JEDI

1ère

Journée Endocrinologie,

Diabétologie et Infectiologie

Cortisol & infection

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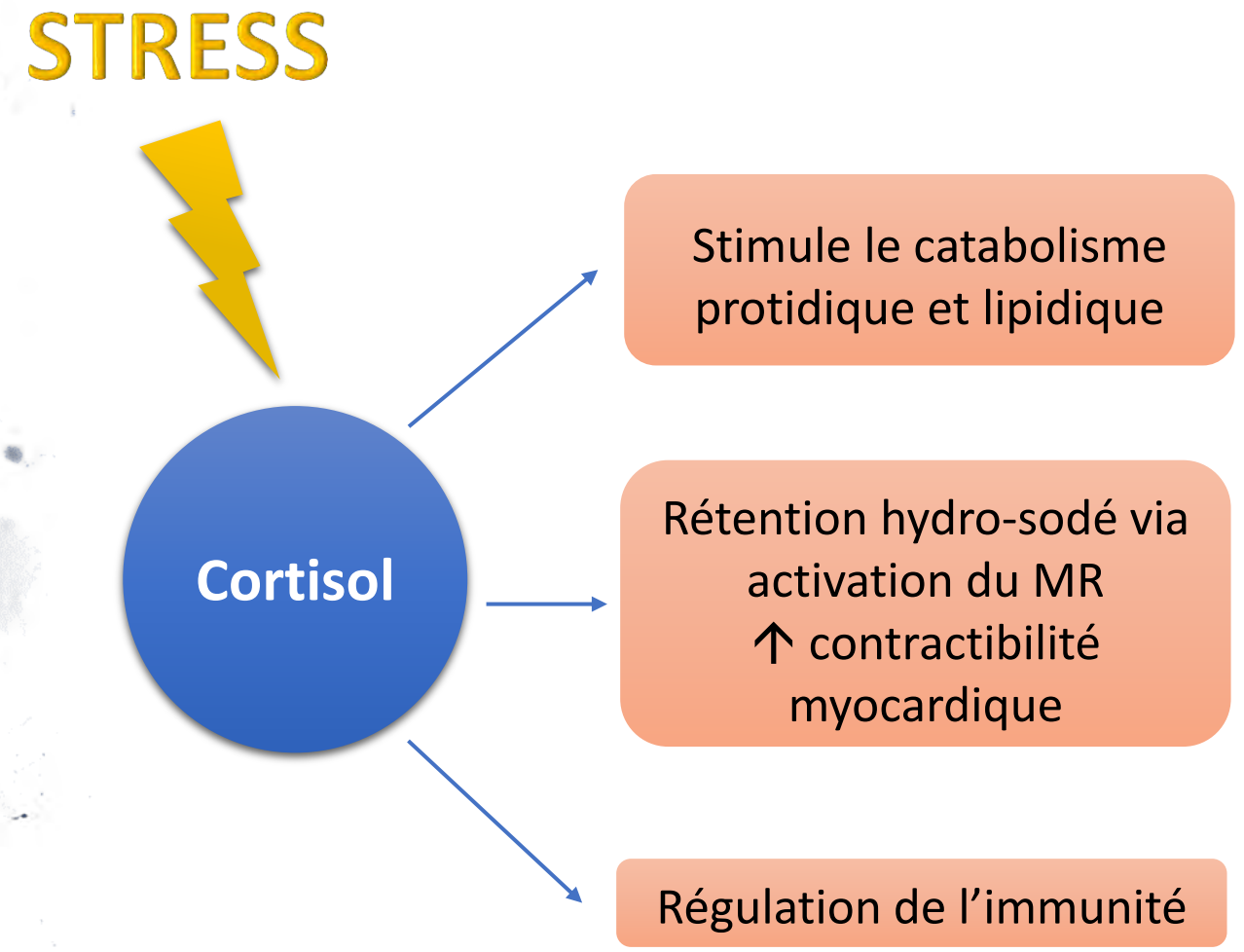
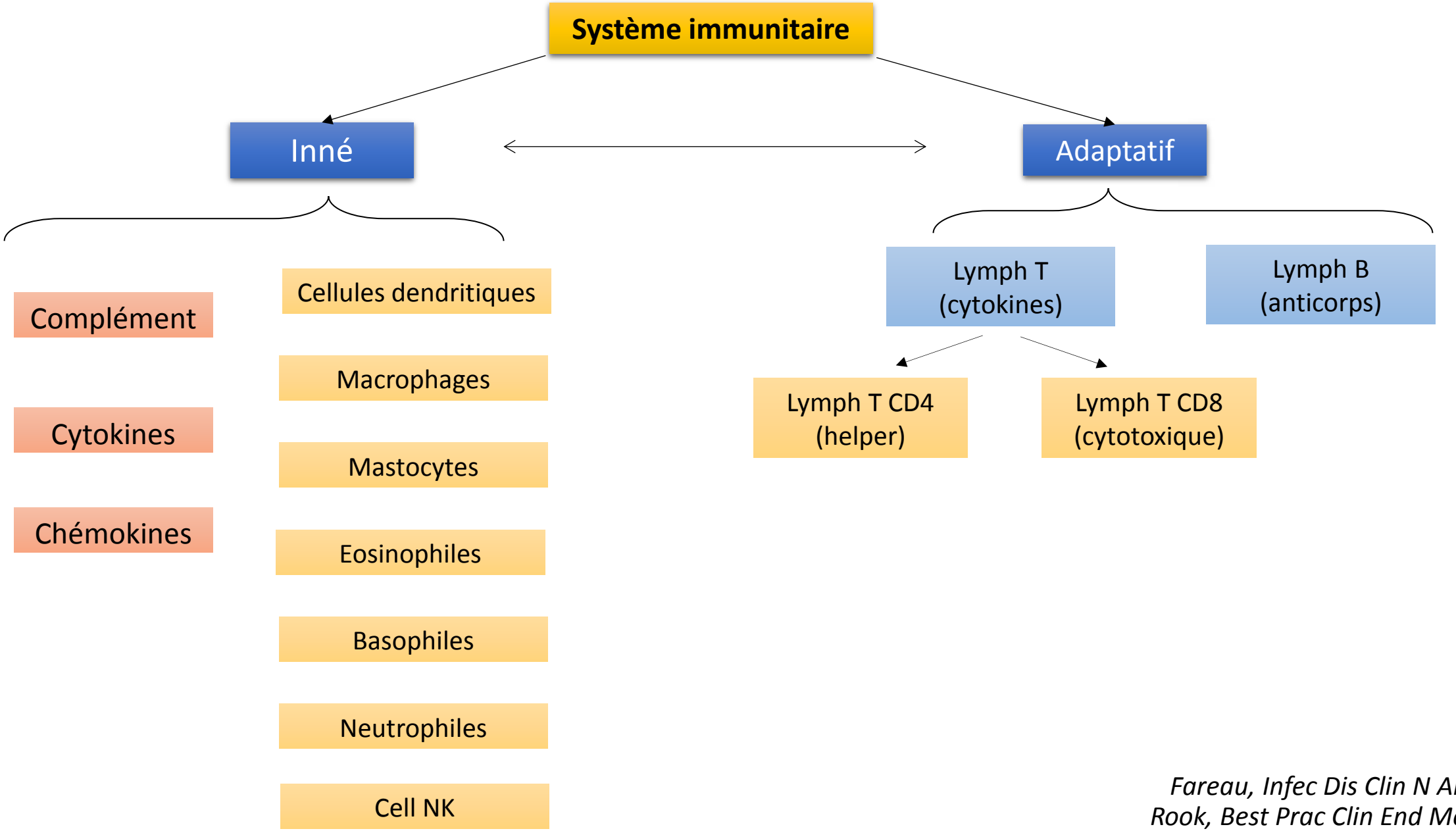
Plan:

1. Cortisol & infection
2. Hypercorticisme & infection
3. Insuffisance surrénalienne & infection

1. Cortisol & infection





Fareau, Infec Dis Clin N Am, 2007
Rook, Best Prac Clin End Met, 1999
Cruz-Topete, NeuroImm, 2015
Cain, Nat Rev, 2017

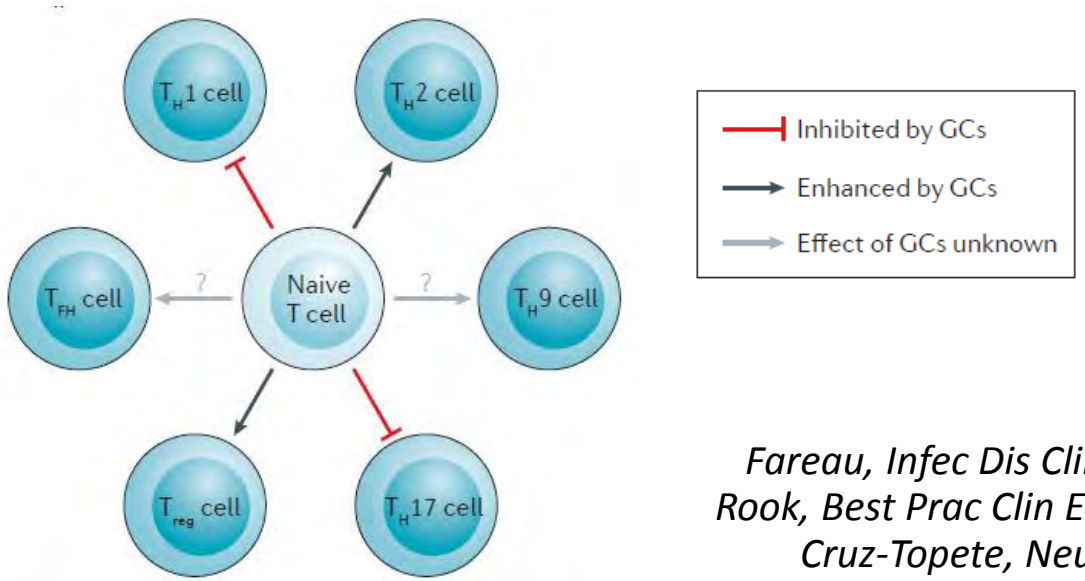
Rôle anti-inflammatoire des glucocorticoïdes

Inné

- Inhibition de la voie classique et alternative
- ↓ Cytokines pro-infl (IL-1, TNFα, IL6)
- ↓ Médiateurs enz (PLA2, COX2)
- Inhibition présentation d'AGs
- Monocytopénie Macro immatures
- Mastocytes
- Eosinopénie
- Basophiles
- Altération fonction des PNN
- Inhibition cell NK

Adaptatif

- Lymph T (cytokines)
  - Lymph T CD4 (helper)
  - Lymph T CD8 (cytotoxique)
- ↓ développement et prolif des Lymph B



Fareau, Infec Dis Clin N Am, 2007
Rook, Best Prac Clin End Met, 1999
Cruz-Topete, NeuroImm, 2015
Cain, Nat Rev, 2017

Rôle pro-inflammatoire du cortisol

Inné

↑ facteurs du compléments

↑ Récepteurs cellulaires à des cytokines pro-infl

Chémokines

↑ Récep de reconnaissance des Ags

Stimulation activation des macro et fonction phagocytaire des mono

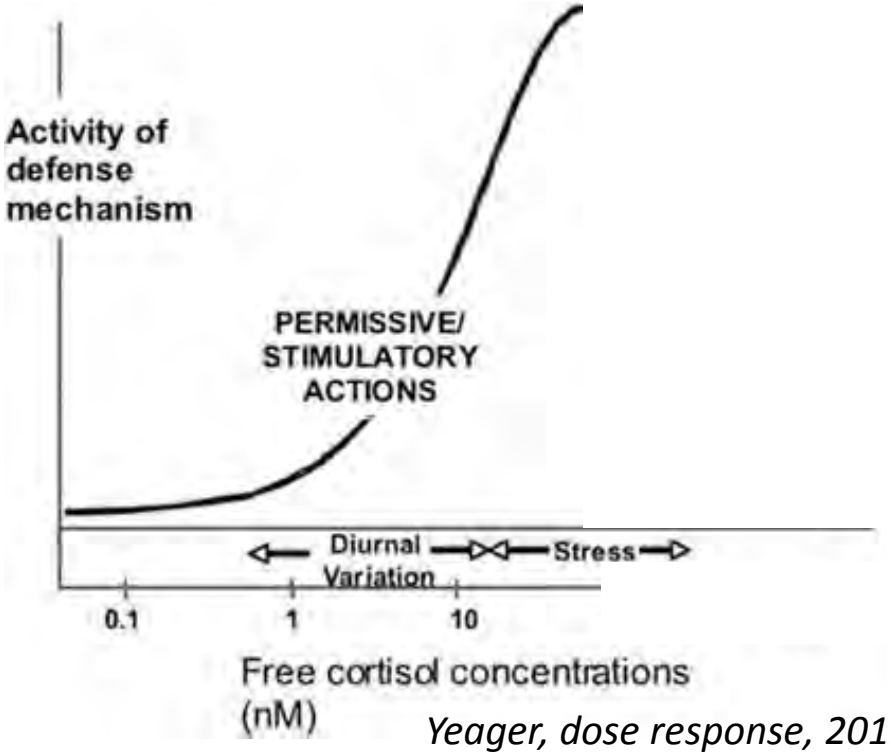
Mastocytes

Eosinophiles

Basophiles

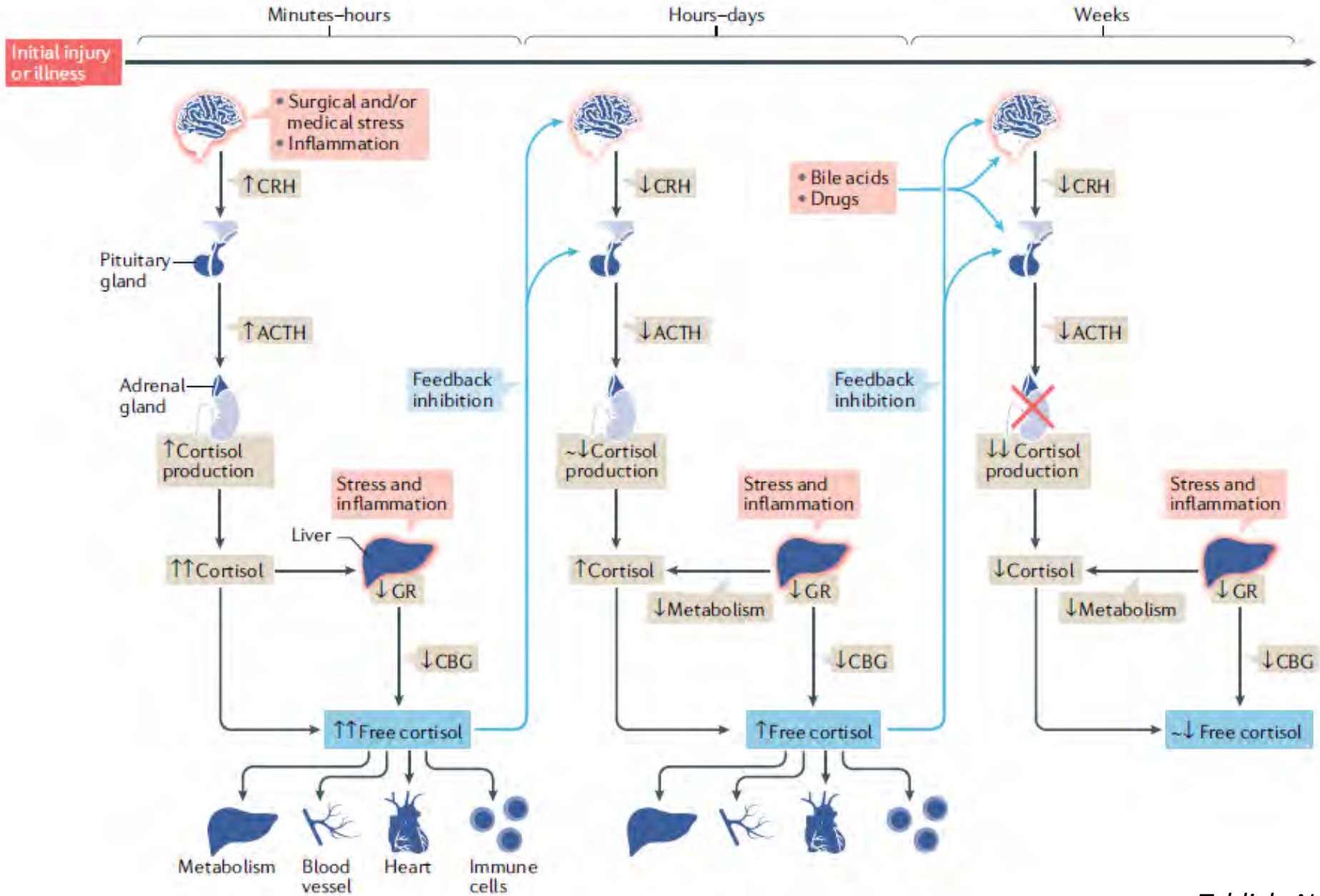
Retarde apoptose des PNN

Cell NK



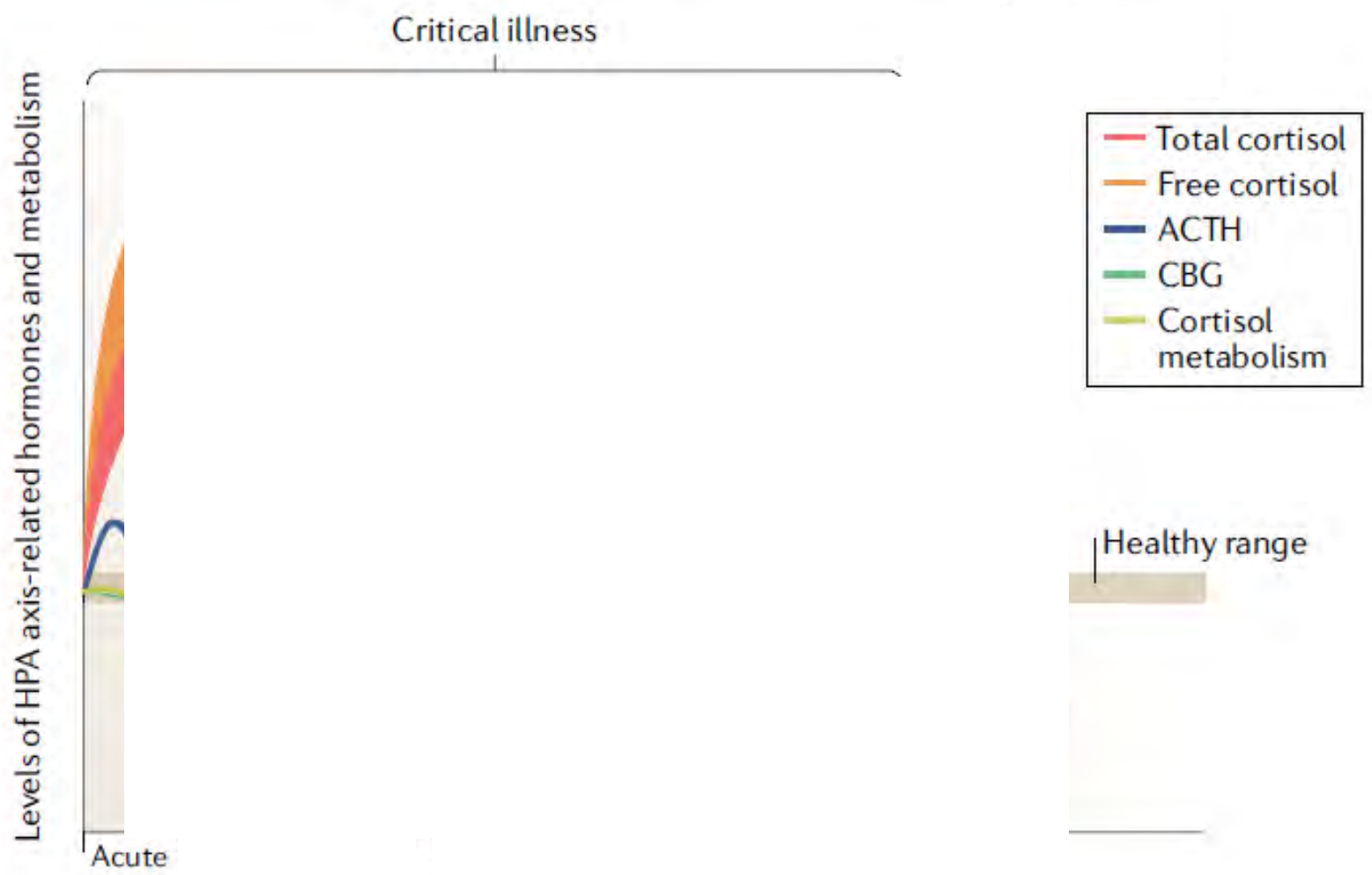
Yeager, dose response, 2011

Yeager, Anesthesia & Analgesia, 2018
Cruz-Topete, NeuroImmunoModulation, 2015
Cain, Nat Rev, 2017



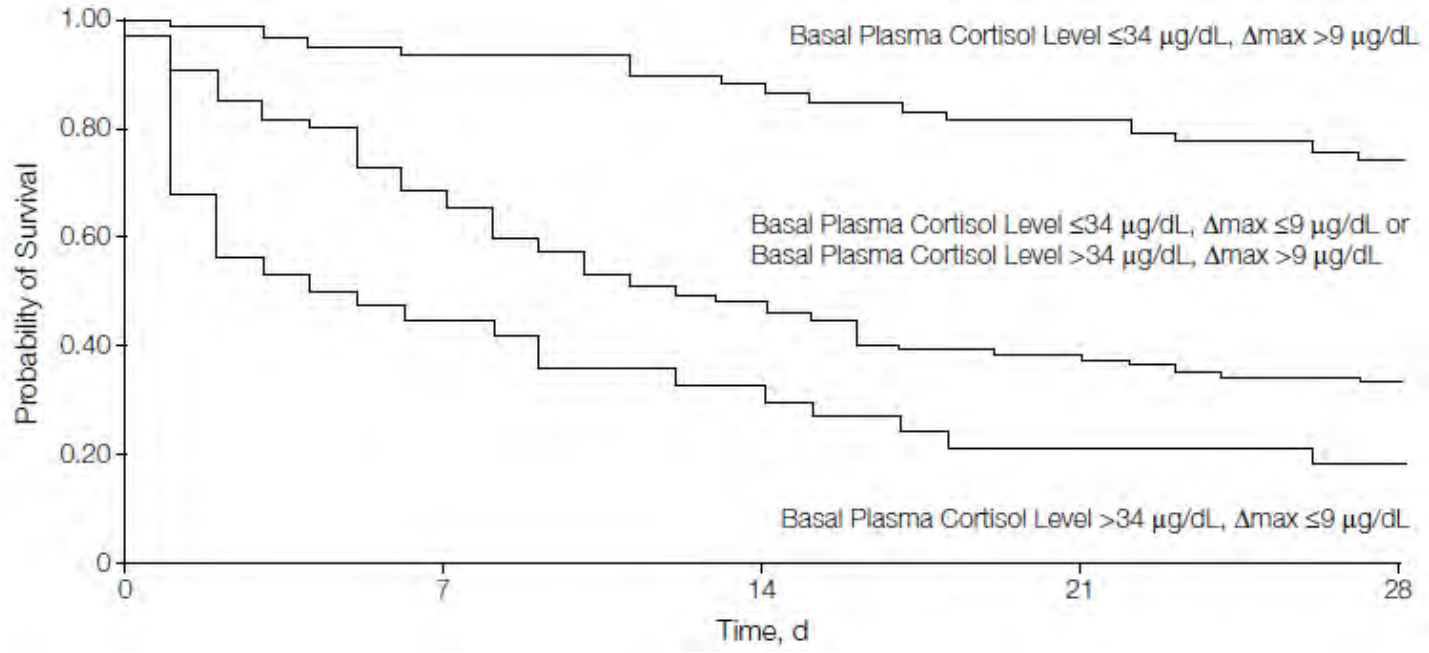
Teblick, Nat Rev, 2019

Cinétique du bilan glucocorticoïdes lors d'un stress



Teblick, Nat Rev, 2019

Un cortisol très élevé ou une réponse insuffisance au Synacthène sont associés à un mauvais pronostic lors d'un choc septique



Annane, JAMA, 2000

2. Hypercorticisme & infection

Via l'immuno-suppression

Via l'hyperglycémie induite

Foie: néoglucogénèse, ↓ synthèse de glycogène

Muscle: ↓ capture de glucose, ↑ catabolisme

Tissus adipeux: ↑ lipolyse

Pancréas: ↓ insuline, ↑ glucagon

Via altération de la barrière cutanée

Atrophie et défaut de cicatrisation

Parfois la fièvre absente et douleur atténuée → diagnostic difficile

L'infection, une cause importante de morbidité dans le syndrome de Cushing (SC)

343 patients et 35300 contrôles

Outcome	Period (y before/ after diagnosis)	Rate (95% CI) per 1000 Person-years in CS Cohort	Rate (95% CI) per 1000 Person-years in Control Cohort	Hazard Ratio (95% CI), Age- and Sex-adjusted Model	Hazard Ratio (95% CI), Fully Adjusted Model[a]
VTE	3 y before	4.3 (1.1–9.3)	0.5 (0.4–0.7)	8.4 (3.0–23.4)	6.8 (2.4–19.3)
	1 y after	15.3 (4.9–31.4)	0.9 (0.6–1.2)	20.6 (7.8–53.9)	17.1 (6.4–45.8)
	>1 to 30 y after	1.9 (0.8–3.6)	1.3 (1.2–1.4)	1.6 (0.8–3.4)	1.4 (0.6–2.9)
AMI	3 y before	2.1 (0.2–5.9)	0.9 (0.8–1.2)	2.2 (0.5–8.9)	2.1 (0.5–8.6)
	1 y after	6.1 (0.7–16.9)	1.4 (1.0–1.8)	4.5 (1.1–18.4)	3.5 (0.8–14.7)
	>1 to 30 y after	6.0 (3.8–8.8)	1.9 (1.8–2.1)	3.6 (2.4–5.5)	2.8 (1.8–4.4)
Stroke	3 y before	5.3 (1.7–10.9)	1.1 (0.9–1.3)	5.0 (2.1–12.4)	4.5 (1.8–11.1)
	1 y after	9.1 (1.8–22.0)	1.4 (1.1–1.9)	6.5 (2.0–21.0)	4.3 (1.3–14.2)
	>1 to 30 y after	4.3 (2.5–6.7)	2.7 (2.5–2.8)	1.8 (1.1–3.0)	1.5 (0.9–2.5)
Heart failure	3 y before	4.3 (1.1–9.3)	0.6 (0.5–0.8)	6.8 (2.5–18.6)	6.0 (2.1–17.1)
	1 y after	6.1 (0.7–17.0)	0.9 (0.6–1.3)	6.7 (1.6–28.1)	3.1 (0.7–14.2)
	>1 to 30 y after	1.6 (0.6–3.1)	1.9 (1.8–2.0)	1.0 (0.4–2.2)	0.8 (0.3–1.7)
Fractures	3 y before	14.9 (7.9–24.0)	4.2 (3.8–4.7)	3.4 (2.0–6.0)	3.2 (1.9–5.6)
	1 y after	20.1 (7.4–39.2)	4.6 (3.8–5.4)	4.3 (1.9–9.7)	3.8 (1.7–8.7)
	>1 to 30 y after diagnosis	8.3 (5.5–11.6)	7.2 (6.9–7.4)	1.2 (0.8–1.7)	1.1 (0.8–1.6)
Infections	3 y before	5.5 (1.8–11.3)	2.1 (1.8–2.4)	2.6 (1.1–6.4)	2.4 (1.0–5.9)
	1 y after	51.7 (29.6–80.0)	2.4 (1.9–3.0)	22.3 (12.9–38.5)	17.8 (10.1–31.3)
	>1 to 30 y after	12.7 (9.1–16.9)	3.7 (3.5–3.9)	3.7 (2.7–5.1)	2.9 (2.1–4.1)
Peptic ulcers	3 y before	5.4 (1.7–11.0)	0.8 (0.6–1.0)	6.5 (2.6–16.0)	5.5 (2.2–13.9)
	1 y after	12.3 (3.3–27.0)	1.0 (0.6–1.3)	12.5 (4.4–35.5)	8.9 (3.0–26.3)
	>1 to 30 y after	1.9 (0.8–3.6)	1.6 (1.5–1.7)	1.3 (0.6–2.8)	1.1 (0.5–2.2)

Dekkers, JCEM, 2013

L'infection, une cause de mortalité

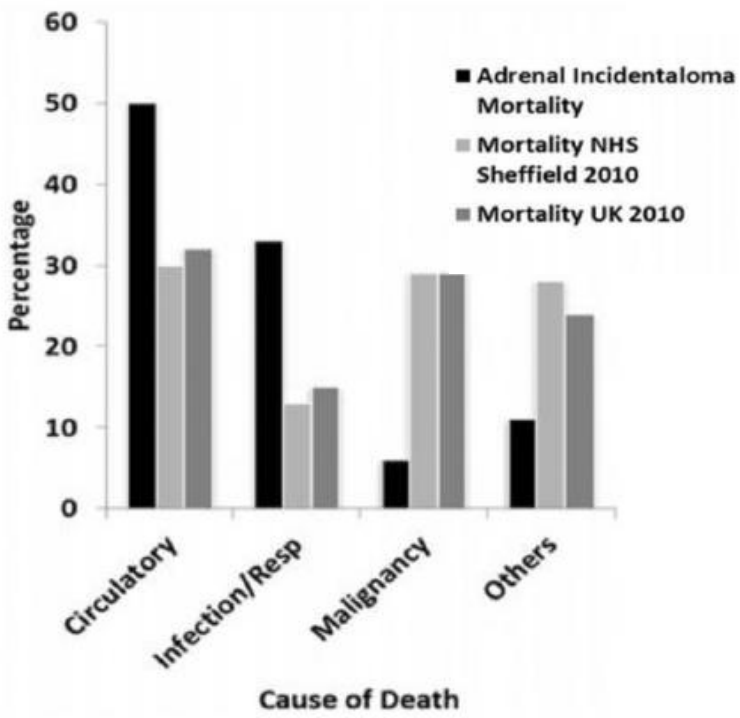
418 patients avec SC

311 maladie de Cushing	74 SC surrénalien	33 SC ectopique
9% décès (n=28)	3% décès (n=2)	30% décès (n=10)
21.4% infection/sepsis	0% infection/sepsis	30% infection/sepsis

Ntali, EJE, 2013

111 incidentalomes surrénaliens avec cortisol après 1mg-DXM > 1,8ug/dL

5/17 décès infection/sepsis

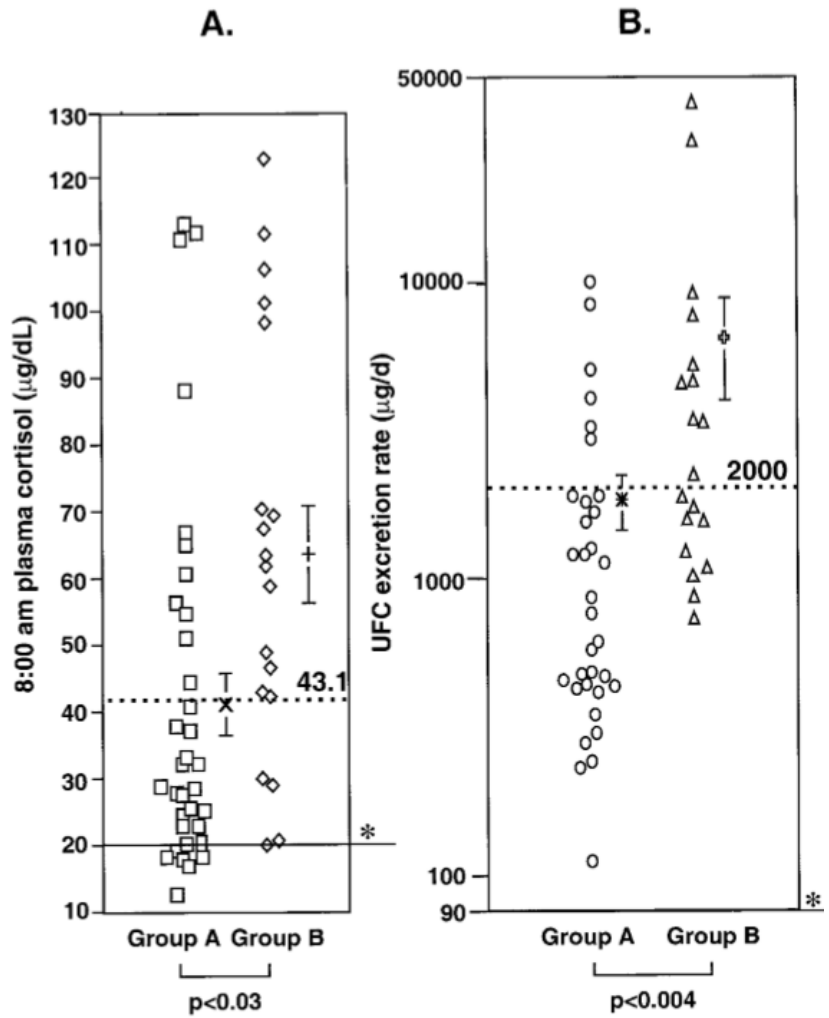


Debono, JCEM, 2014

Le risque d'infection est plus élevé chez les patients présentant un hypercorticisme majeur

54 patients avec SC ectopique

Type of infections	Number of infections
Group A: mild infections	
Bacterial	
Bacterial cervicitis (*Escherichia coli* and *Klebsiella pneumoniae*)	1
Persistent bacteriuria (*K. pneumoniae*)	1
Acute and chronic maxillary sinusitis	2
Axillary folliculitis	1
Viral	
HPV cervicitis	1
Fungal	
Mucocutaneous candidiasis	4
Fungal dermatitis	4
Fungal bursitis (*Candida parapsilosis*)	1
Tinea versicolor	1
Group B: severe infections with or without sepsis	
Bacterial	
Deep abcesses (wound, diverticular)	6
Cellulitis	4
Epididymitis	1
Sphenoid sinusitis	1
Pneumonia (bacterial) (including pulmonary abcess and empyema)	5
Septic arthritis/osteomyelitis	2
Catheter-related bacteremia	1
Urosepsis (*E. coli, K. pneumoniae,* and *Enterococcus faecalis*)	3
Gram-negative septicemia (*Pseudomonas aeruginosa*)	1
Protozoal	
Pneumocystis carinii pneumonia	2
Viral	
Herpes zoster disseminated infection	2
Fungal	
Candida glabrata fungemia	1



Sarlis, JCEM, 2000

Cause des infection dans l'hypercortisolisme

Infection fungique
Altération de la fonction des PNN et des macrophages

Fungal
Candida albicans
Aspergillus fumigatus
Pneumocystis jiroveci
Cryptococcus neoformans
Histoplasmosis capsulatum
Coccidioides immitis
Zygomycoses spp
Fusarium spp
Blastomyces spp

Infection bactérienne
Les plus fréquentes
Altération barrière cutanée

Infection virale
Déficit immunitaire à médiation cellulaire
Plus sévère, plus longue et plus souvent disséminée

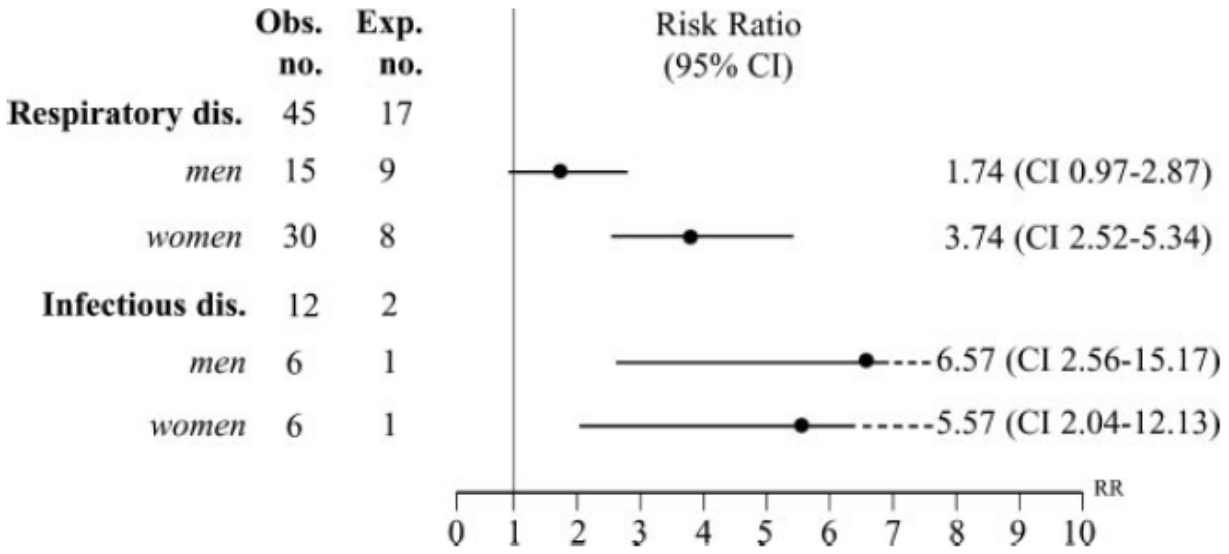
Infection parasitaire
Souvent en cas d'autres causes d'immunosuppression associée

Fareau, Infec Dis Clin N Am, 2007

3. Insuffisance surrénalienne & infection

L'infection, une cause de mortalité dans l'insuffisance surrénalienne

Cohorte de 1675 insuffisant surrénalien primaire



Bergthorsdottir, JCEM, 2006

L'infection, une cause de morbidité dans l'insuffisance surrénalienne

1580 maladie d'Addison (AD)

Table 3: Absolute and relative risk of infections in AD patients and matched cohort.

	AD cohort (n = 1580)	Matched unexposed cohort (n = 3158)
Lower respiratory tract infections		
Outcome events, n. (%)	130 (8.2)	137 (4.3)
Person-years	10,337	22,836
Crude incidence rate/1000-person years	12.58	6.00
Follow-up years, median (IQR)	4.87 (1.78-10.20)	5.78 (2.37-11.12)
Unadjusted incidence rate ratio (95% CI)	2.10 (1.65-2.66)	
p-value	p <0.001	
Adjusted incidence rate ratio (95% CI)†	2.11 (1.64-2.69)	
p-value	p <0.001	
Urinary tract infections		
Outcome events, n. (%)	282 (17.9)	396 (12.5)
Person-years	9,248	21,003
Crude incidence rate/1000-person years	30.49	18.85
Follow-up years, median (IQR)	4.09 (1.44-9.14)	5.08 (2.11-10.26)
Unadjusted incidence rate ratio (95% CI)	1.62 (1.39-1.88)	
p-value	p <0.001	
Adjusted incidence rate ratio (95% CI)†	1.51 (1.29-1.77)	
p-value	p <0.001	
Gastro-intestinal infections		
Outcome events, n. (%)	194 (12.3)	110 (3.5)
Person-years	9,598	22,662
Crude incidence rate/1000-person years	20.21	4.85
Follow-up years, median (IQR)	4.49 (1.67-9.31)	5.63 (2.37-11.03)
Unadjusted incidence rate ratio (95% CI)	4.16 (3.30-5.26)	
p-value	p <0.001	
Adjusted incidence rate ratio (95% CI)†	3.80 (2.99-4.84)	
p-value	p <0.001	

†Adjusted for age, gender, smoking status, BMI, Townsend Deprivation Index and Charlson Comorbidity Index.

Tresoldi, JCEM, 2019

Infection liée au traitement substitutif ?

602 hyperplasie congénitale des surrénales (CAH)

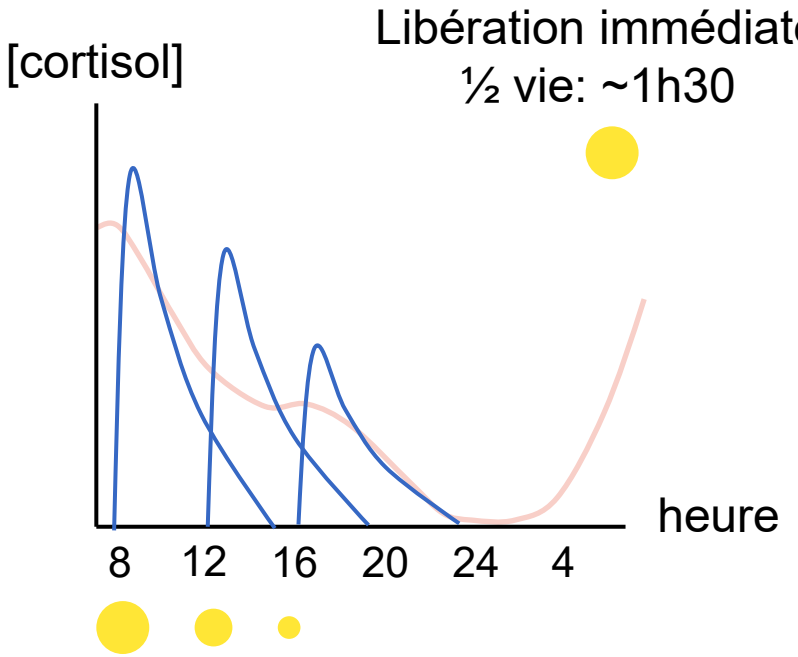
Table 4: Absolute and relative risk of infections in CAH patients and matched control cohort.

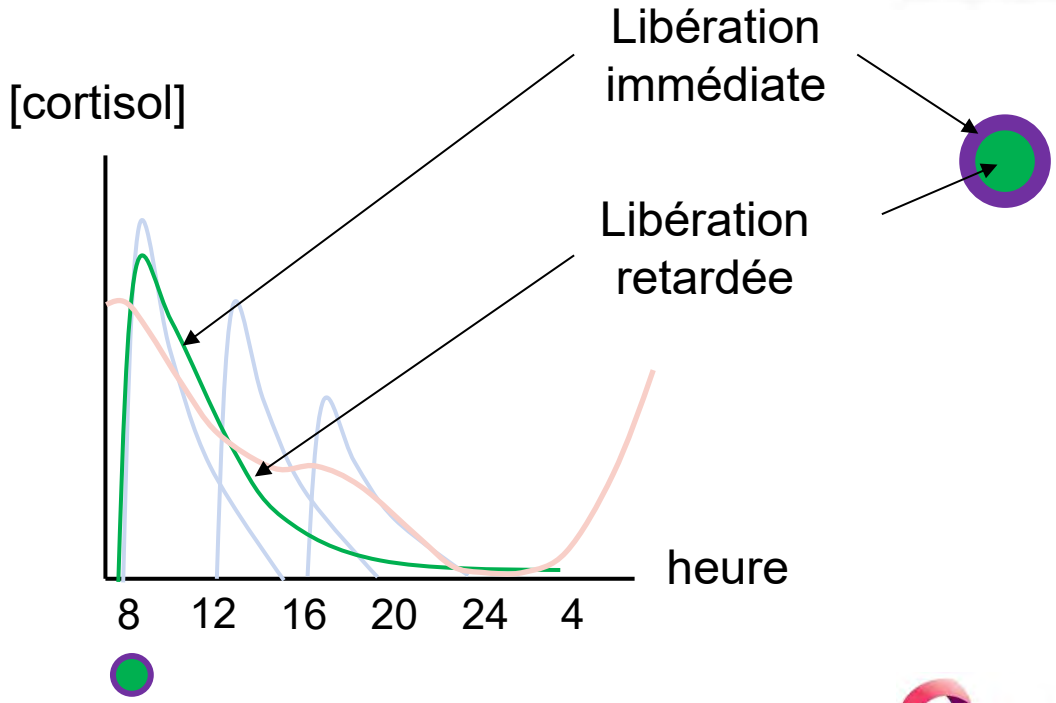
	CAH cohort (n = 602)	Matched unexposed cohort (n = 1204)	CAH cohort on glucocorticoids (n = 254)	Matched unexposed cohort (n = 508)
Lower respiratory tract infections				
Outcome events, n. (%)	22 (3.7)	19 (1.6)	12 (4.7)	7 (1.4)
Person-years	3843	7842	1924	3567
Crude incidence rate/1000-person years	5.72	2.42	6.24	1.96
Follow-up years, median (IQR)	4.83 (1.92-9.54)	5.10 (2.04-9.80)	6.00 (2.60-12.06)	5.17 (2.45-10.77)
Unadjusted incidence rate ratio (95% CI)	2.36 (1.28-4.36)		3.18 (1.25-8.07)	
p-value	p = 0.01		p = 0.02	
Adjusted incidence rate ratio (95% CI)†	2.36 (1.25-4.43)		3.23 (1.21-8.61)	
p-value	p = 0.01		p = 0.02	
Urinary tract infections				
Outcome events, n. (%)	83 (13.8)	130 (10.8)	45 (17.7)	43 (8.5)
Person-years	3478	7217	1709	3374
Crude incidence rate/1000-person years	23.87	18.01	26.33	12.75
Follow-up years, median (IQR)	4.15 (1.59-8.80)	4.64 (1.83-8.80)	4.97 (2.09-9.77)	4.84 (2.22-9.77)
Unadjusted incidence rate ratio (95% CI)	1.32 (1.01-1.74)		2.07 (1.36-3.14)	
p-value	p = 0.05		p <0.001	
Adjusted incidence rate ratio (95% CI)†	1.40 (1.06-1.85)		2.20 (1.43-3.34)	
p-value	p = 0.02		p <0.001	
Gastro-intestinal infections				
Outcome events, n. (%)	29 (4.8)	52 (4.3)	23 (9.1)	23 (4.5)
Person-years	3773	7678	1825	3486
Crude incidence rate/1000-person years	7.69	6.77	12.60	6.60
Follow-up years, median (IQR)	4.70 (1.83-9.63)	4.94 (2.04-9.69)	5.82 (2.12-11.38)	5.14 (2.47-10.38)
Unadjusted incidence rate ratio (95% CI)	1.13 (0.72-1.79)		1.91 (1.07-3.40)	
p-value	p = 0.59		p = 0.03	
Adjusted incidence rate ratio (95% CI)†	1.10 (0.69-1.75)		1.93 (1.06-3.52)	
p-value	p = 0.70		p = 0.03	

†Adjusted for age, gender, smoking status, BMI, Townsend Deprivation Index and Charlson Comorbidity Index.

Tresoldi, JCEM, 2019

Les patients insuffisants surrénaliens traités ont une exposition anormale au cortisol





DuoCort
Plenadren

Une diminution du nombre d'infection est observée avec l'hydrocortisone à libération modifiée

Etude randomisée en simple aveugle: traitement conventionnel versus PLENADREN
89 patients avec maladies d'Addison

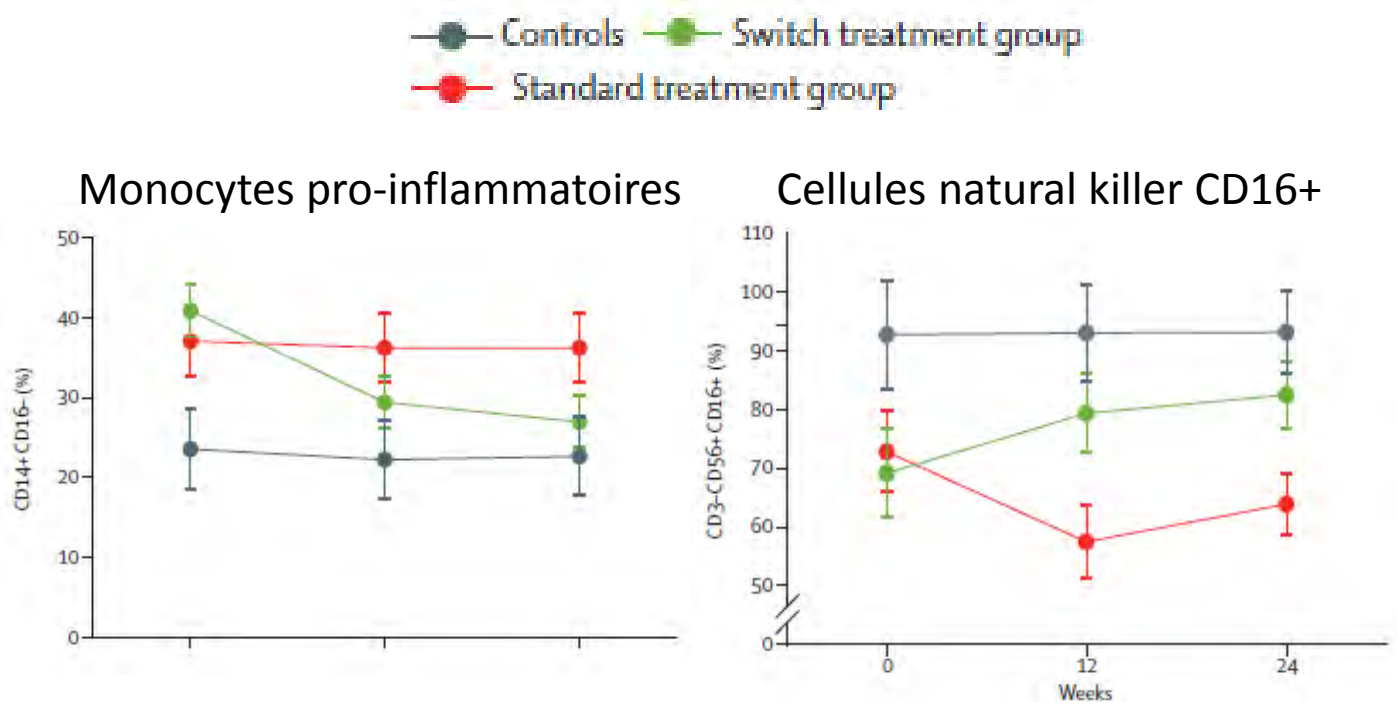
Diminution du nombre d'infection

	Switch treatment group (n=43)		Standard treatment group (n=40)		Treatment-related difference	
	12 weeks (n=43)	24 weeks (n=43)	12 weeks (n=40)	24 weeks (n=35)	Baseline to 12 weeks	Baseline to 24 weeks
Infections†						
Total score (IN1–IN5)	..	−1·3 (−2·1 to −0·5)	..	0·4 (−0·4 to 1·1)	..	−1·7 (−2·6 to −0·8; p=0·0002)
Flu or flu-like events in 6 months	..	−1·2 (−1·7 to −0·7)	..	−0·4 (−0·9 to 0·2)	..	−1·0 (−1·6 to −0·4; p=0·001)

Nombre cumulé d'infection des voies aériennes hautes < avec PLENADREN (17 vs 38; p=0·016)

Isidori, Lancet, 2017

L'hydrocortisone à libération modifiée restaure un profil phénotypique cellulaire proche des sujets contrôles

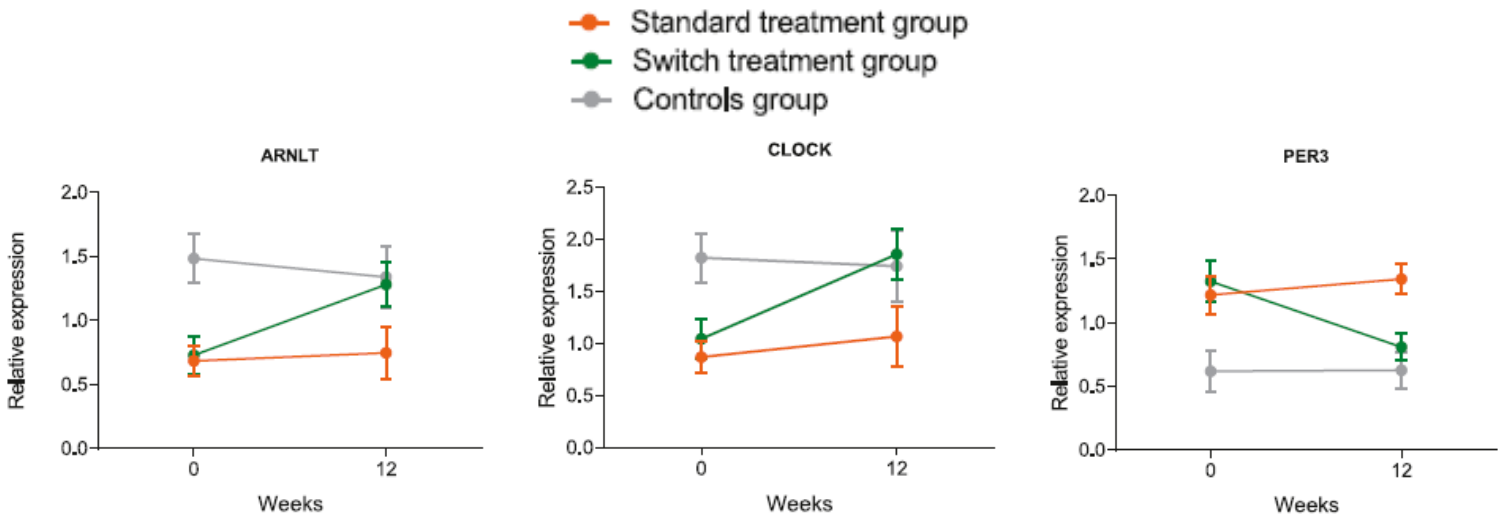


Isidori, Lancet, 2017

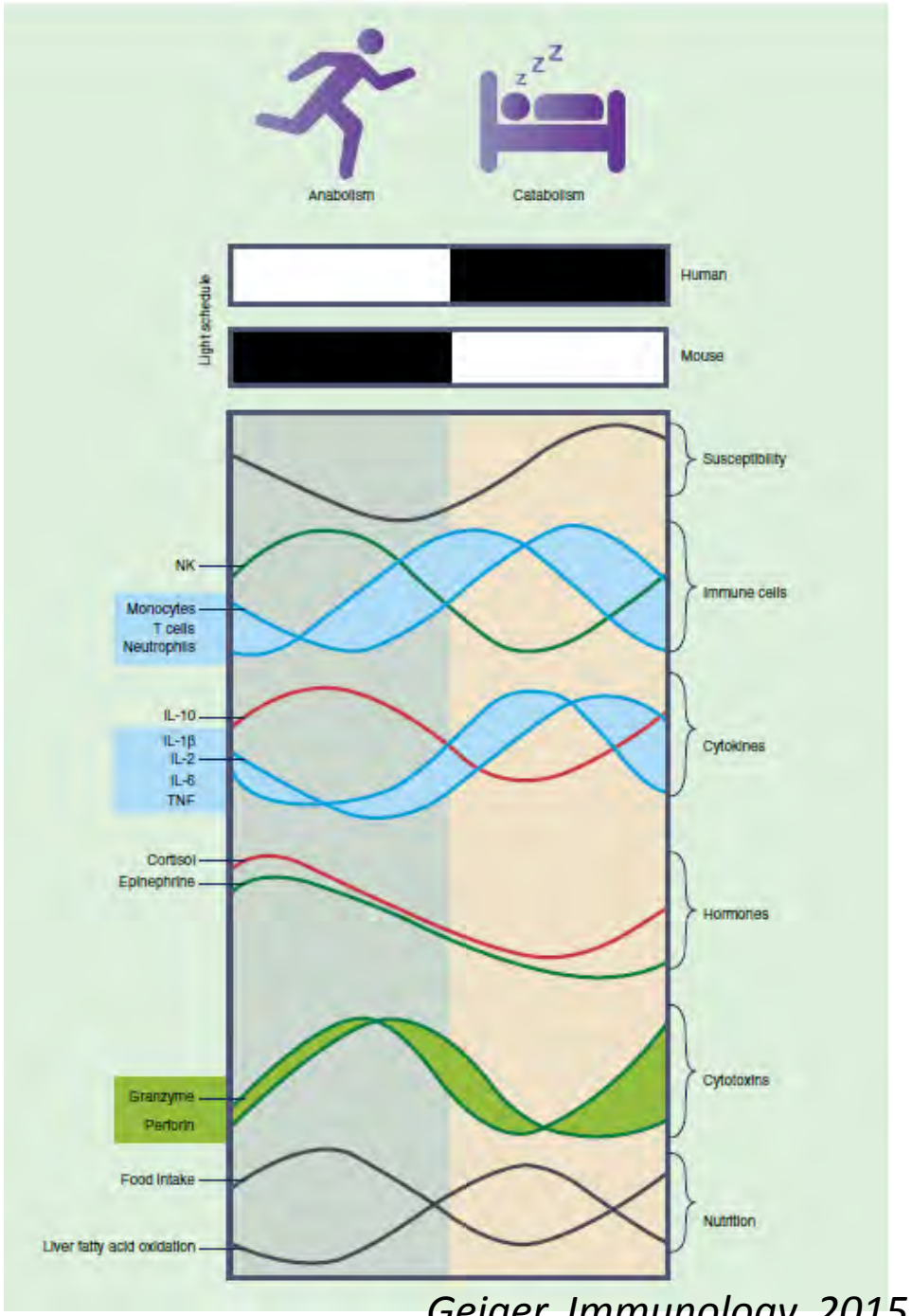
Le rétablissement d'un rythme circadien normal du cortisol est impliqué dans l'amélioration du profil immunitaire

La fonction immunitaire suit un rythme circadien pour lequel le cortisol pourrait être impliqué

Rétablissement d'une expression normale des gènes de l'horloge dans les cellules mononuclées périphériques



Venneri, JCEM, 2018

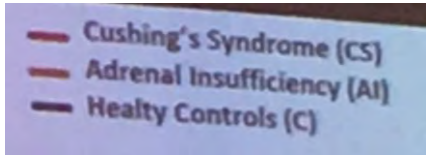


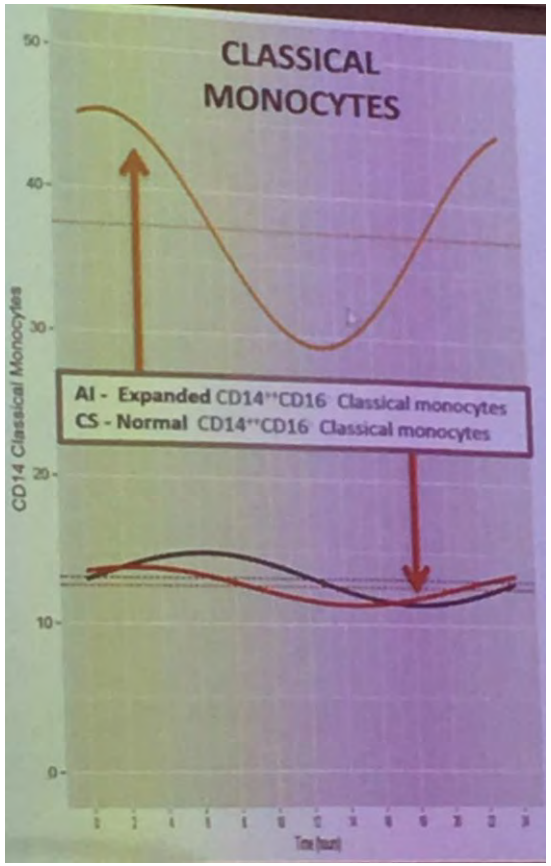
Geiger, Immunology, 2015

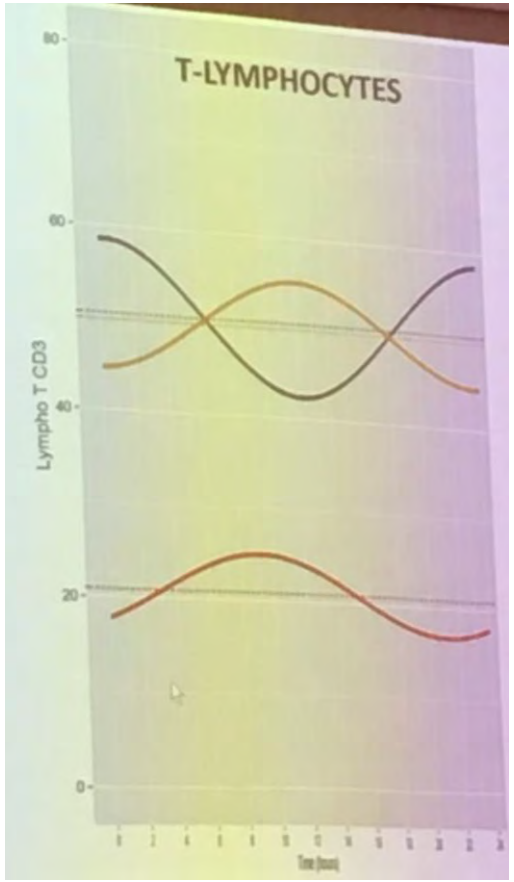
Conclusion

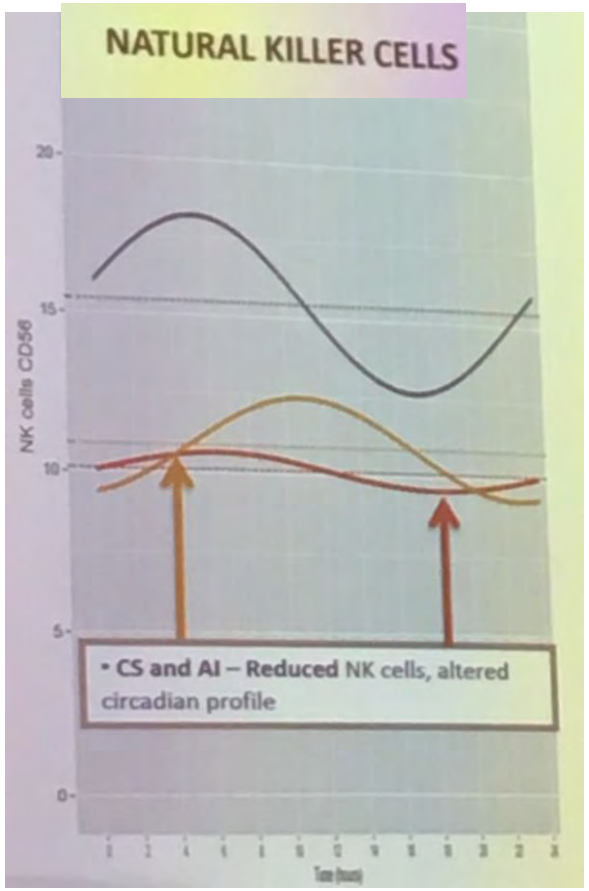
- Le cortisol joue un rôle important sur la fonction immunitaire innée et adaptative.
- Une élévation du cortisol adaptée dans l'ampleur et le timing est importante pour la lutte contre le stress et notamment le sepsis.
- Les patients atteints de syndrome de Cushing et d'insuffisance surrénalienne sont plus à risque d'infections, cause de morbi-mortalité.
- Ce risque infectieux est clairement lié à:
  - La sévérité de l'hypercortisolisme pour le syndrome de Cushing
  - La perte du rythme nycthéméral pour l'insuffisance surrénalienne

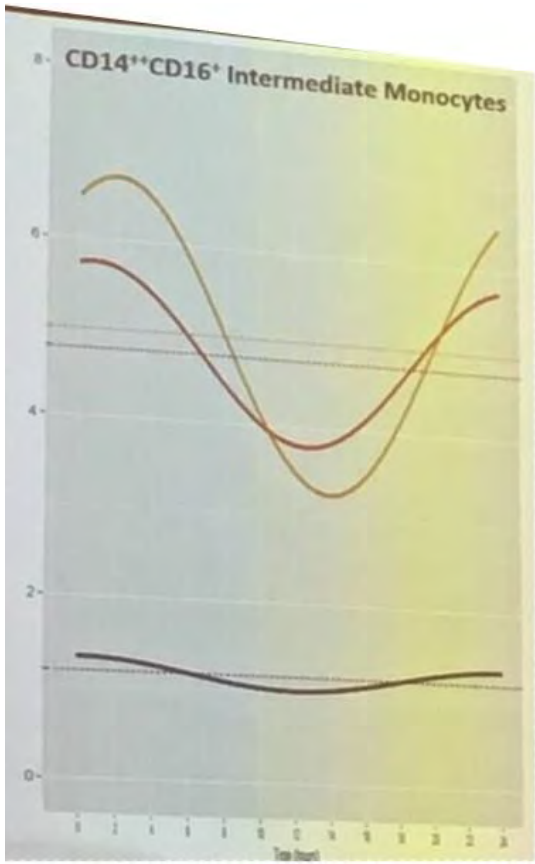
Merci de votre attention


Cushing's Syndrome (CS)
Adrenal Insufficiency (AI)
Healty Controls (C)


CLASSICAL MONOCYTES
CD14 Classical Monocytes
AI - Expanded CD14++CD16 Classical monocytes
CS - Normal CD14++CD16 Classical monocytes
Time (hours)

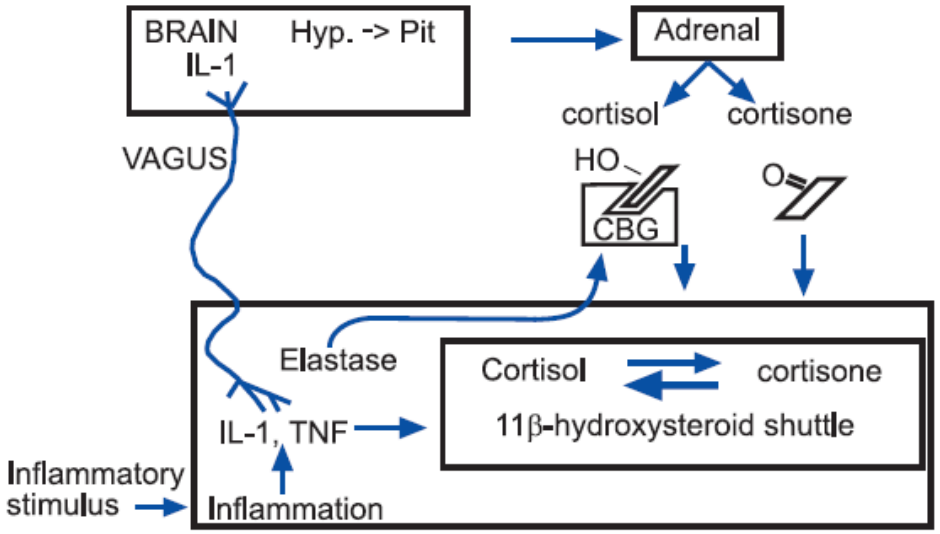

T-LYMPHOCYTES
Lympho T CD3
Time (hours)


NATURAL KILLER CELLS
NK cells CD56
• CS and AI – Reduced NK cells, altered circadian profile
Time (hours)


CD14++CD16+ Intermediate Monocytes
Time (hours)

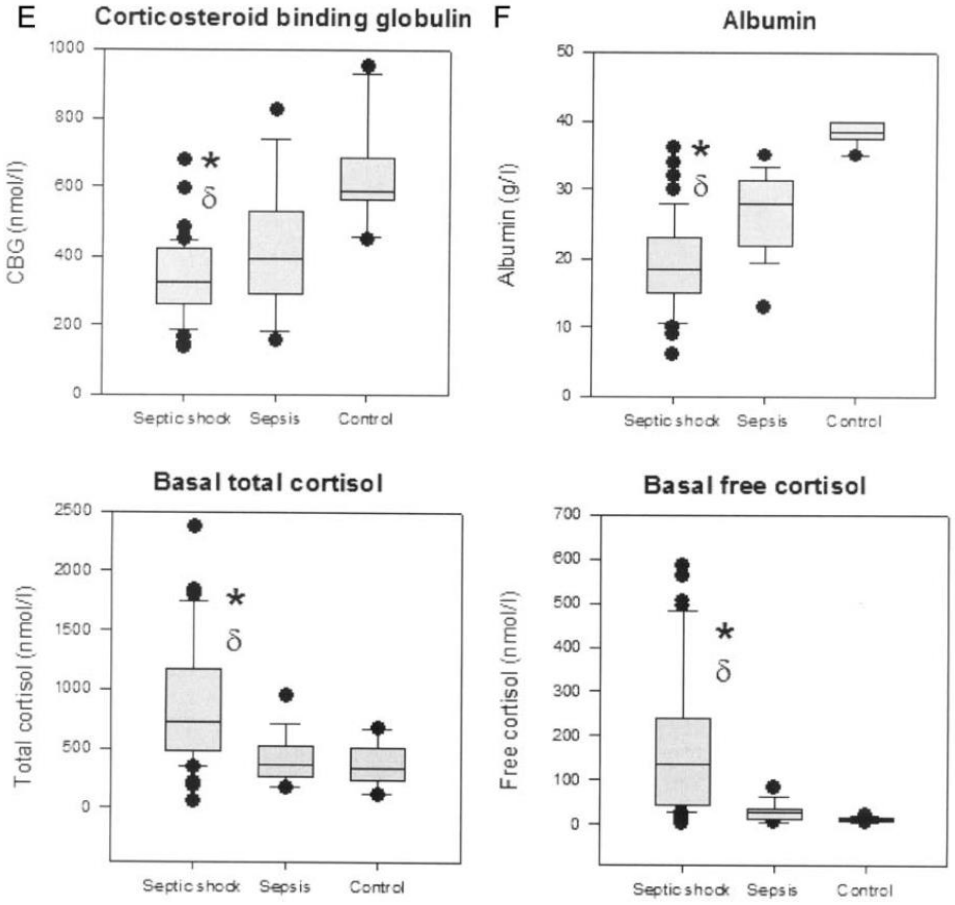
Mécanisme de l'hypercortisolisme

1. Activation initiale de l'axe HPA



Rook, Best Prac Clin End Met, 1999

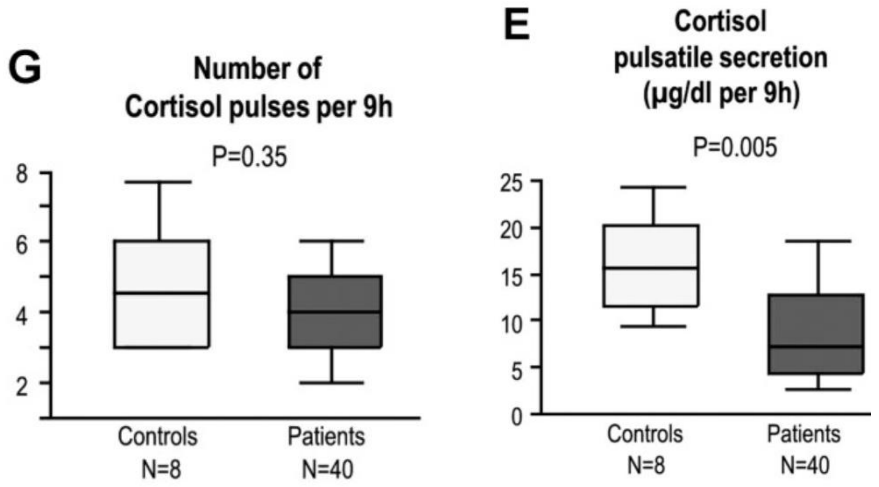
2. Augmentation du cortisol libre



Torpy, HMR, 2007

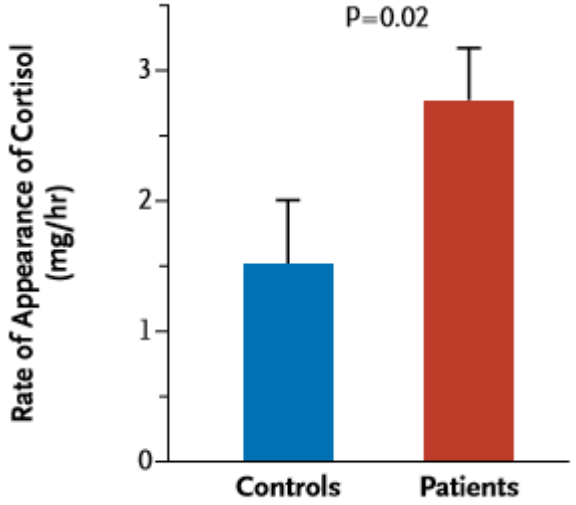
Mécanisme de l'hypercortisolisme

3. ↓ amplitude des pulses de cortisol et d'ACTH



Boonen, Am J Physiol Endoc Metab, 2014

4. ↑ Modeste de la production de cortisol

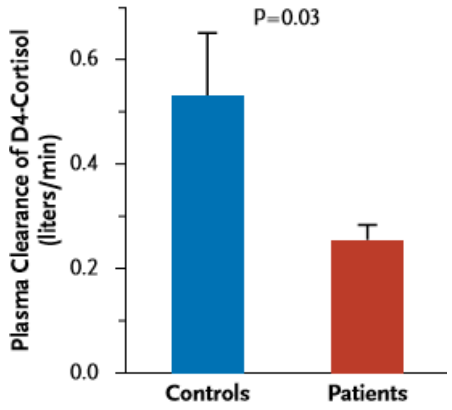


Boonen, NEJM, 2003

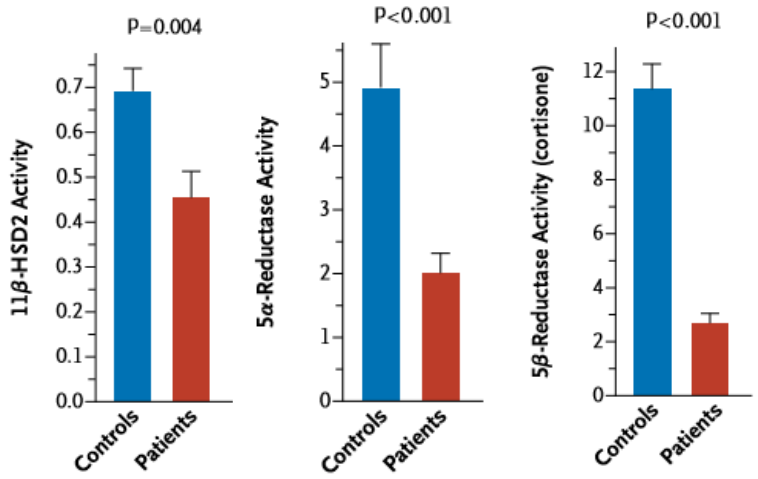
Mécanisme de l'hypercortisolisme

4. ↓ métabolisme du cortisol

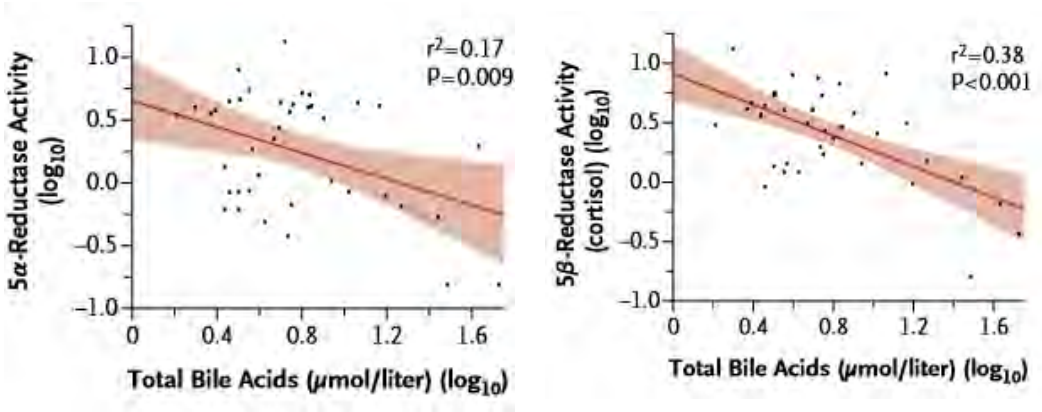
↓ *clairance du cortisol*



↓ *activité 5β-réductase, 5α-réductase et 11βHSD2*



Corrélation à l'↑ des acides biliaires



Boonen, NEJM, 2003

Porteurs d'un variant pathogène de CYP21A2

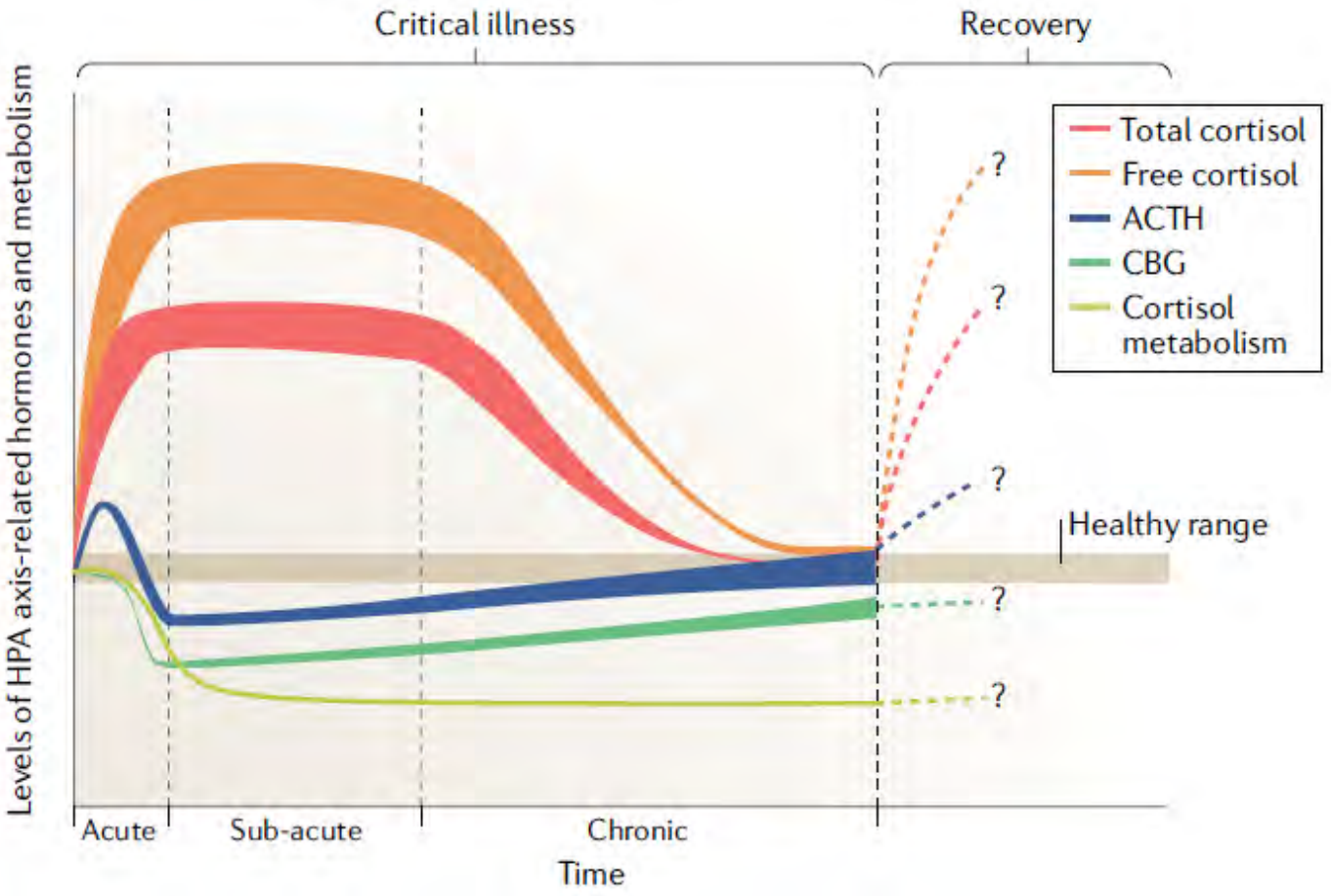
Table 3. Causes of Death

	Carriers, N = 1143		Controls, N = 114,234			
	Dead, n	%	Dead, n	%	HR	*P*
Infections	45	3.94	5640	4.94	0.651 (0.485–0.874)	0.004
Pneumonia	2	0.17	725	0.63	0.220 (0.055–0.881)	0.032[a]
Sepsis	4	0.35	362	0.32	1.031 (0.383–2.771)	0.95
Erysipelas	0	0	13	0.01		0.99
Hepatitis	0	0	52	0.04		0.99
Influenza	0	0	23	0.02		0.99
Diabetes	13	1.14	1268	1.11	0.856 (0.494–1.484)	0.58
Hypopituitary	0	0	9	0.01		0.99
Adrenal	1	0.09	17	0.01	5.894 (0.773–44.954)	0.09
Dementia	15	1.31	943	0.83	1.348 (0.801–2.268)	0.26
Alcohol	6	0.52	569	0.50	0.932 (0.417–2.085)	0.86
Cerebrovascular disease	89	7.47	8531	7.79	0.862 (0.700–1.064)	0.17
Stroke	19	1.66	1378	1.21	1.175 (0.744–1.855)	0.49
Heart	44	3.85	4177	3.66	0.860 (0.638–1.159)	0.32
Chronic obstructive pulmonary disease	8	0.70	754	0.66	0.945 (0.470–1.900)	0.87
Gastrointestinal	13	1.14	1413	1.24	0.772 (0.446–1.334)	0.35
Intestinal	0	0	55	0.05		0.99
Renal failure	12	1.05	596	0.52	1.630 (0.913–2.909)	0.10
Injury	24	2.10	2896	2.54	0.739 (0.494–1.104)	0.14
Cancer	49	4.29	4799	4.20	0.855(0.645–1.134)	0.28

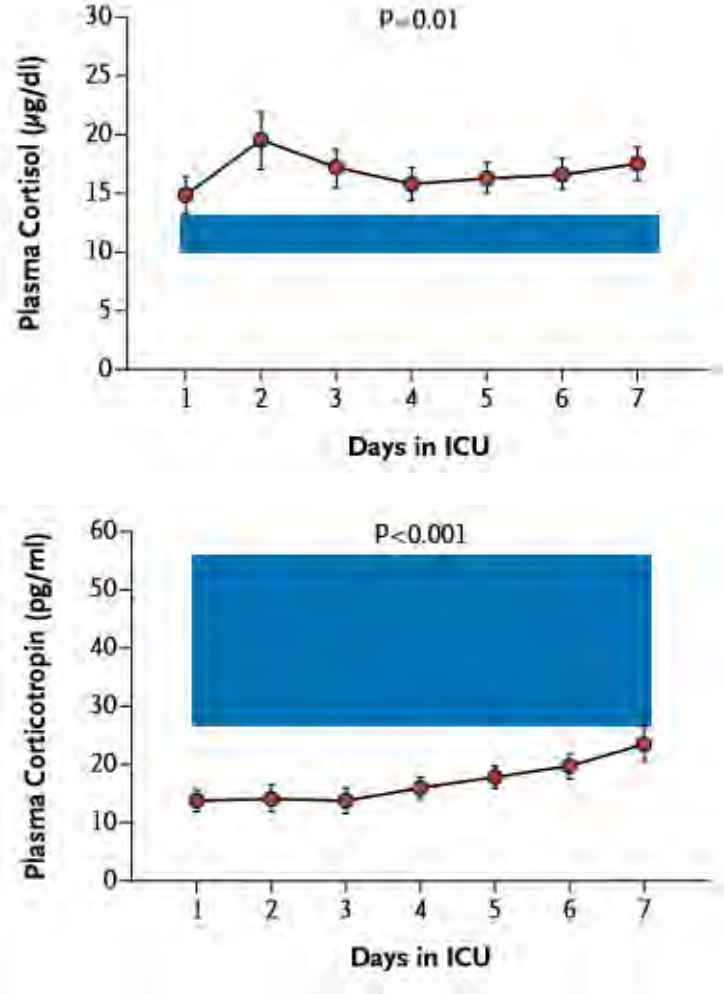
[a]Fisher exact test for pneumonia 0.056.

Nordenström, JCEM, 2019

Cinétique du bilan glucocorticoïdes lors d'un stress



Teblick, Nat Rev, 2019



Boonen, NEJM, 2003