5]; Gritta Janka, Prof[6]; Frank M. Brunkhorst, Prof[7]; Didier Keh, Prof[1]; Gunnar Lachmann, PD[1,8]

Objectives: Hemophagocytic lymphohistiocytosis is a cytokine release syndrome caused by uncontrolled immune activation resulting in multiple organ failure and death. In this systematic review, we aimed to analyze triggers, various treatment modalities, and mortality in critically ill adult hemophagocytic lymphohistiocytosis patients.

Data Sources: MEDLINE database (PubMed) at October 20, 2019.

Study Selection: Studies and case series of patients greater than or equal to 18 years old, of whom at least one had to be diagnosed with hemophagocytic lymphohistiocytosis and admitted to an ICU.

Data Extraction: Source data of studies and case series were summarized and analyzed on an individual basis. Multivariable logistic regression analysis was performed adjusting for age, sex, and trigger groups. Each single treatment agent was entered as a dichotomous variable to determine treatments associated with survival, regardless if given alone or in combination.

Data Synthesis: In total, 661 patients from 65 studies and case series were included. Overall mortality was 57.8%. Infections were the most frequent trigger (49.9%), followed by malignancies (28.0%), autoimmune diseases (12.1%), unknown triggers (9.4%), and drugs (0.6%). Treatment with IV immunoglobulins was associated with improved survival (odds ratio, 0.548; 95% CI, 0.337–0.891; $p = 0.015$), while treatment with cyclosporine was associated with increased risk of death (odds ratio, 7.571; 95% CI, 3.702–15.483; $p < 0.001$). Considering different trigger groups separately, same results occurred only for infection-triggered hemophagocytic lymphohistiocytosis. No information was available on disease severity and other confounding factors.

Conclusions: Mortality of hemophagocytic lymphohistiocytosis in the ICU is high. Most common triggers were infections. Results of survival analyses may be biased by treatment indication and disease severity. Future studies prospectively investigating treatment tailored to critically ill hemophagocytic lymphohistiocytosis patients are highly warranted. (*Crit Care Med* 2020; 48:e1137–e1146)

Key Words: hemophagocytic lymphohistiocytosis; hemophagocytic syndrome; macrophage activation syndrome; mortality; treatment

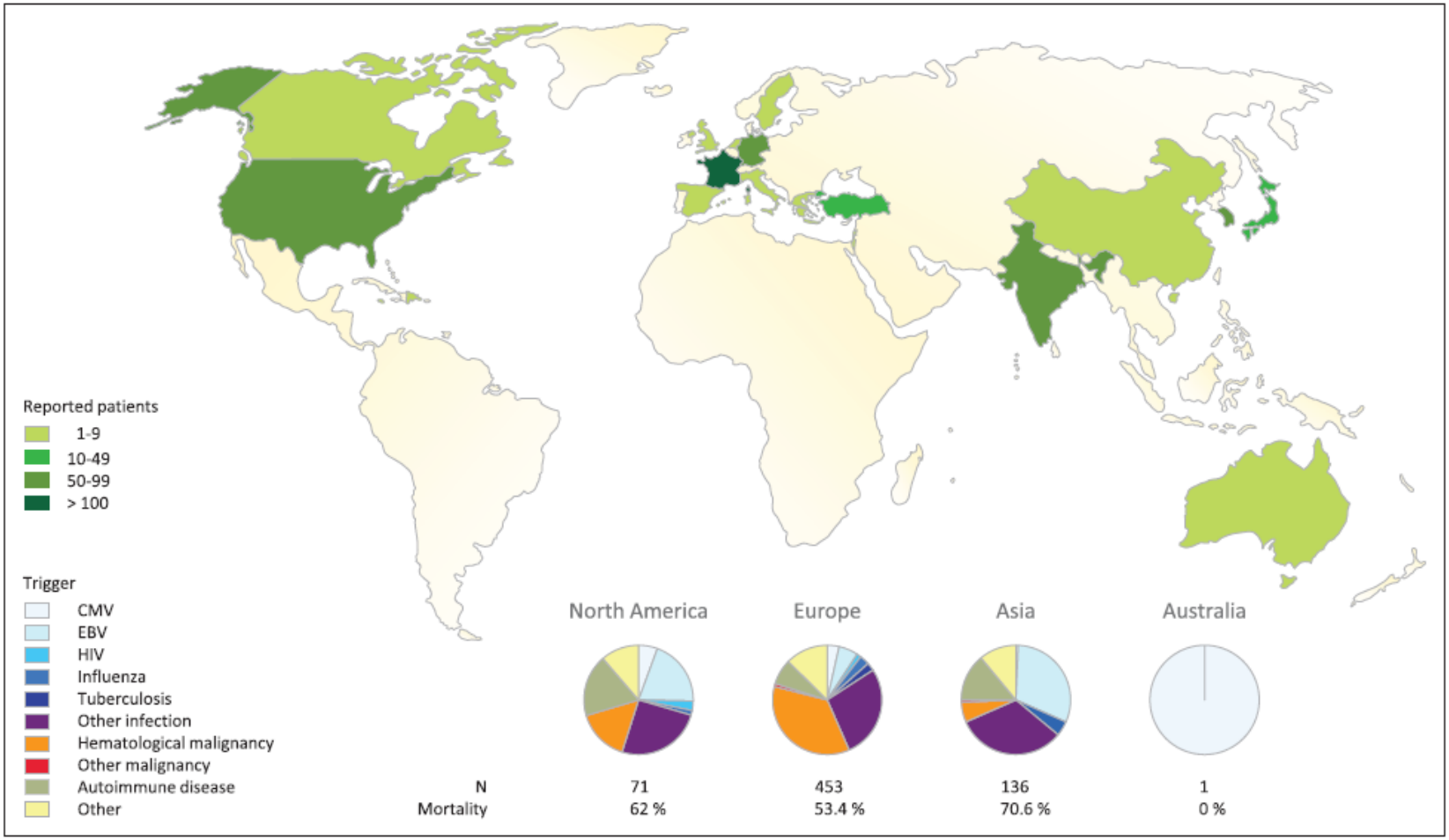


Figure 2. Map of reported numbers of patients with frequent triggers and mortality. CMV = cytomegalovirus, EBV = Epstein-Barr virus, HIV = human immunodeficiency virus.

TABLE 2. Hemophagocytic Lymphohistiocytosis-Specific Treatment Strategies and Corresponding Mortality Between Trigger Groups

HLH-Specific Treatment	Total ($n = 661$)	Infectious Trigger ($n = 330$)	Malignant Trigger ($n = 185$)	Autoimmune Trigger ($n = 80$)	Unknown Trigger ($n = 62$)	Drug-Induced ($n = 4$)	p (Mortality)
None, *n* (mortality %)	118 (57.6)	77 (50.6)	23 (69.6)	4 (25.0)	11 (90.9)	3 (66.7)	0.046[a]
Corticosteroids only, *n* (mortality %)	67 (56.7)	31 (48.4)	10 (90.0)	16 (43.8)	10 (70.0)	0	0.066[a]
IV immunoglobulins only, *n* (mortality %)	33 (27.3)	21 (9.5)	5 (60.0)	3 (0)	3 (100)	1 (100)	0.001[a]
Modified HLH-94 protocol, *n* (mortality %)	387 (62.0)	177 (66.1)	138 (60.9)	38 (36.8)	34 (73.5)	0	0.004[a]
Anticytokines + antibodies, *n* (mortality %)	32 (40.6)	15 (53.3)	6 (33.3)	8 (12.5)	3 (66.7)	0	0.203[a]
Extracorporeal devices, *n* (mortality %)	11 (63.6)	5 (60.0)	2 (100)	4 (50.0)	0	0	0.474[a]
Other, *n* (mortality %)	13 (53.8)	4 (50.0)	1 (100)	7 (57.1)	1 (0)	0	0.556[a]

HLH = hemophagocytic lymphohistiocytosis.

[a]*p* values calculated for the respective mortality using the χ^2 test.

For detailed treatment regiments, see Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/CCM/F757).

The reporting of mortality rates based on treatment agents is not meant to assign prognostic value to any particular agent given the retrospective nature of the reports and the inability to control for severity of illness and other clinical features.

Modified HLH 94 protocol : corticoïdes + ciclosporine et/ou étoposide et/ou Ig iv

REVIEW ARTICLE

Consensus-Based Guidelines for the Recognition, Diagnosis, and Management of Hemophagocytic Lymphohistiocytosis in Critically Ill Children and Adults

Melissa R. Hines, MD[1]
Tatiana von Bahr Greenwood, MD[2]
Gernot Beutel, MD[3]
Karin Beutel, MD[4]
J. Allyson Hays, MD[5]
AnnaCarin Horne, MD, PhD[2]
Gritta Janka, MD, PhD[6]
Michael B. Jordan, MD[7]
Jan A. M. van Laar, MD[8]
Gunnar Lachmann, MD[9]

OBJECTIVE: Hemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome that often requires critical care support and remains difficult to diagnose. These guidelines are meant to aid in the early recognition, diagnosis, supportive care, and treatment of patients with hemophagocytic lymphohistiocytosis in ICUs.

DATA SOURCES: The literature searches were performed with PubMed (MEDLINE).

STUDY SELECTION: Keywords and medical subject headings terms for literature search included "macrophage activation syndrome," hemophagocytic lymphohistiocytosis," and "hemophagocytic syndrome."

DATA EXTRACTION: The Histiocyte Society developed these consensus rec-

Organ Dysfunction in Secondary Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome-Hemophagocytic Lymphohistiocytosis Stratified by Severity and Response Criteria in ICUs According to Expert Consensus (19, 60, 61)

Proposed Severity of Secondary HLH in ICU-Admitted Patients		Therapy See Statement 9 Text and Supplementary Material (http://links.lww.com/CCM/G882) for Recommendations
Mild	No evidence of organ dysfunction except coagulation/hematologic system	Treat underlying trigger; consider glucocorticoid therapy in case of rapid deterioration
Moderate	Evidence of moderate organ dysfunction (SOFA or pSOFA score 2 or less per organ system excluding coagulation/hematologic system) Possible need for supplemental oxygen	Treat underlying trigger; strongly consider glucocorticoid therapy
Severe	Evidence of severe organ dysfunction (SOFA or pSOFA Score 3 or more of at least one organ system excluding coagulation/hematologic system) and/or any need for organ replacement therapy due to organ failure, including positive-pressure ventilation, renal replacement therapy, vasopressors, and extracorporeal life support	Treat underlying trigger; glucocorticoid therapy; add etoposide or additional immunomodulatory therapy based on underlying disease

Recommended Therapies for Hemophagocytic Lymphohistiocytosis

HLH Type	Severity	Therapy
Primary and familial HLH	All	Per Ehl et al (58) based on HLH-94 therapy (17, 68)
Secondary HLH	Mild	Consider addition of corticosteroid therapy (58)
	Moderate	Dexamethasone 10 mg/m^2 daily divided every 12 hr (17, 58, 68) or equivalent methylprednisolone dosing (2 mg/kg/d) (58); consider addition of anakinra 2–10 mg/kg/d, divided in two to four daily doses (subcutaneous or IV) (22, 56, 62, 64, 65)
	Severe, progressive, or refractory	Addition of etoposide with dose reduction as follows (35, 66, 67) 100 mg/m^2 once weekly in older teens 75 mg/m^2 once weekly in adults 50 mg/m^2 once weekly in the elderly Renal dose reduction is recommended, per Ehl et al (58); dose reduction for hypoalbuminemia, hyperbilirubinemia alone, other evidence of liver dysfunction, and/or cytopenias is not recommended (58)

Macrophage activation syndrome-HLH	Mild	Steroids (such as methylprednisolone 30 mg/kg/d with max 1 g/d, for 3–5 d) with or without IVIG (69)
	Moderate	Consider addition of anakinra (dosing as above) and/or cautiously dosed cyclosporine (2 mg/kg/d in two divided doses aiming for serum levels of 100–150 ng/mL) and/or consideration of tocilizumab (35, 62, 70)
	Severe, progressive, or refractory	Consider addition of etoposide or cyclophosphamide (63, 69)
Malignancy-associated HLH	HLH-triggered organ damage (e.g., cytopenias, cholestatic icterus, pulmonary infiltrates, encephalopathy, or renal failure)	Two-step approach (11, 67) Etoposide (75–100 mg/m^2), corticosteroids, and IVIG Once stabilized, start cancer-directed therapy
Additional Therapies	**Agent**	**Indication**
Adjunctive therapies	IVIG (18, 35, 56)	General anti-inflammatory and antiviral effects
	Plasmapheresis (71)	Anti-inflammatory effects; use with caution if giving a monoclonal antibody
	Cytokine adsorption columns (72)	Anti-inflammatory effects
Salvage therapies and agents under investigation	Alemtuzumab (73) Tocilizumab (74) Emapalumab (75) Ruxolitinib (76–79)	These agents have some evidence for specific use in HLH. Please see Supplementary Material (http://links.lww.com/CCM/G882) for list of current clinical trials

Noseda *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:117
https://doi.org/10.1186/s40425-019-0598-9

Journal for ImmunoTherapy of Cancer

SHORT REPORT Open Access

Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: analysis of WHO global database of individual case safety reports

Roberta Noseda[1*], Raffaela Bertoli[1], Laura Müller[1] and Alessandro Ceschi[1,2]

Table 1 Geographical pattern of immune checkpoint inhibitor-related haemophagocytic lymphohistiocytosis reporting rate

Country of primary source	Total number of ICI-related safety reports	Number of ICI-related HLH safety reports	ICI-related HLH reporting rate (%)
France	3526	14	0.4
Japan	6421	11	0.2
Germany	1901	3	0.2
Switzerland	830	1	0.1
Canada	1279	1	0.08
US of America	24'998	8	0.03

Abbreviations: *ICI* immune checkpoint inhibitor, *HLH* haemophagocytic lymphohistiocytosis

Drugs	
Anti-CTLA-4 (ipilimumab) monotherapy	7 (18)
Anti-PD-1 monotherapy	
nivolumab	14 (37)
pembrolizumab	7 (18)
Anti-PD-L1 monotherapy	
Atezolizumab	1 (3)
ipilimumab and nivolumab combination therapy	5 (13)
nivolumab and ipilimumab sequential therapy	3 (8)
pembrolizumab and ipilimumab sequential therapy	1 (3)

Table 3 Haemophagocytic lymphohistiocytosis features and immune-related adverse events reported in patients treated with immune checkpoint inhibitors

Clinical features of HLH	Patients No. (%) [a] (n = 38)
Pyrexia	2 (5)
Pulmonary involvement	
Cough	1 (3)
Neurological involvement	
Encephalopathy	1 (3)
Headache	1 (3)
Psychiatric changes	
Delirium	1 (3)
Cutaneous involvement	
Generalised erythema	1 (3)
Drug eruption	1 (3)
Gastrointestinal involvement	
Enterocolitis	1 (3)
Diarrhoea	2 (5)
Renal involvement	
Renal failure	1 (3)
Renal tubular necrosis	1 (3)
Haematological and coagulation features of HLH	
Anaemia	1 (3)
Thrombocytopenia	2 (5)
Leukopenia/ White blood cell count decreased	2 (5)
Neutrophil count decreased	1 (3)
Disseminated intravascular coagulation	3 (8)
International normalised ratio abnormal	1 (3)
Pancytopenia/ Bone marrow failure	2 (5)
Concurrent irAEs	
Autoimmune hepatitis	2 (5)
Interstitial lung disease	2 (5)
Myositis	1 (3)
Thyroiditis	1 (3)
Cardiac[b]	1 (3)

Abbreviations: *HLH* haemophagocytic lymphohistiocytosis, *irAEs* immune-related adverse events

[a] Some patients reported more than one adverse drug reaction besides HLH

[b] Atrial fibrillation and left ventricular failure

DRESS

= Drug Reaction with Eosinophilia and Systemic Symptoms

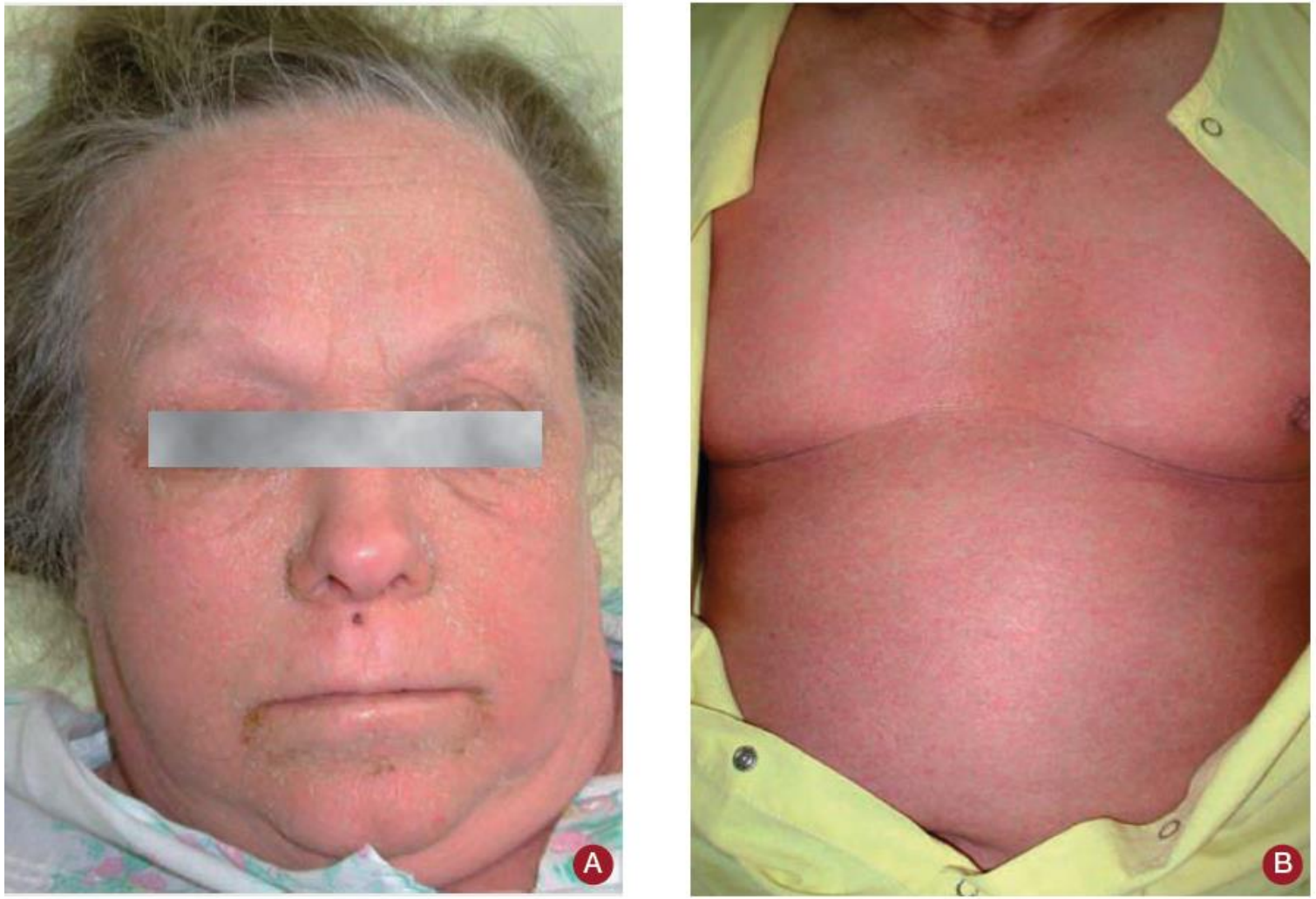


FIGURE 1 A) Œdème du visage au cours d'un DRESS à l'allopurinol.
B) Exanthème maculopapuleux au cours d'un DRESS à l'allopurinol.

Tableau clinique

= toxidermie survenant deux à six semaines après l'initiation d'une nouvelle molécule

- touche surtout les afro-antillais
- état général très altéré, contexte pseudogrippal
- rash (pas toujours) : peu spécifique, pouvant toucher plus de la moitié de la surface corporelle
- œdème de la face avec respect des muqueuses, infiltration cutanée secondaire à l'œdème
- adénopathies
- forte fièvre
- hyperéosinophilie
- lymphocytes atypiques circulants
- présence d'au moins une atteinte viscérale : hépatique (cytolyse), rénale (néphrite tubulo-interstitielle), pulmonaire (pneumopathie interstitielle à éosinophiles), cardiaque, pancréatique, thyroïdienne, cérébrale (méningo-encéphalite), état de choc non septique, syndrome d'activation macrophagique

TABLEAU 2

Principaux médicaments imputables au DRESS

Anticonvulsivants
- *Phénobarbital*
- *Carbamazépine*
- *Valproate de sodium*

Allopurinol

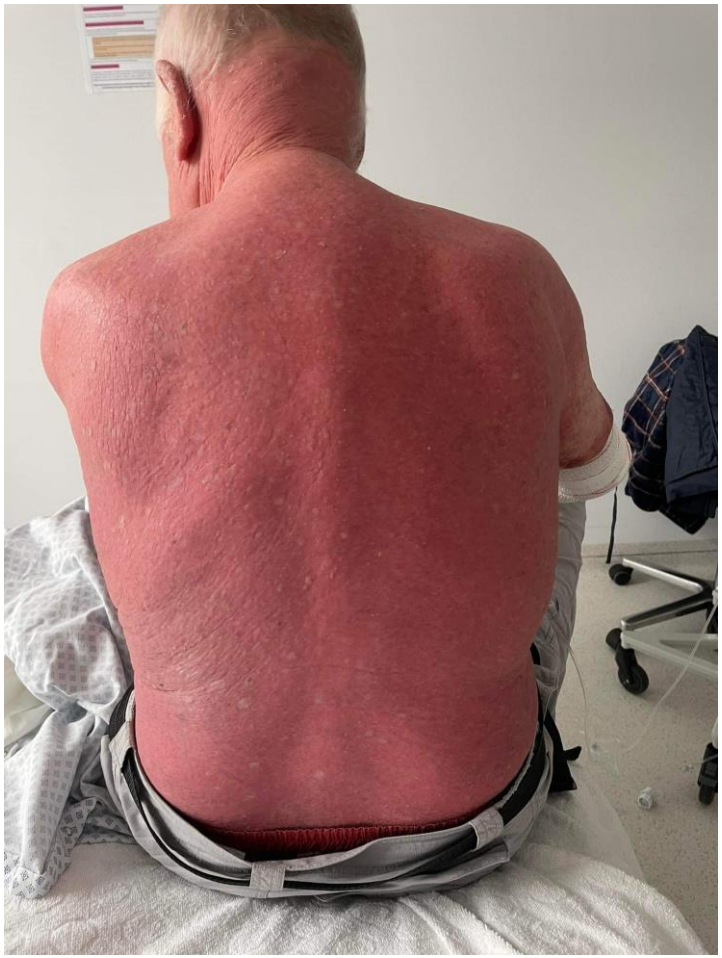
Minocycline

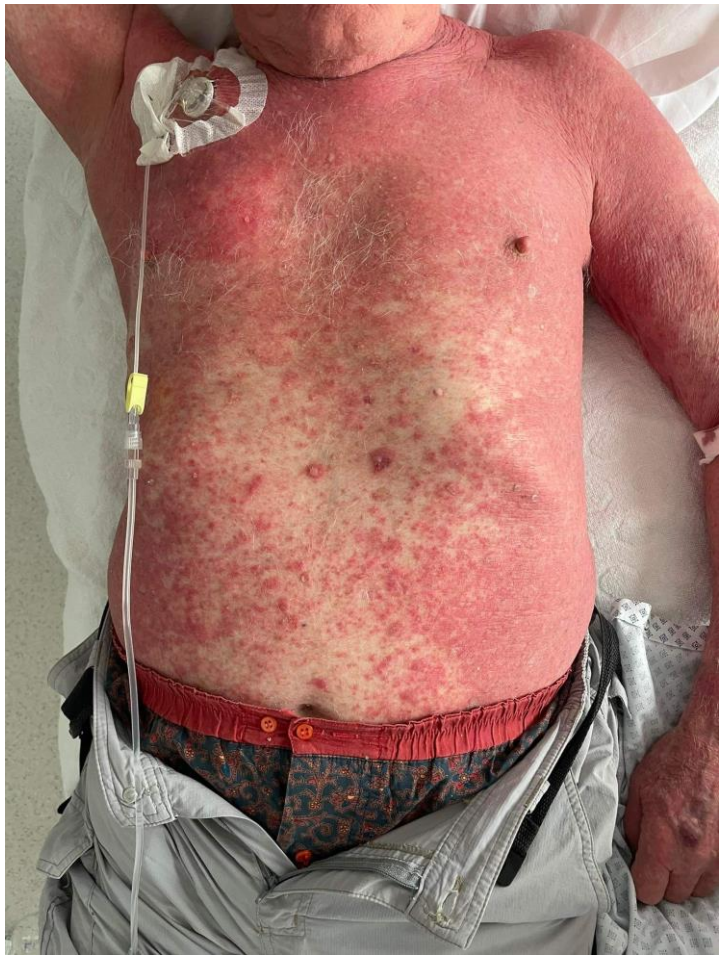
Sulfamides
- *Sulfasalazine*
- *Adiazine*
- *Disulone*

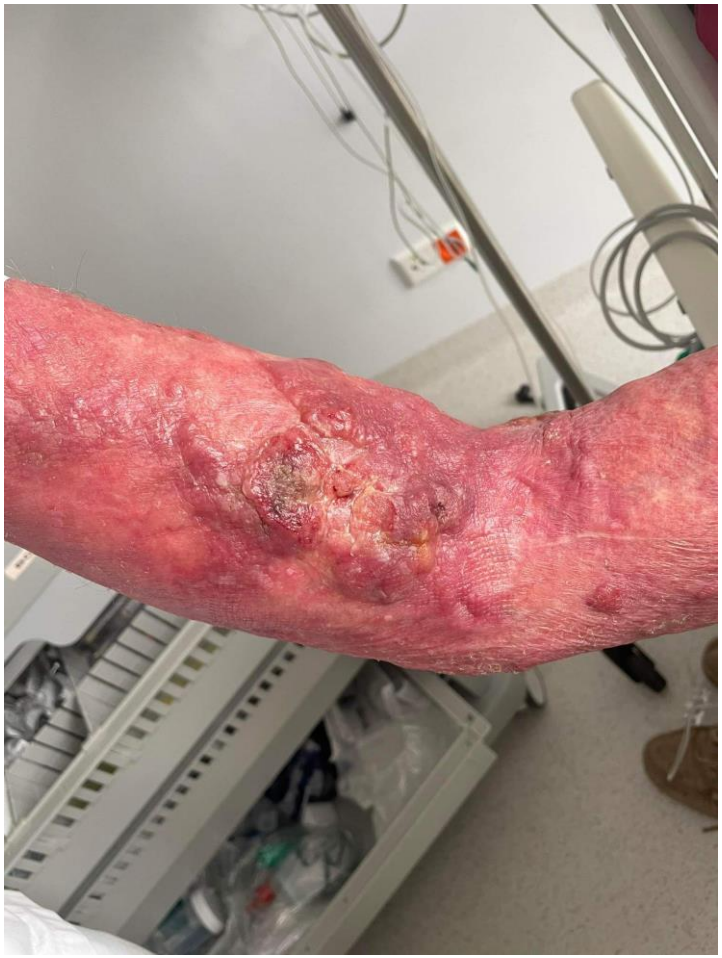
Ranélate de strontium

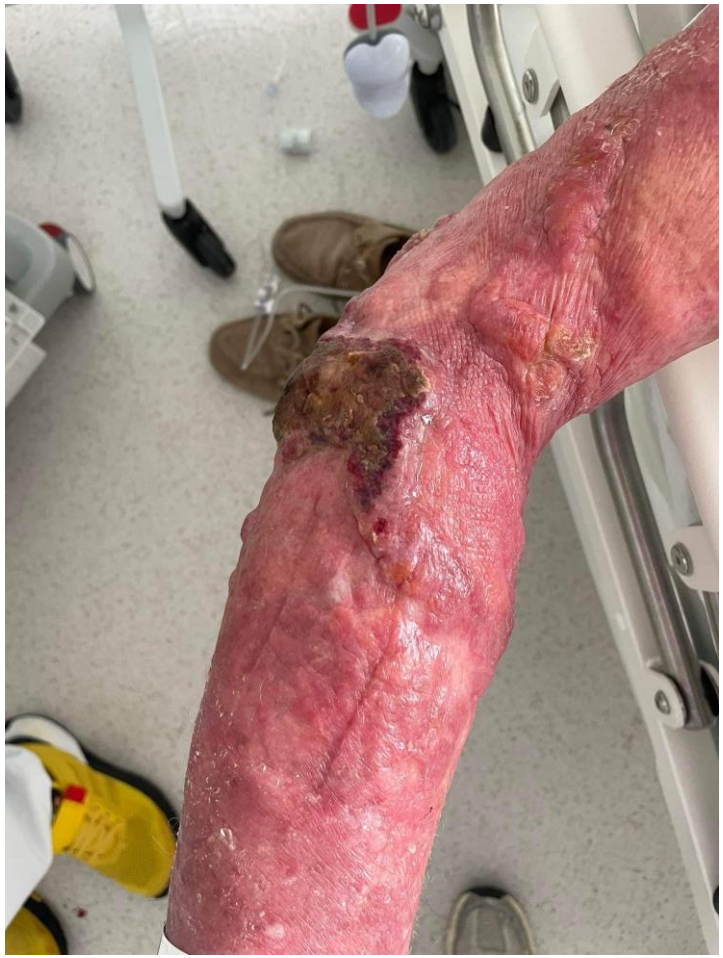
Abacavir

DRESS au Brentuximab (anti-CD30)









DRESS

Biologie

- hyperéosinophilie
- syndrome mononucléosique
- PCR HHV6 (le syndrome surviendrait grâce à une réactivation virale d'un virus du groupe herpétique)

Traitement

- dermocorticoïdes puissants
- dans les formes menaçantes : corticothérapie par voie générale, voire étoposide, IgG

Évolution

- dure au moins deux semaines
- peut s'étaler par vagues sur un an

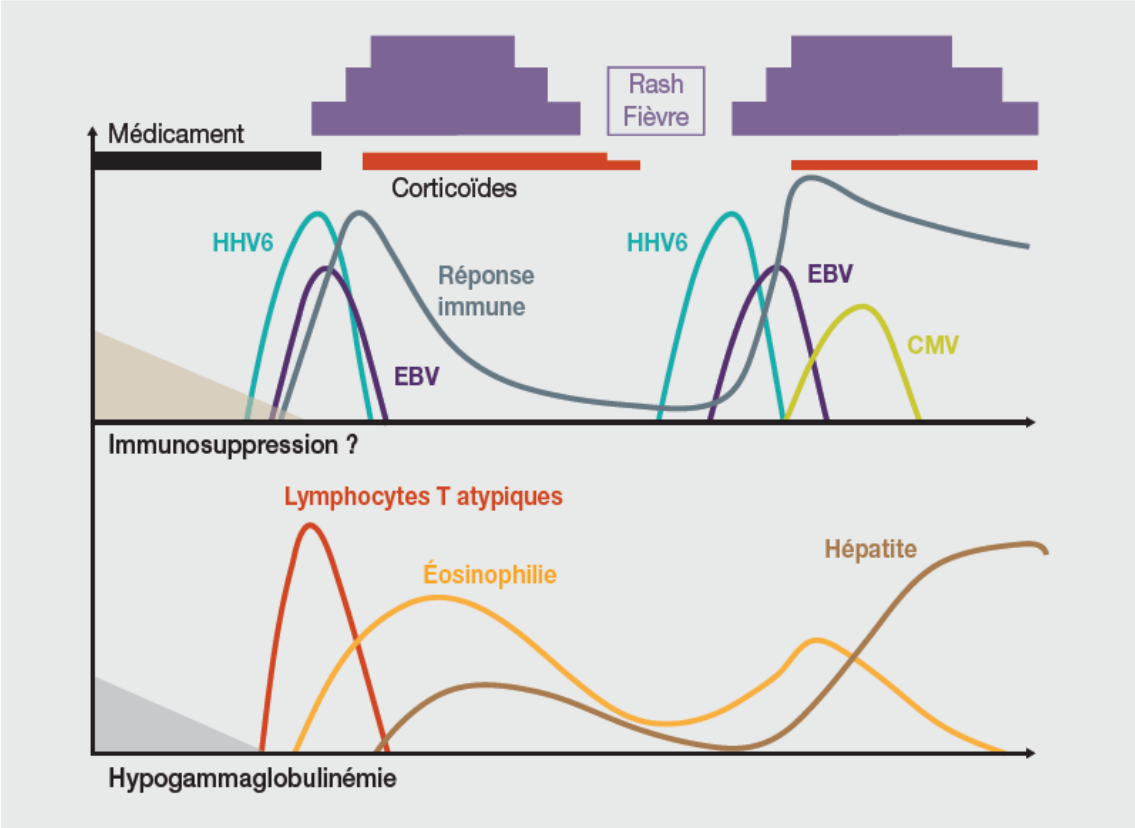


FIGURE 2 Représentation schématique de l'histoire naturelle du DRESS comme conséquence de réactivations séquentielles virales et de la réponse immune antivirale. D'après la réf. 3. CMV : cytomégalovirus ; EBV : virus d'Epstein-Barr ; HHV-6 : *Human Herpesvirus* 6.