DISFUNCTIA IMUNITARA A PACIENTULUI CRITIC. RISCUL INFECTIOS LA PACIENTUL CRITIC

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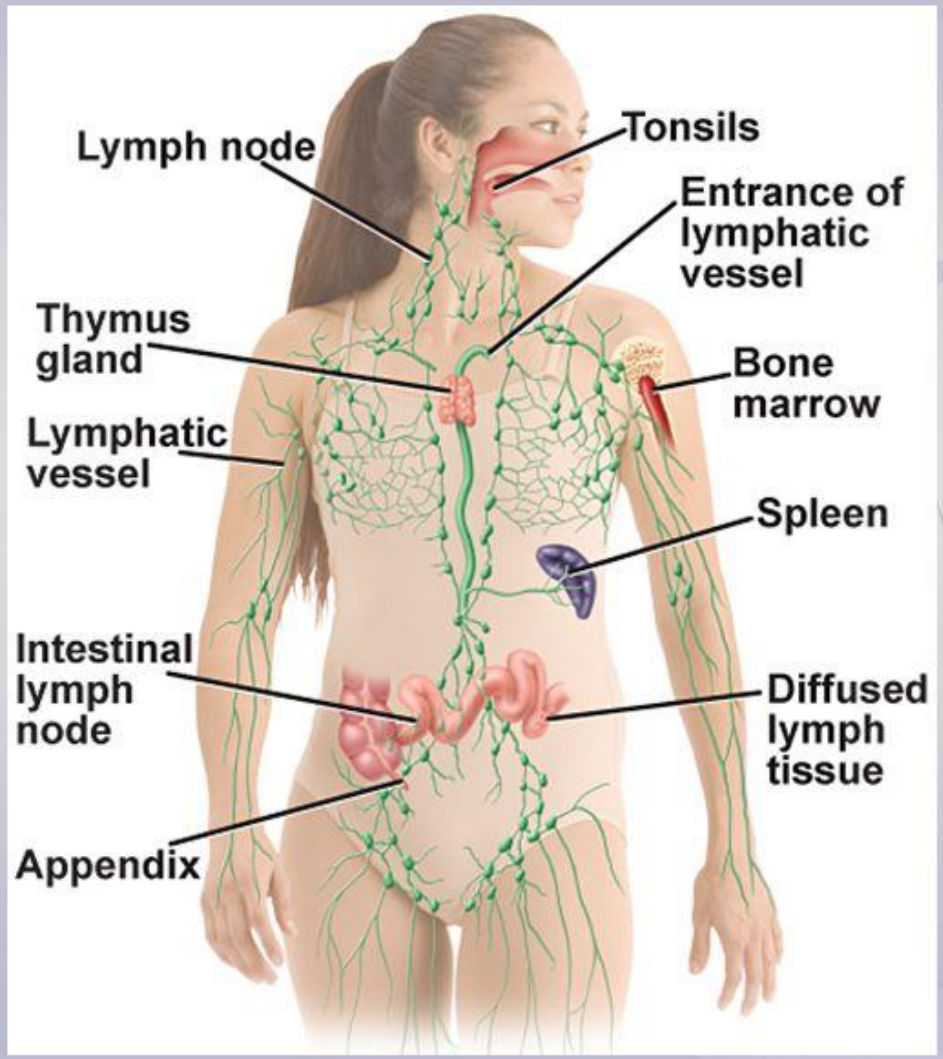
Human Immune System



- Lymphatic system – network of vessels that collects, filters, and returns plasma that leaks from the bloodstream.
- Organs and cells that filter lymph and blood and destroy foreign microorganisms

IMUNITATE

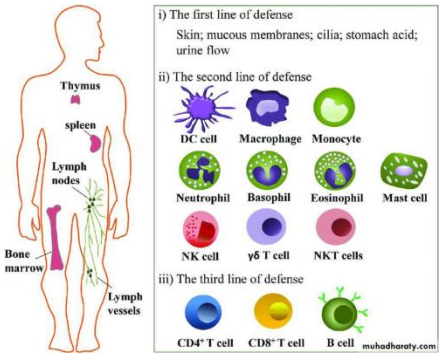
modalitatea prin care organismele multicelulare rezista atacurilor microorganismelor invadatoare

Imunitate innascuta

- Prima linie de aparare antimicrobiana
- Activata la cateva ore de la “intalnirea” cu patogenii
- Celulele imunitatii inascute
  - **Neutrofile**
  - **Macrofage/monocite**
  - **Celule dendritice**
- Factorii complement

Imunitate dobandita (adaptativa)

- **Limfocitele B si T-** pot elimina …tinte
- Activat la 2-4 zile dupa intalnirea cu patogenii
- Acest raspuns- **MEMORIE IMUNITARA** - activat rapid la o noua intalnire cu acelasi patogen



Declansarea raspunsului imunitar si hiperinflamatia

- Faza precoce de recunoastere microbiana de sistemul imunitar
- Patogenul prezinta structuri moleculare(PAMS, DAMPs)- recunoscute de receptorii PRR (pathogen recognition receptors- TLR si NLR) care activeaza sistemul imunitar
- Dupa recunoasterea patogenului, sistemul imunitar declanseaza o cascada de fenomene inflamatorii pentru eradicarea patogenului
  - Eliberare de diferiti mediatori ai reactiei inflamatorii
  - Activarea macrofagelor si a celulelor fagocitice
  - Activarea limfocitelor T si B

Reglarea neuroendocrinea a raspunsului imunitar

- Semnalele periferice(aferente nervoase si mediatori solubili)
- Reglarea imunitatii prin intermediul axului hipotalamo hipofizar si sistemul nervos vegetativ
- Mediatorii cresc productia de CRH in hipotalamus – productie de acetilcolina- stimuleaza productia de glucocorticoizi in SR
- Activarea SN parasimpatic(n vag)- declanseaza productia de Ach de limfocitele din splina
- Ach inhiba productia de citokine proinflamatorii a macrofagelor

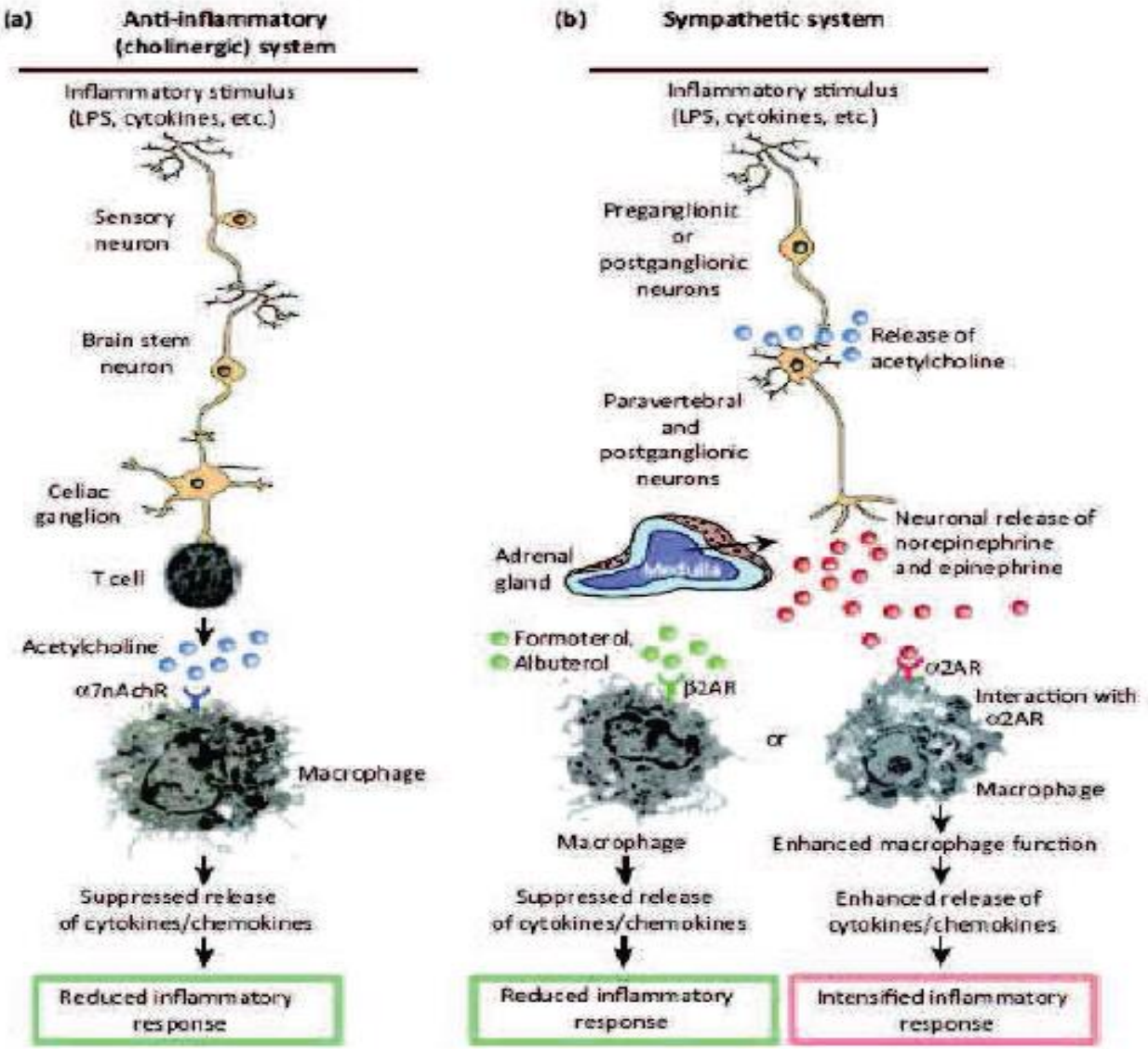
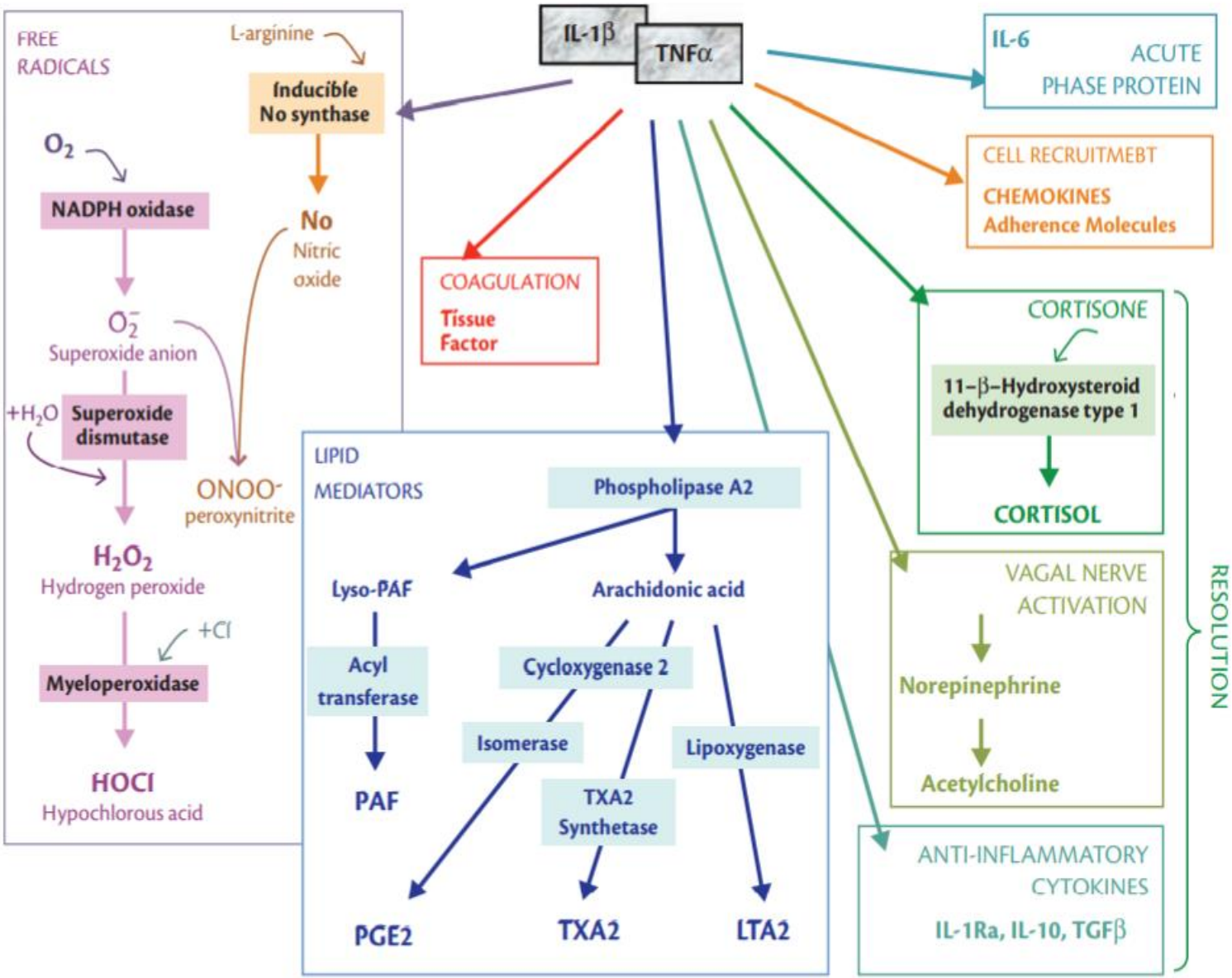


Figure 8 Rôles des systèmes sympahtique et parasympathique dans les syndromes septiques, d'après Bosmann et Ward, Trends in Immunology, 2013



99.1 Interleukin-1 (IL-1) and tumour necrosis factor (TNF) orchestrate a cascade of inflammatory events.

SEPSIS

disfunctie de organe, amenintatoare de viata, consecutiva unui raspuns inadecvat al gazdei la o infectie

- **Socul septic-** hipotensiune arteriala, cu hiperlactatemie si necesar de suport vasopressor
- Prima cauza de mortalitate in reanimare
- In ultimii ani, decesele precoce(primele 2 saptamani) datorate socului hemoragic au diminuat
- Au crescut decesele tardive, la cateva saptamani dupa episodul acut, iar cauza majora este dereglarea majora a proceselor imunitare innascute si adaptative
- Aceasta dereglare antreneaza o imunosupresie pe termen lung, cu complicatii infectioase iterative
  - Asociata cu o stare inflamatorie si catabolica, numita PICS
  - **PICS- persistent inflammation, immunosuppression and catabolism syndrome**
  - Sepsis-ul nu mai este considerat un sindrom de hiperinflamatie aberanta, ci mai degraba **un sindrom de imunitate protectoare aberanta**!

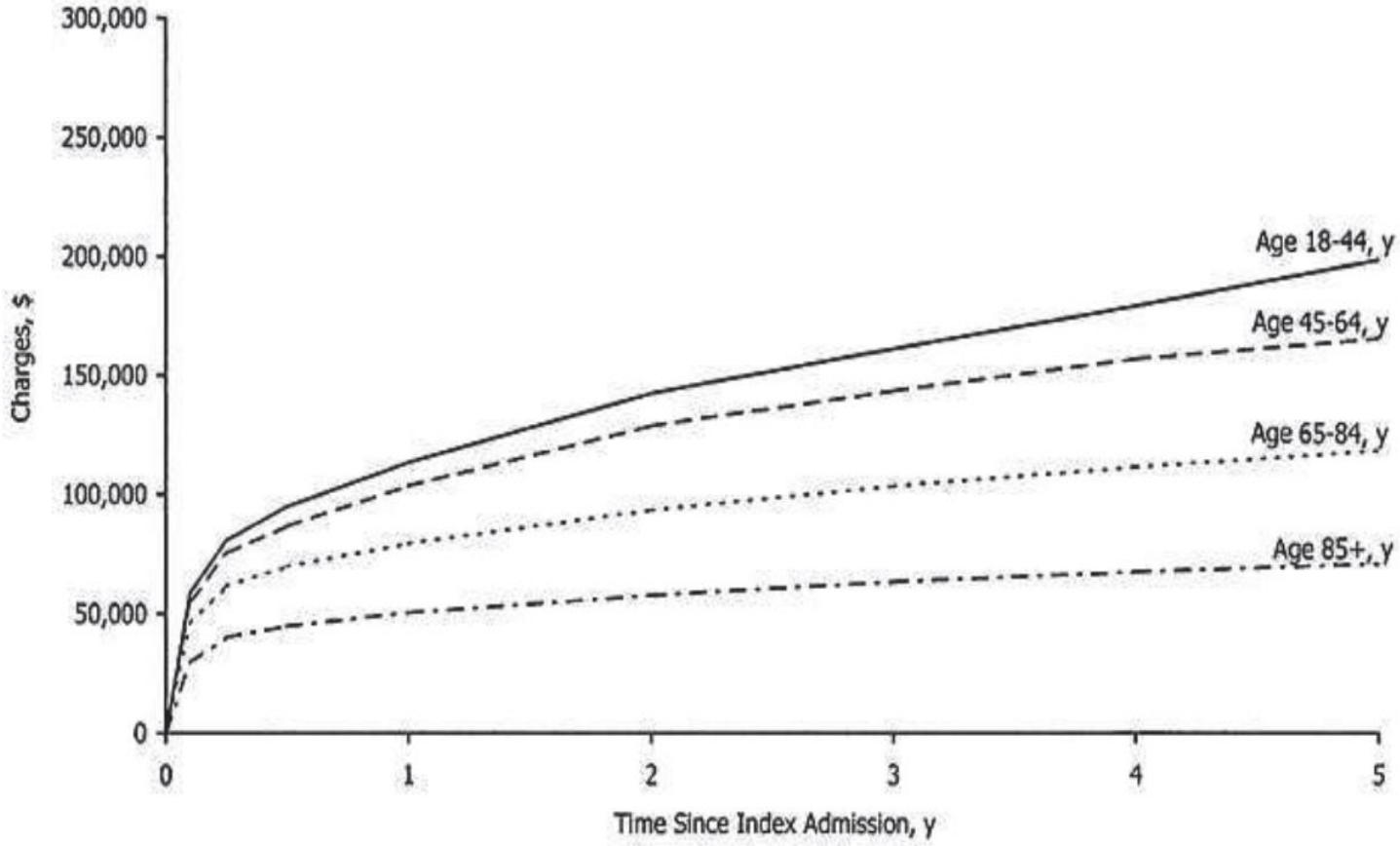


Figure 3 Coûts associés aux syndromes septiques durant les 5 années suivant l'épisode, en fonction de l'âge au moment de l'épisode, d'après Tiru *et al.*, Pharmaco Economics, 2015 [12]

Sindrom de disfunctie organica multipla

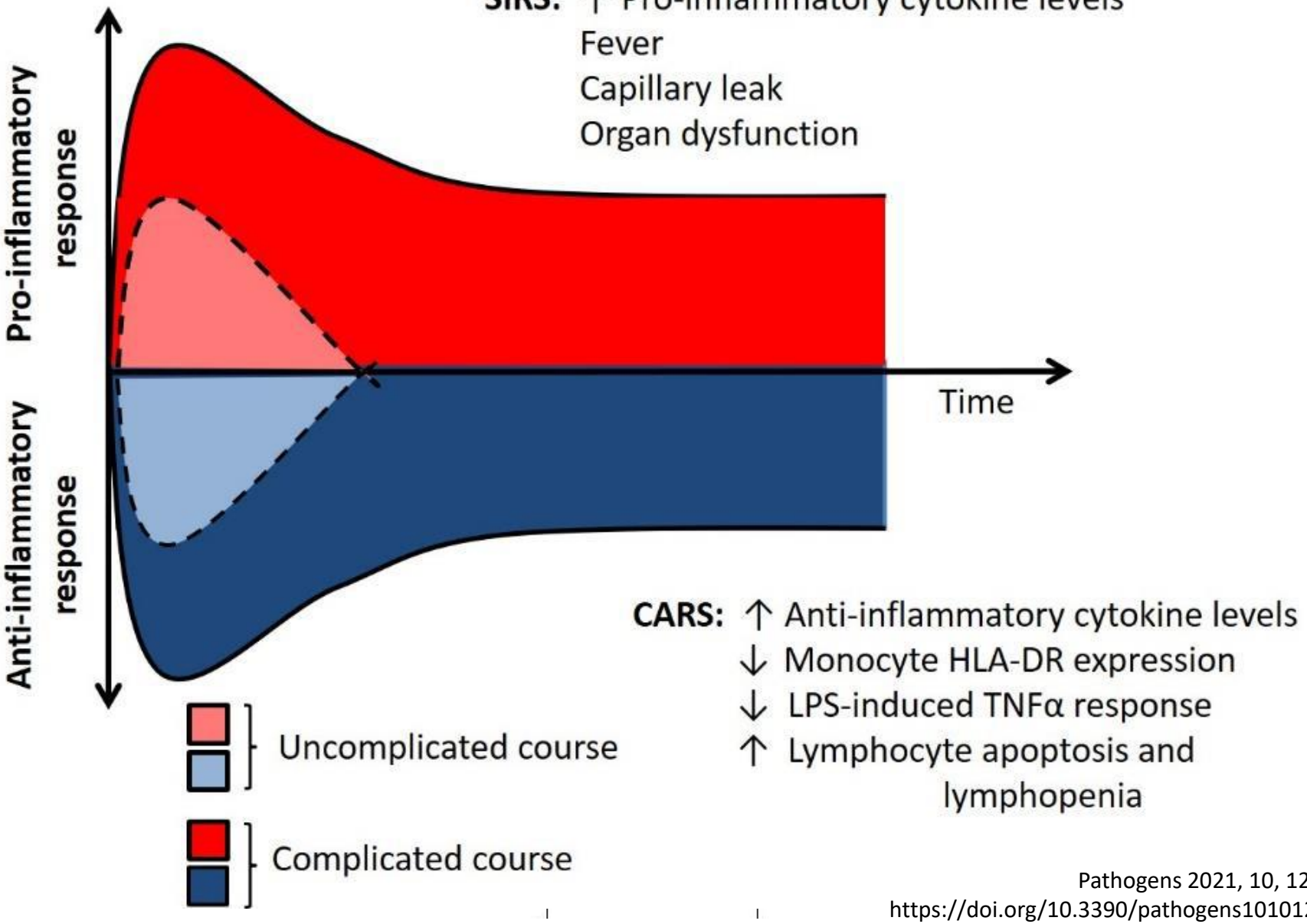
- Activarea sistemului coagularii-
  - Local- microtromboze care limiteaza extinderea focarului infectios
  - Citokinele proinflamatorii activeaza coagularea la nivel sistemic
  - Contribuie la vasodilatatia din socul septic
  - Hipoxia celulara altereaza metabolismele intermediare- elibereaza DAMPs- amplifica recrutarea celulelor imunitare si agraveaza fenomenele hiperinflamatorii
- Sistemul complementului- prin activare moduleaza recrutarea leucocitelor, raspunsul imunitar si secretia de citokine

IMUNODEPRESIE

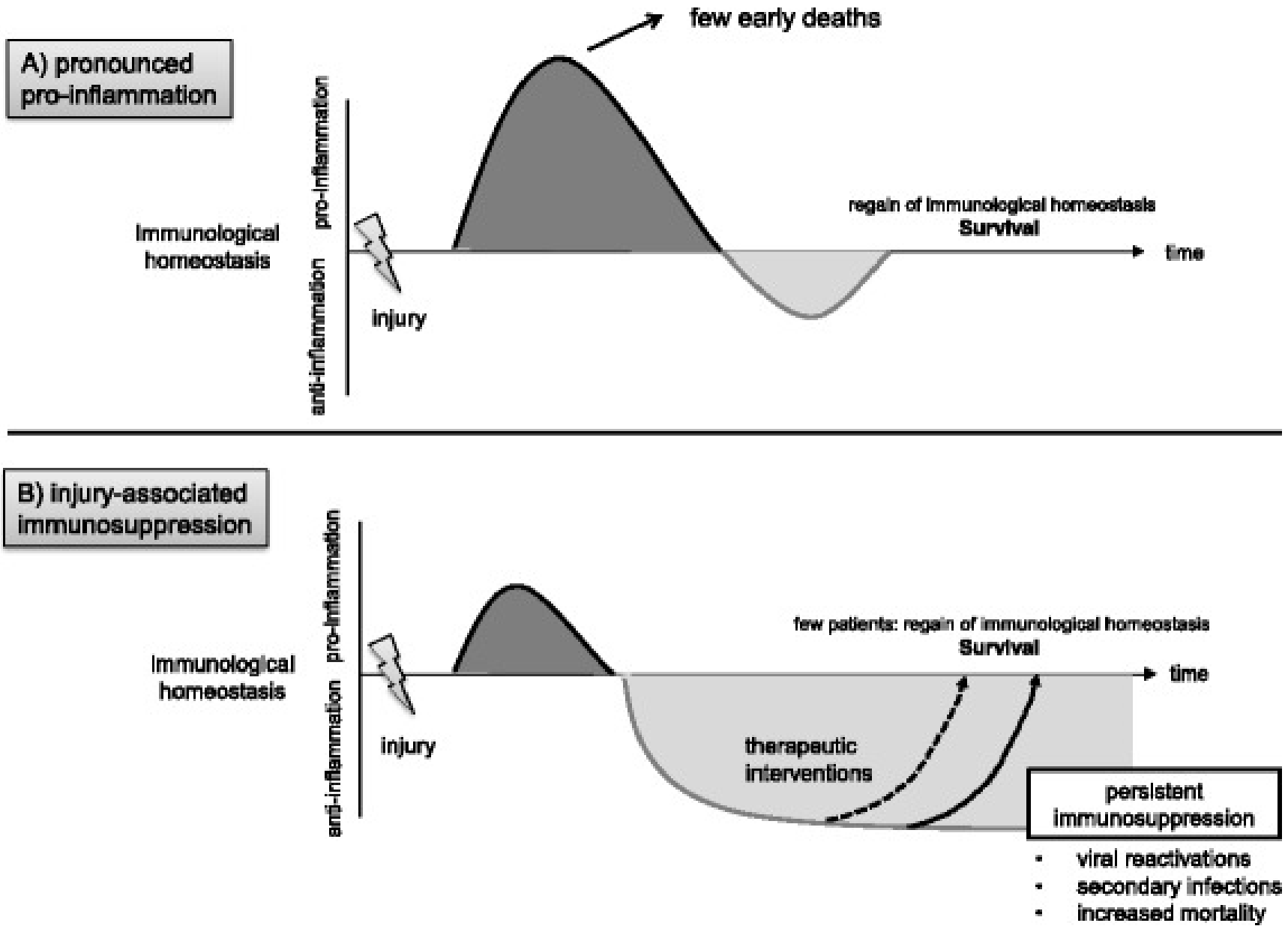
- Raspunsul global al gazdei este rezultanta raspunsurilor proinflamatorii si anti inflamatoare, declansate de maniera simultana
- Raspunsul proinflamator
  - secretie masiva de citokine proinflamatorii
  - Activare importanta a celulelor imunitare inascute
  - Consecinte- acidoza, hipercatabolism, disfunctii de organe, soc

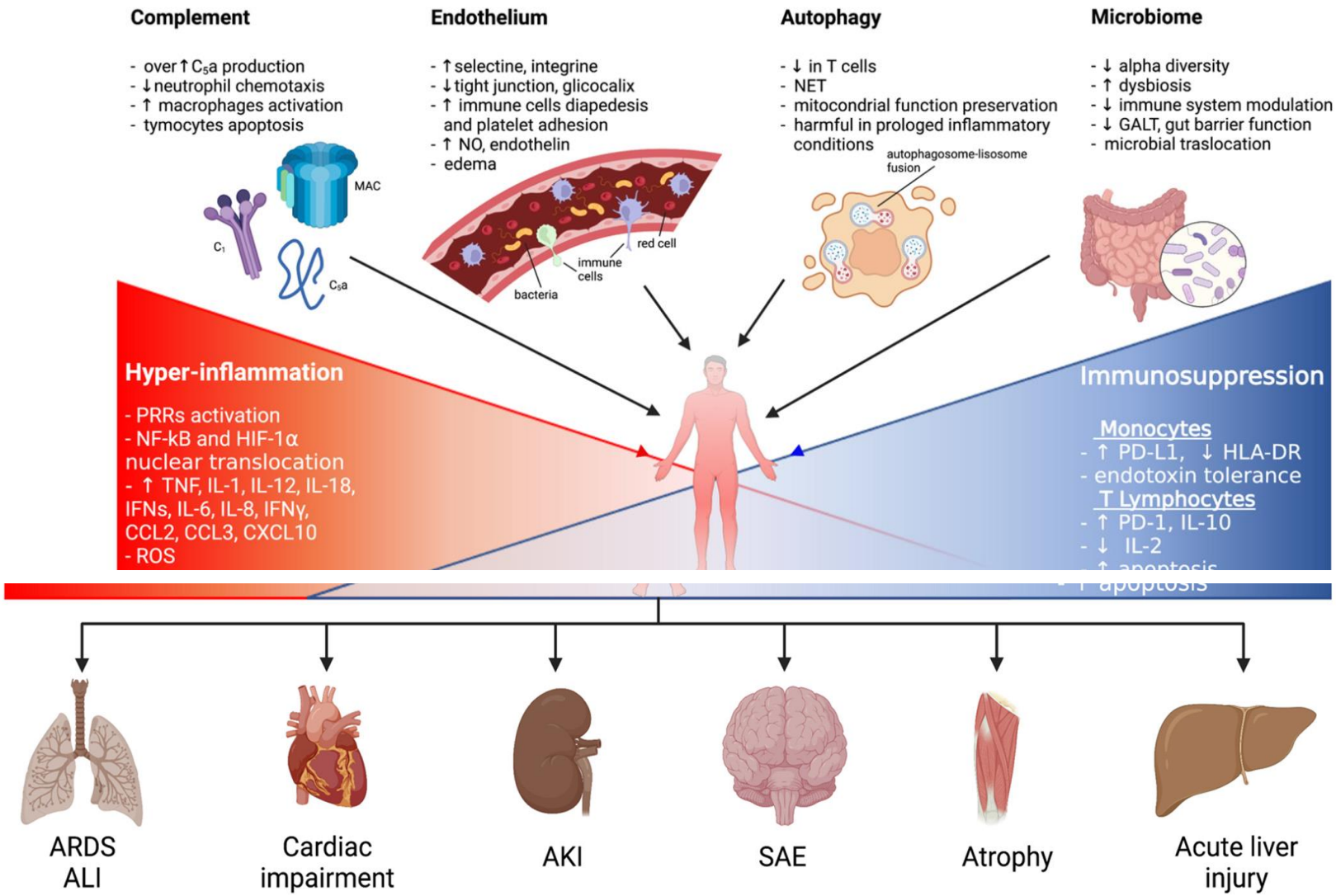
IMUNODEPRESIE

- Raspunsul anti inflamator
  - Alterari ale celulelor imunitatii innascute dar si adaptative
  - Apoptoza, alterari functionale, modificari fenotipice
  - Consecinte: incapacitatea de a controla infectia initial si/sau a celor secundare
  - Creste riscul de deces prin incapacitatea restabilirii homeostaziei sistemului imunitar



Pathogens 2021, 10, 1239.
https://doi.org/10.3390/pathogens10101239


A) pronounced pro-inflammation
few early deaths
pro-inflammation
Immunological homeostasis
anti-inflammation
injury
regain of immunological homeostasis
Survival
time
B) injury-associated immunosuppression
pro-inflammation
Immunological homeostasis
anti-inflammation
injury
few patients: regain of immunological homeostasis
Survival
time
therapeutic interventions
persistent immunosuppression
viral reactivations
secondary infections
increased mortality



Int. J. Mol. Sci. 2022, 23, 803. https://doi.org/10.3390/ijms23020803
https://www.mdpi.com/journal/ijms

Disfunctia monocitara si alterarea raspunsului imun innascut

- 3 functii principale:
  - Fagocitoza microorganismelor patogene
  - Prezentarea antigenelor catre limfocitele T
  - Productia de citokine
- In sindroamele septice- monocitele- alterari fenotipice si functionale

Alterari care vizeaza alte componente ale rasounsului imun innascut

- PMN neutrofile- fagocitoza, mareste expresia markerilor de activare
  - Rol important in faza initiala
  - Mai putin cunoscut in faza de imunosupresie
- Celulele dendritice
  - modificari similare monocitelor
  - Participa la raspunsul imunsupresor

Alterarea raspunsului imun adaptativ

- Limfocite T
  - LT CD4- auxiliare-
  - LT CD8- citotoxice
  - **Apoptoza masiva si limfopenie- durata si amploarea- asociate cu gravitatea sindromului septic si rata de supravietuire**

Microbiomul uman si mecanismele de aparare ale gazdei

(A. Roquilly, E. Montassier, 2021)

- Microbiomul are un rol major in mentinerea homeostaziei
- Biomasa de microbiom creste pe durata spitalizarii, dar diversitatea sa diminua inainte de aparitia unor infectii dobandite in spital
- Studii la pacienti spitalizati, considerati “imunocompetenti” au demonstrat alterari profunde de functie ale celulelor imunitare- stare numita **“ imunosupresie legata de alterarea microbiomului”**
- **Pentru prevenirea si tratamentul infectiilor, tinta ar trebui sa fie normalizarea diversitatii microbiomului, mai degraba decat sterilizarea tubului digestiv sau a cailor aeriene**

Microbiomul uman- perspective terapeutice

(A. Roquilly, E. Montassier, 2021)

- Microbiomul uman ar putea furniza biomarkeri diagnostici si prognostici pentru anumite patologii, dar si predictia raspunsului la tratamentul dat
- Microbiota ar putea fi “modulata” sa restabileasca o microbiota intestinala care sa “favorizeze insanatosirea”
- Probiotice/prebiotice de noua generatie
- Aplicate in reanimare aceste terapii ar putea ameliora prognosticul pacientilor spitalizati prin restabilirea microbiotei normale

Disfunctia imunitara indusa de ventilatia mecanica

(JM Tadier et al, 2013)

- Ventilatia mecanica- salvatoare de viata!
- Fortele mecanice generate- stimuleaza structurile pulmonare, celulele immune pulmonare- declanseaza un semnal biologic, declanseaza o reactie inflamatorie
- “inflamatie sterila”- declanseaza reactie inflamatorie locala, apoi sistemica, disfunctie organica multipla- **biotrauma**

Disfunctia imunitara indusa de ventilatia mecanica

(JM Tadier et al, 2013)

- Consecinte clinice:
  - Reducerea volumelor tidal de ventilatie mecanica – aprox 6 ml/kg greutate ideala- reduce reactia inflamatorie locala
  - Imunodepresia amplificata- creste risc de infectii nosocomiale, inclusiv de activare virala
  - Leziunile induse antreneaza translocare bacteriana plaman- sange- diminua raspunsul inflamator dupa o noua expunere la bacterii

Disfunctia imunitara indusa de ventilatia mecanica

(JM Tadier et al, 2013)

- Este dovedit ca la om VM poate induce rapid imunodepresie, chiar aplicata durate scurte de timp
- Strategii preventive si terapeutice
  - Scurtarea duratei VM
  - Decubit ventral
  - Utilizarea curarelor
  - Recrutarea alveolara
  - Diminuarea Vt si a presiunilor maxime in inspir
  - ECMO- si tehnicile de epurare extracorporeala a gazelor sanguine induc un grad de imunosupresie

NORADRENALINA
rol in disfunctia imuna la pacientul critic septic

(Bauer – Dorries, Rev Med Suisse, 2017)

- Vasopresor de electie la pacientul critic
- **Agonist al receptorilor adrenergici alfa 1 arteriali si venosi**
- Agonist beta 1
- STIMULAREA ADRENERGICA PRELUNGITA CONTRIBUIE LA DISFUNCTIA DE ORGANE
- La cresterea dozei – agonist receptori beta 2 (exprimati de celulele imune!)
  - Efecte metabolice
  - Efecte imunologice- pot contribui la disfunctia imunologica din sepsis, respectiv la imunosupresia din socul septic
- **Efecte asupra multiplicarii bacteriene si virulentei, independent de receptorii adrenergici-** stimuland transportul ionului de fier si mimand actiunea unui auto inductor microbian implicat in quorum sensing

Agent vasopressor	Doza initiala	Doza de mentinere	Dozele maxime in socul refractar	Rol in terapia
noradrenalina	5-15 mcg/kg/min In socul cardiogenic 0.05 mcg/kg/min	2- 80 mcg/min 0.025- 1 mcg/kg/min Socul cardiogenic – 0.05- 0.4 mcg/kg/min	80- 250 mcg/min (1-3.3 mcg/kg/min)	Vasopresor initial de elective in socul septic, cardiogenic, hipovolemic Varietate larga de doze utilizate in clinica Trebuie diluata, initial 4mg in 250 ml G5% in apa sau Solutie salina(16 mcg/ml)

NORADRENALINA
rol in disfunctia imuna la pacientul critic septic

(Bauer – Dorries, Rev Med Suisse, 2017)

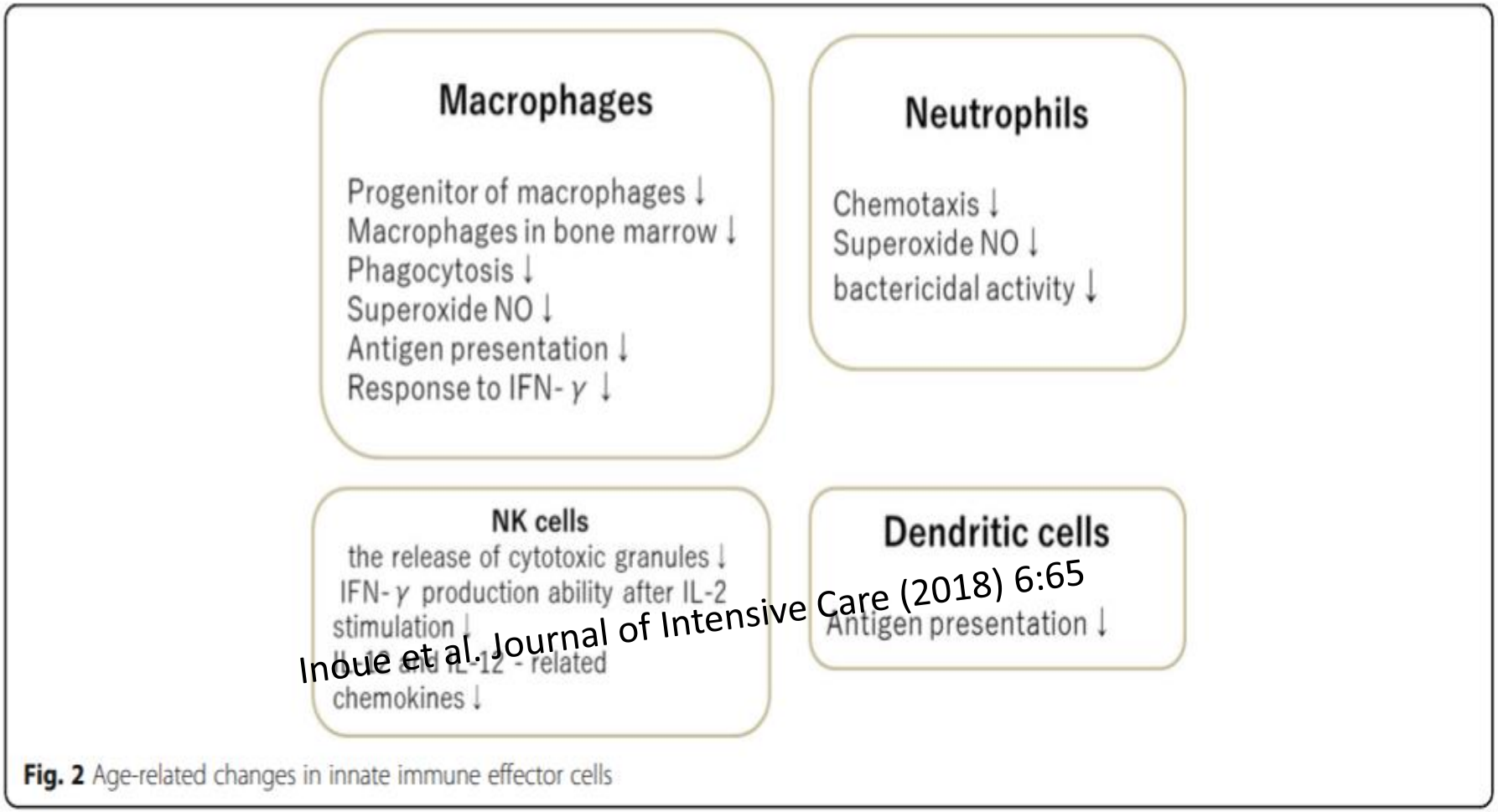
Concluzia:

Medicul intensivist va recurge la catecolamine doar in situatii critice, cu limitarea dozei la minimum necesar si pe periada de timp cea mai scurta posibil~

CONCLUZII

- Disfunctia imunitara a pacientului critic incepe din momentul agresiunii, sterile sau infectioase
- Are rol major in aparitia complicatiilor septice si cresterea morbiditatii si mortalitatii
- Biomarkeri sunt validati sau in curs de validare pentru diagnostic, monitorizare, stratificarea riscului si a prognosticului
- Adaptarea suportului de functii vitale
- **PRIMUM NON NOCERE**!

Modificari induse de varsta la nivelul celulelor imune efectoare



Inoue et al. Journal of Intensive Care (2018) 6:65

Fig. 2 Age-related changes in innate immune effector cells

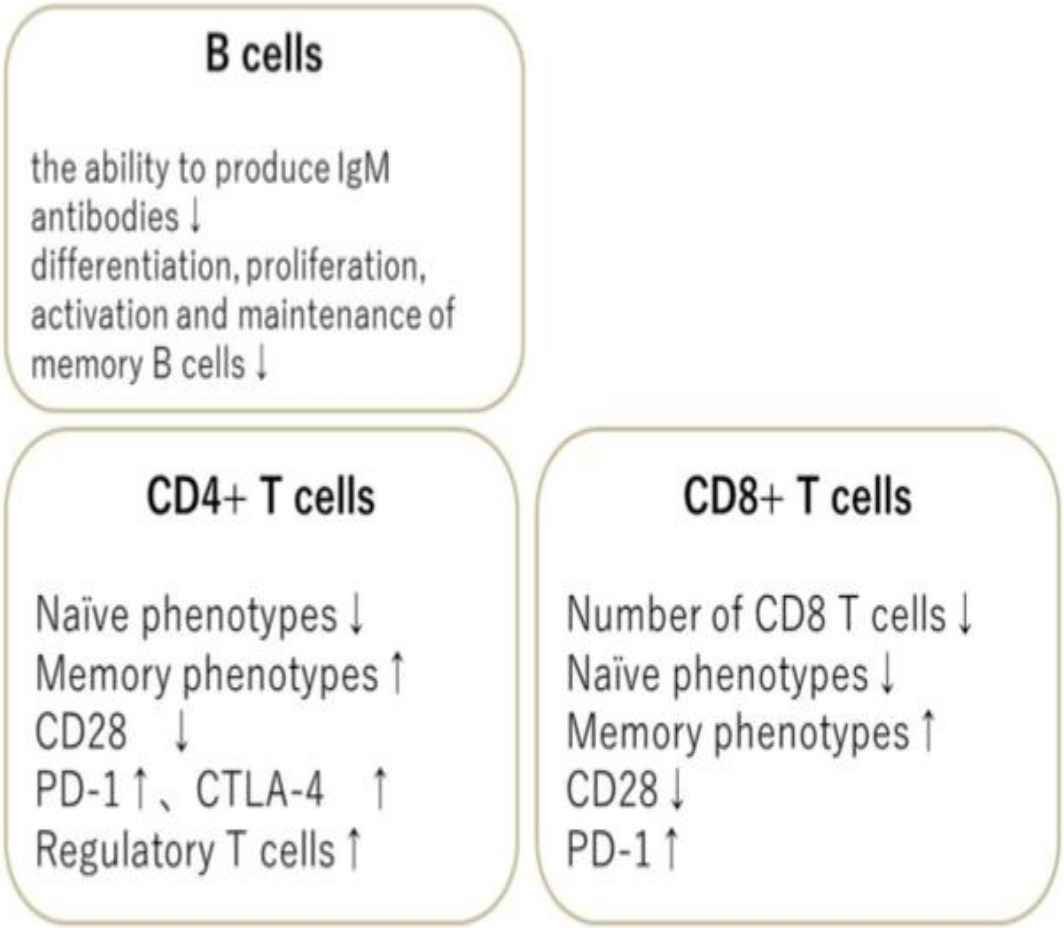


Fig. 3 Age-related changes in adaptive immune effector cells

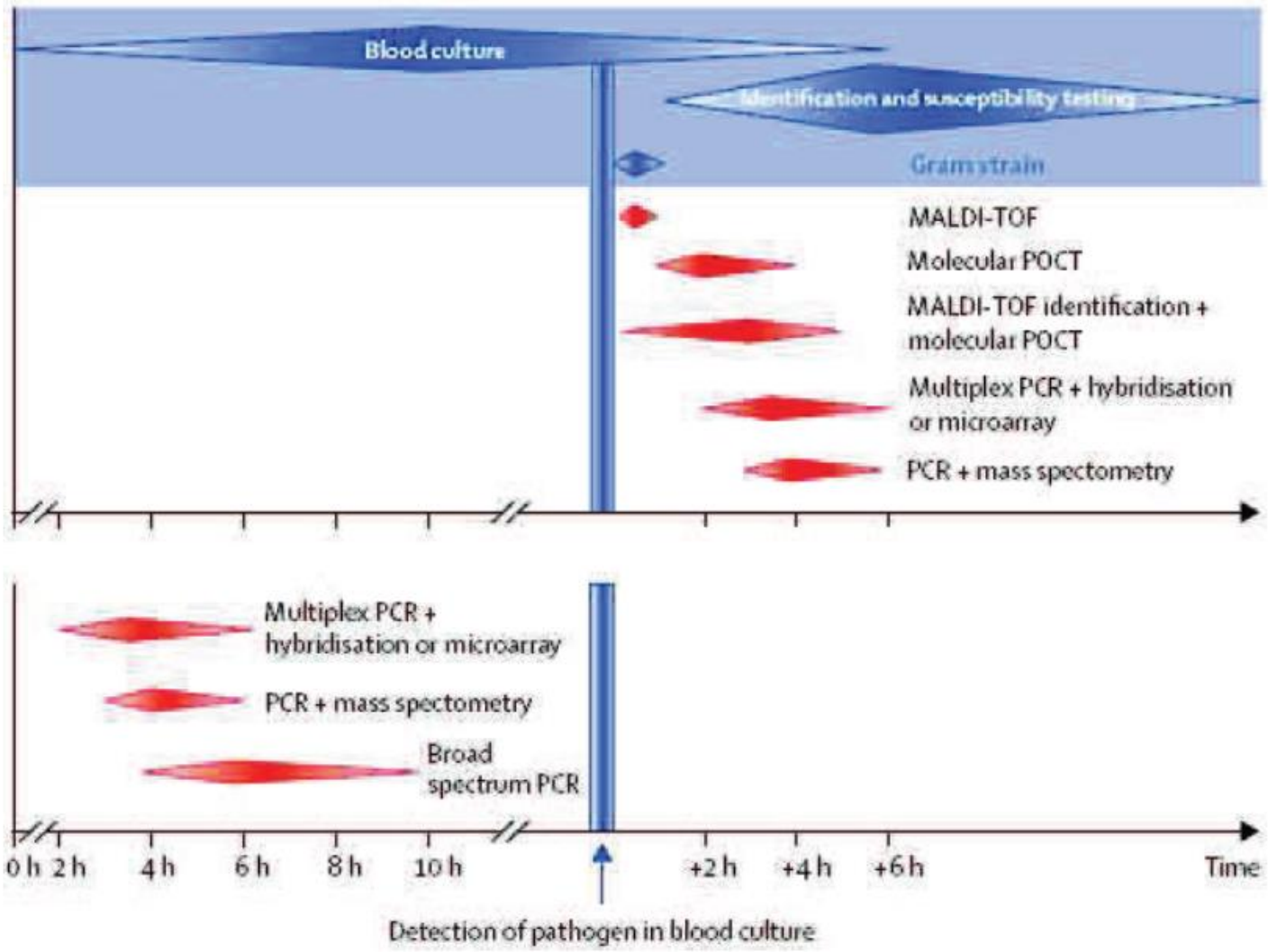


Figure 4 Diminution du temps avant résultat des tests de diagnostic microbiologique grâce à l'utilisation de nouvelles techniques, d'après Cohen *et al.*, The Lancet, 2015

Sepsis biomarker	Clinical study	Type of measurement	Outcome
aPTT**	C	c	High negative predictive value
CD11b***	B	s	Higher values in neonates with sepsis than in those with possible infection
CD25	A	s	Distinguished between sepsis and SIRS
CD64***	C	s	Low sensitivity and specificity to distinguish between viral and bacterial infections
Complement	B	s	Distinguished between sepsis and SIRS
EA complex	C	s	Diagnosis of sepsis, increased earlier than CRP
ELAM-1 (cellular and soluble)	C(s)	c	Increased in trauma patients with sepsis compared with no sepsis
Endocan	B	s	Distinguished between sepsis and SIRS
E-Selectin (cellular and soluble)	B	s	Distinguished between sepsis and SIRS
Fibrin degradation products	B	s	High negative predictive value
G-CSF	C	s	Distinguished between sepsis and SIRS
Gelsolin	B(s)	c	Higher in septic patients compared with patients without sepsis
IL-1 receptor antagonist	C	s	Early diagnosis of sepsis before symptoms in newborns
IL-8*	C	s	Higher in septic neutropenic patients compared with febril neutropenic patients without sepsis
IL-10	A	s	Higher in septic shock compared with cardiogenic shock
IL-12***	C	s	Diagnosis of sepsis in pediatric patients
IL-18	B(s)	s	Distinguished between Gram-positive and Gram-negative sepsis. Higher in trauma patients with sepsis than in those without
IP-10***	C	s	Early diagnosis of sepsis in newborns
Laminin	A	s	Distinguished between Candida sepsis and bacterial sepsis
LBP	C	s	Distinguished between Gram-positive sepsis and Gram-negative
MCP-1	C	s	Distinguished between sepsis and SIRS in neutropenic pediatric patients
NO, nitrate, nitrite	B	s	Higher in septic shock compared with cardiogenic shock
Osteopontin	B	s	Distinguished between sepsis and SIRS
PAI-1	B	s	Higher in patients with sepsis and DIC compared with no-septic patients with DIC
Pentraxin 3	C	s	Distinguished between septic shock and SIRS
Peptidoglycan	B(s)	c	Higher in postoperative patients with infection compared with no-infected postoperative patients