Società Medico Chirurgica di Ferrara

dal 1846 *insieme a*

Università degli Studi di Ferrara

Vivere, diagnosticare e trattare la malattia di Addison: dalla storia ai nostri giorni

Inquadramento clinico

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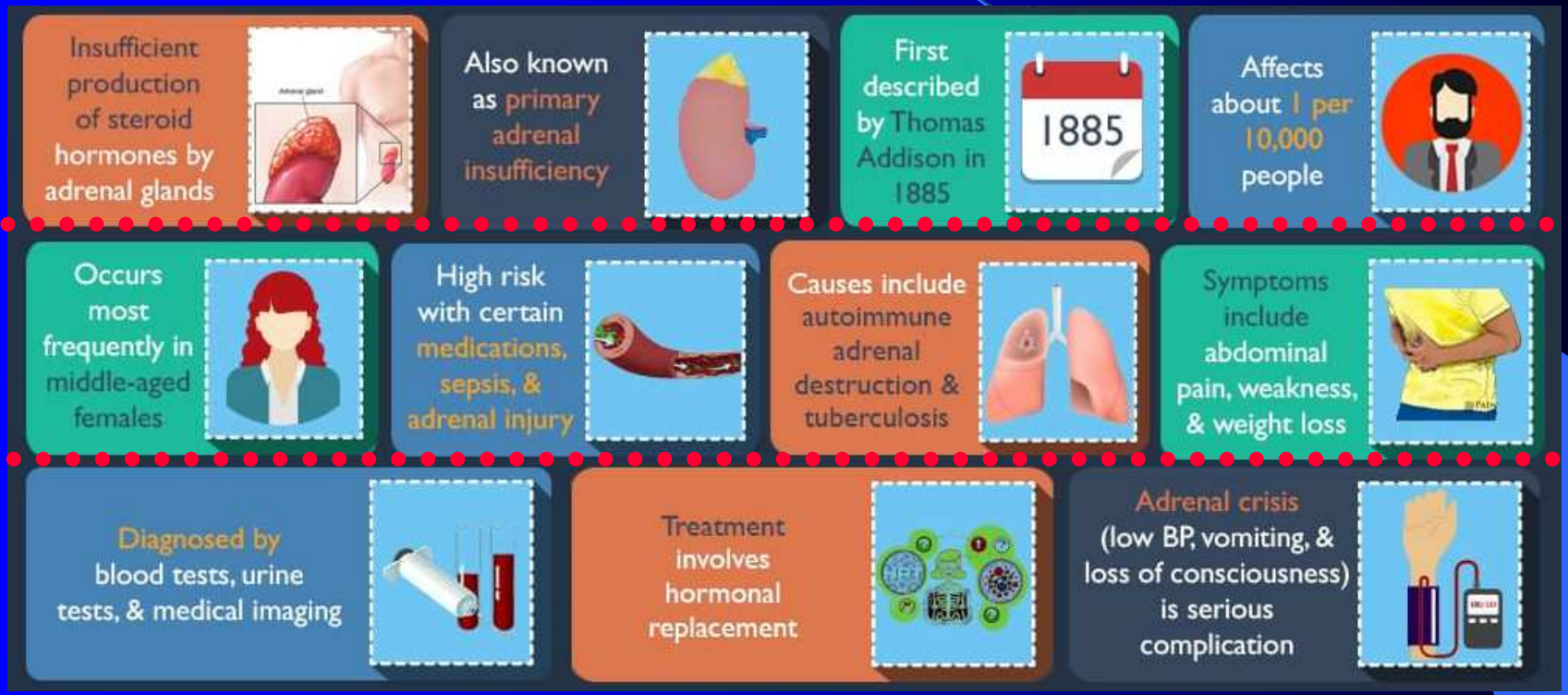
UNIVERSITÀ DEGLI STUDI DI FERRARA

Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di FERRARA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

INQUADRAMENTO CLINICO

MALATTIA DI ADDISON



INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

Insufficienza surrenalica primitiva

SPECIAL FEATURE

Clinical Practice Guideline

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

«PAI is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids. PAI is a severe and potentially life-threatening condition due to the central role of these hormones in energy, salt, and fluid homeostasis»

J Clin Endocrinol Metab, February 2016, 101(2):364–389

INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

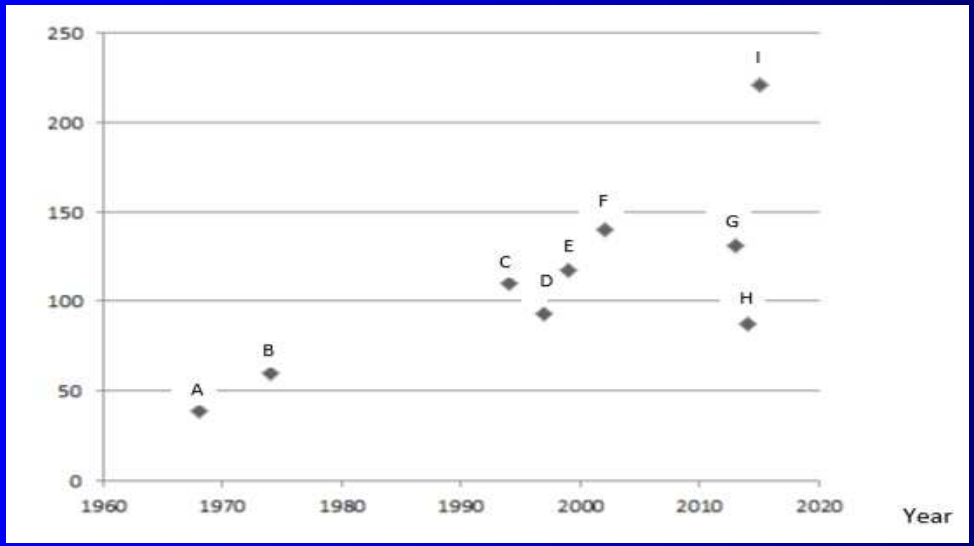
Insufficienza surrenalica primitiva

Malattia rara
prevalenza ~ 100–140 casi/milione di abitanti e in aumento

pregressa sottostima

miglioramento diagnostico

Prevalenza: numero di pazienti per milione



Bensing et al Eur J Endocrinol 2016

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INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

Insufficienza surrenalica primitiva

In precedenza…

Tubercolosi	50%
Neoplasie/metastasi	30%
Emorragie	10%

Addison T. On the Constitutional and Local Effects of Disease of the Supra-renal Capsules. London, UK: Samuel Highley; 1855

…ma ai giorni nostri

Adrenalite autoimmune	80%
Tubercolosi	10%
Neoplasie/metastasi	
Surrenectomia	10%
Malattie genetiche	
Emorragie	

Erichsen et al. Eur J Endocrinol 2009; 160: 233–237
Laureti et al. J Clin Endocrinol Metab 1999; 84: 1762

Arlt et al. Lancet 2003; 361: 1881–1893
Bornstein et al. N Engl J Med 2009; 360: 2328–2339
Betterle et al. Endocr Dev 2011; 20: 161–172

INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

Insufficienza surrenalica primitiva

The Adrenal Gland: Central Relay in Health and Disease

18th Adrenal Cortex Conference, 2018 Munich

▶ **Table 1** Incidence and prevalence of adrenal diseases in Europe.

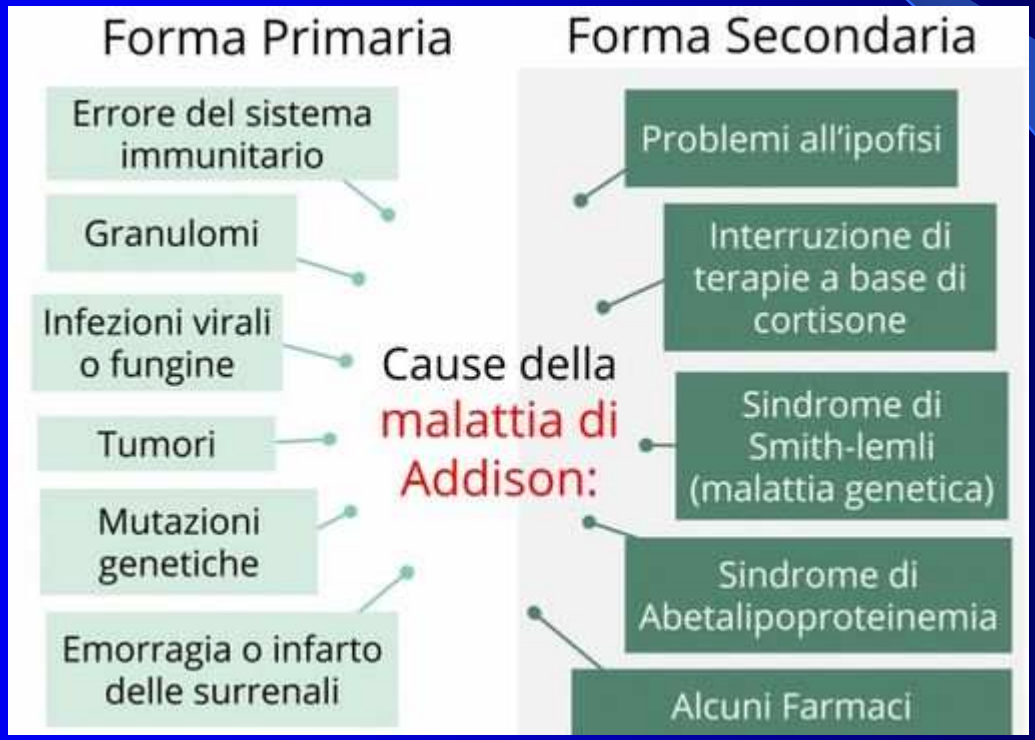
	Annual incidence	Prevalence	Morbidity	Mortality
Congenital adrenal hyperplasia	1:10.000–1:15.000		5.8 crises per 100 patient-years; salt wasting: 8.8; simple virilising: 2.5	The HR of dying 2.3 (95 % CI, 1.2–4.3) in CAH males and 3.5 (95 % CI, 2.0–6.0) in CAH females compared with controls
Addison's disease	4.5/1000.000	82–144/ 1000.000	6–8 adrenal crisis/ 100 patients/year	0.5 deaths/100 patient-years from adrenal crisis
Primary aldosteronism	n.k.	4–6 % of hypertensive population	OR for stroke: 4.2; OR for MI: 6.5; OR for AF: 12.1 compared to EH	2 times increased for treated PA (IAH)
Cushing disease	1–3/1000.000	66/1000.000		SMR for all-cause mortality in treated CD: 1.61
Incidentally detected adrenal mass	n.k.	1–2 % of general population	n.k.	n.k.
Adrenocortical carcinoma	0.7–2.0/ 1.000.000			Median survival: 3–4 years, 5-year survival 60–80 % for localized tumors, and 10–20 % for metastatic disease

Reincke M et al. Exp Clin Endocrinol Diabetes 2019; 127: 81–83

INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

Insufficienza surrenalica primitiva



INQUADRAMENTO CLINICO

Table 2. Major Etiologies of PAI and Associated Features

Etiology	Associated Features
Autoimmune	
Isolated	Not associated with other autoimmune disorders
APS type 1 (APECED)	Chronic cutaneous candidiasis, hypoparathyroidism
APS type 2	Autoimmune thyroid disease, type 1 diabetes
Adrenal—infiltration/injury	
Adrenal hemorrhage	Associated with sepsis, anticoagulants, anti-cardiolipin/lupus anti-coagulant syndrome
Adrenal metastases	Malignancies: lung, breast, colon, melanoma, lymphoma
Infections: adrenalitis	Tuberculosis, HIV/AIDS, CMV, candidiasis, histoplasmosis, syphilis, African trypanosomiasis, paracoccidioidomycosis (eg, in South America)
Infiltration	Hemochromatosis, primary amyloidosis
Bilateral adrenalectomy	Procedure for intractable Cushing's syndrome or bilateral pheochromocytoma
CAH: most forms can cause salt loss	Commonest cause of PAI in children (80%); may be diagnosed in older individuals
21-Hydroxylase deficiency	Commonest type of CAH is 21-hydroxylase deficiency, with associated hyperandrogenism
11β-hydroxylase deficiency	Hyperandrogenism, hypertension (in older children and adults)
3β-hydroxysteroid dehydrogenase II deficiency	Ambiguous genitalia in boys, hyperandrogenism in girls
P450 side-chain cleavage deficiency (CYP11A1 mutations)	XY sex reversal
P450 oxidoreductase deficiency	Skeletal malformations, abnormal genitalia
Congenital lipoid adrenal hyperplasia (StAR mutations)	XY sex reversal
Adrenal hypoplasia congenita	X-linked NROB1, Xp21 deletion (with Duchenne's muscular deficiency), SF-1 mutations (XY sex reversal), IMAGe syndrome
ACTH insensitivity syndromes	Type 1: ACTH receptor, melanocortin 2 receptor gene MC2R Type 2: MRAP Familial glucocorticoid deficiency (MCM4, NNT, TXNRD2) TripleA (Allgrove's) syndrome, achalasia, Addison's disease, alacrima, AAAS gene mutation
Drug-induced	Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate, aminoglutethimide, drugs that may accelerate cortisol metabolism and induce adrenal insufficiency T_4 also accelerates cortisol metabolism (at least in part through stimulation of 11β-HSD2) CTLA-4 inhibitors may enhance autoimmunity and cause PAI
Other metabolic disorders	Mitochondrial disease (rare) Adrenoleukodystrophy in males Wolman's disease

J Clin Endocrinol Metab, February 2016, 101(2):364–389

INQUADRAMENTO CLINICO

Etiology	Associated Features
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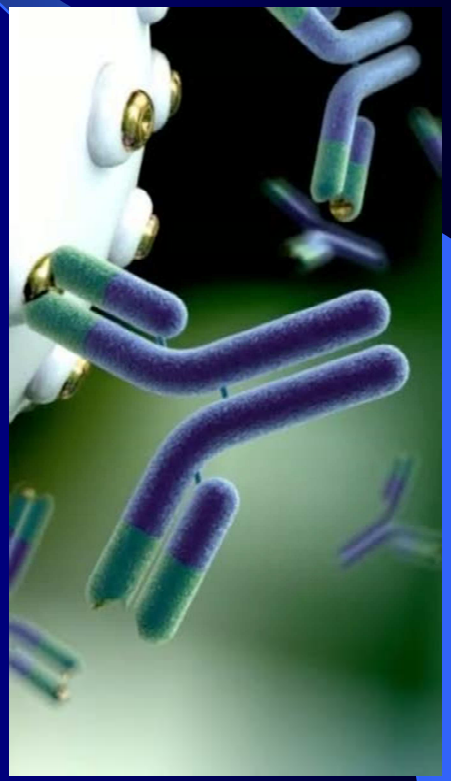
Anticorpi contro la corteccia surrenalica (ACA)

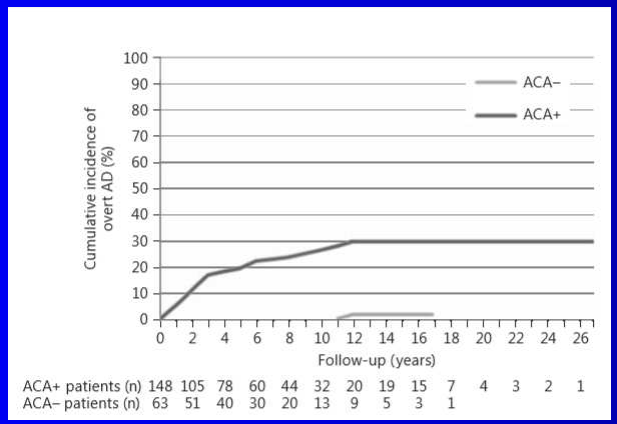
Anticorpi contro l'enzima 21-idrossilasi (21-OHAbs)

90% dei pazienti

presenti alla diagnosi ma anche molti anni prima

predittivi di sviluppo di malattia di Addison



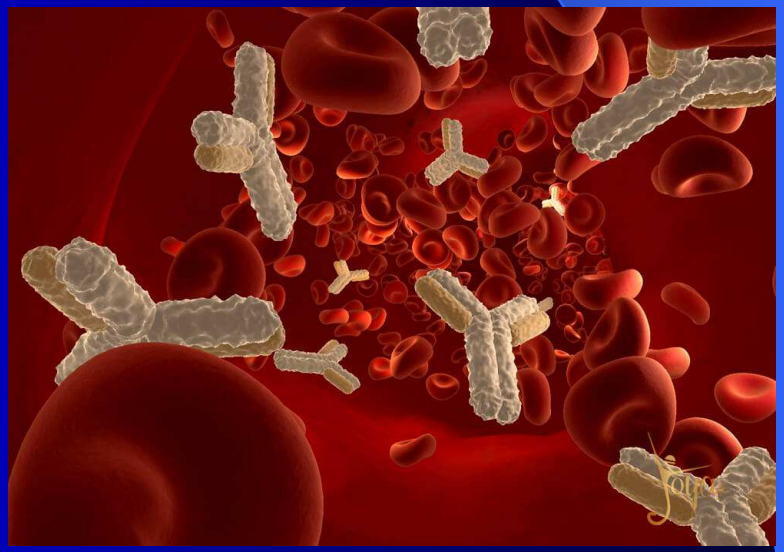


J Clin Endocrinol Metab, February 2016, 101(2):364–389
Betterle et al. In Arvat E, Falorni A (eds): Cortisol Excess and Insufficiency
Front Horm Res. Basel, Karger, 2016, vol 46, pp 133–145 (DOI: 10.1159/000443872)

INQUADRAMENTO CLINICO

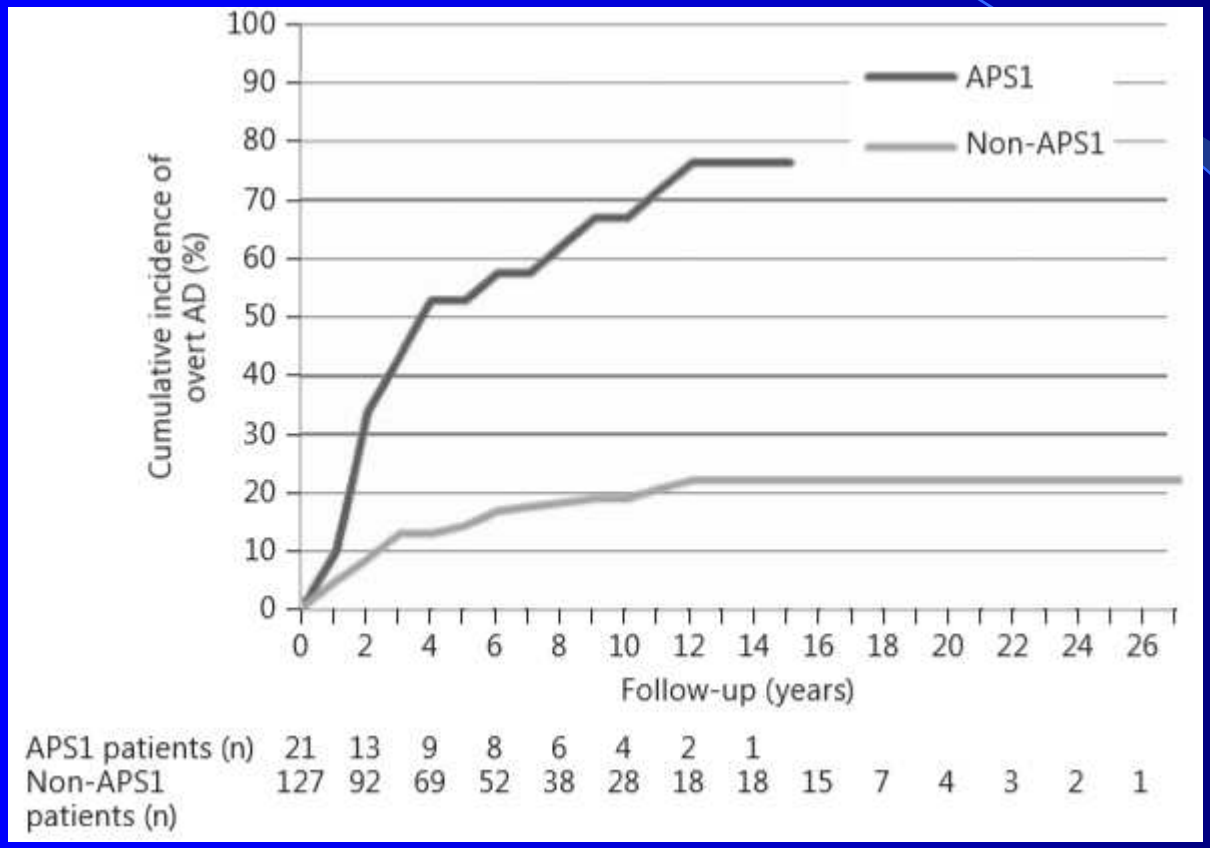
Fattori predittivi di progressione verso la disfunzione surrenalica in pazienti con ACA/21-OH-Ab-positivi

1) genere maschile
2) tipo di malattia autoimmune associata (ipoparatiroidismo, candidiasi mucocutanea vs. tireopatia autoimmune o DM1)
3) titolo ACA/21-OH-Ab
4) livello di funzione surrenalica



INQUADRAMENTO CLINICO

Associazione con APS1



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INQUADRAMENTO CLINICO

	APS-1	APS-2
Manifestations		
Endocrine	**PAI**	**PAI**
	Hypoparathyroidism	**Autoimmune thyroid disease**
	Ovarian failure	**Type 1 diabetes mellitus**
	Type 1 diabetes	
	Autoimmune thyroid disease	
Gastrointestinal	Autoimmune gastritis /pernicious anaemia	Autoimmune gastritis/ pernicious anaemia
	Autoimmune hepatitis	Coeliac disease
	Intestinal malabsorption	
Ectodermal manfistations	Alopecia	Alopecia
	Vitiligo	Vitiligo
	Enamel dysplasia	
	Keratoconjunctivitis	
Hematological	Asplenia	
Others	**Chronic mucocutanous candidiasis**	

Bensing et al. Eur J Endocrinol 2016

INQUADRAMENTO CLINICO

Stadi della malattia di Addison

	Stadio	ACA e/o 21-OHAbs	Renina basale	Aldosterone basale	ACTH basale	Cortisolo basale	Cortisolo +60' post ACTH	Clinica
Potenziale	0	+	N	N	N	N	N	No
Subclinico (deficit mineralcorticoidi)	1	+	↑	N	N	N	N	No
Subclinico (deficit mineralcorticoidi + ridotta riserva glucocorticoidi)	2	+	↑	N/↓	N	N	↓	No
Subclinico (deficit mineralcorticoidi e glucocorticoidi)	3	+	↑	↓	↑	N/↓	↓↓	No
Cinico (grave deficit mineralcorticoidi e glucocorticoidi)	4	+	↑↑	↓	↑↑	↓↓	↓↓	Si

Betterle et al. In Arvat E, Falorni A (eds): Cortisol Excess and Insufficiency
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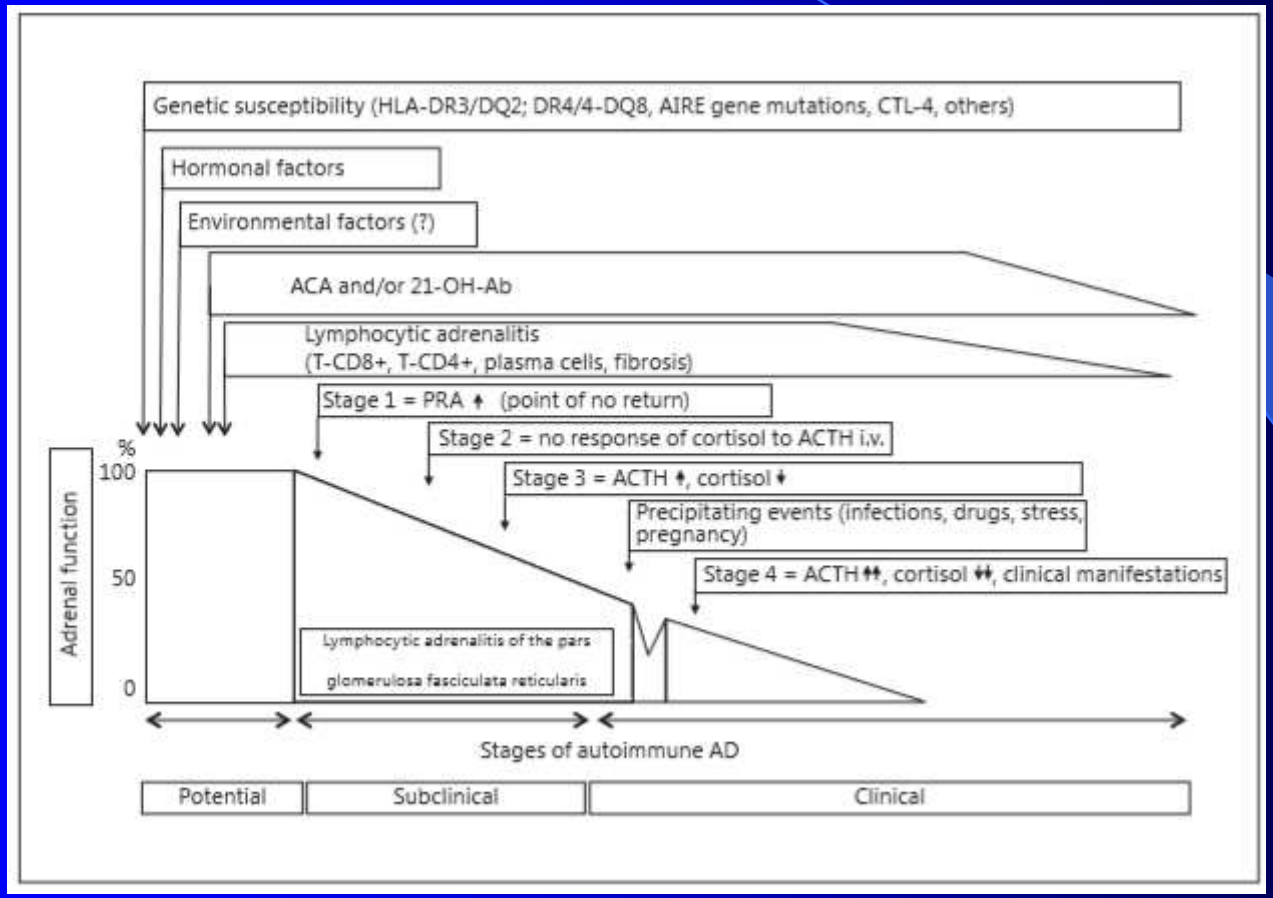
INQUADRAMENTO CLINICO

Fasi della malattia di Addison



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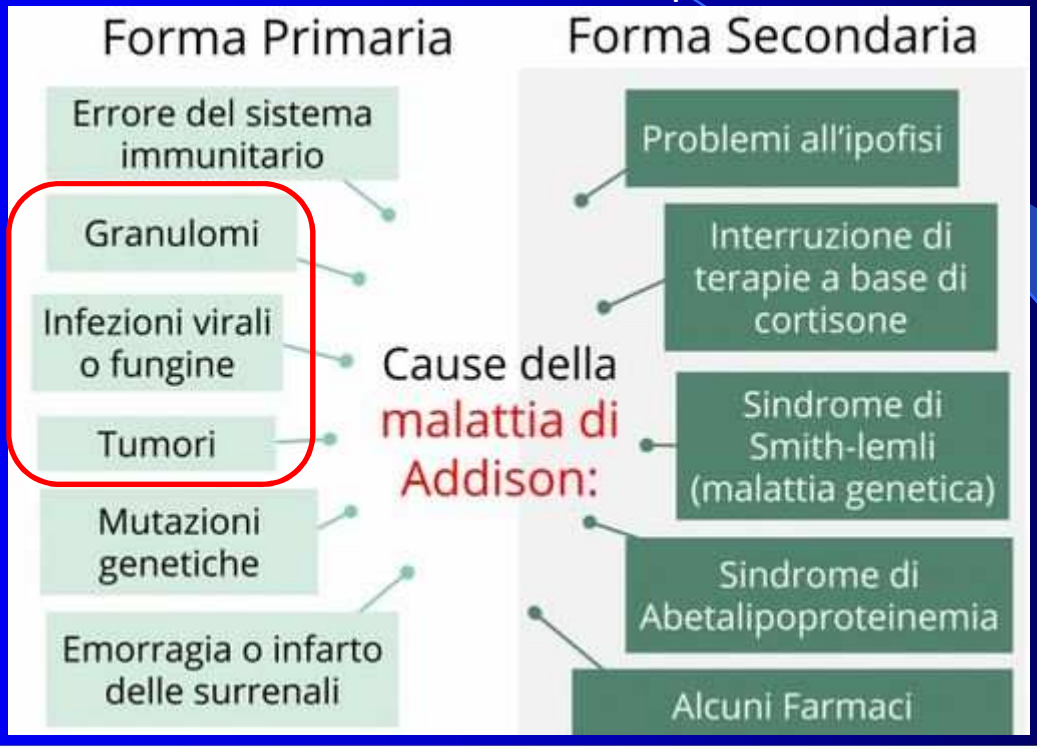
INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

Insufficienza surrenalica primitiva



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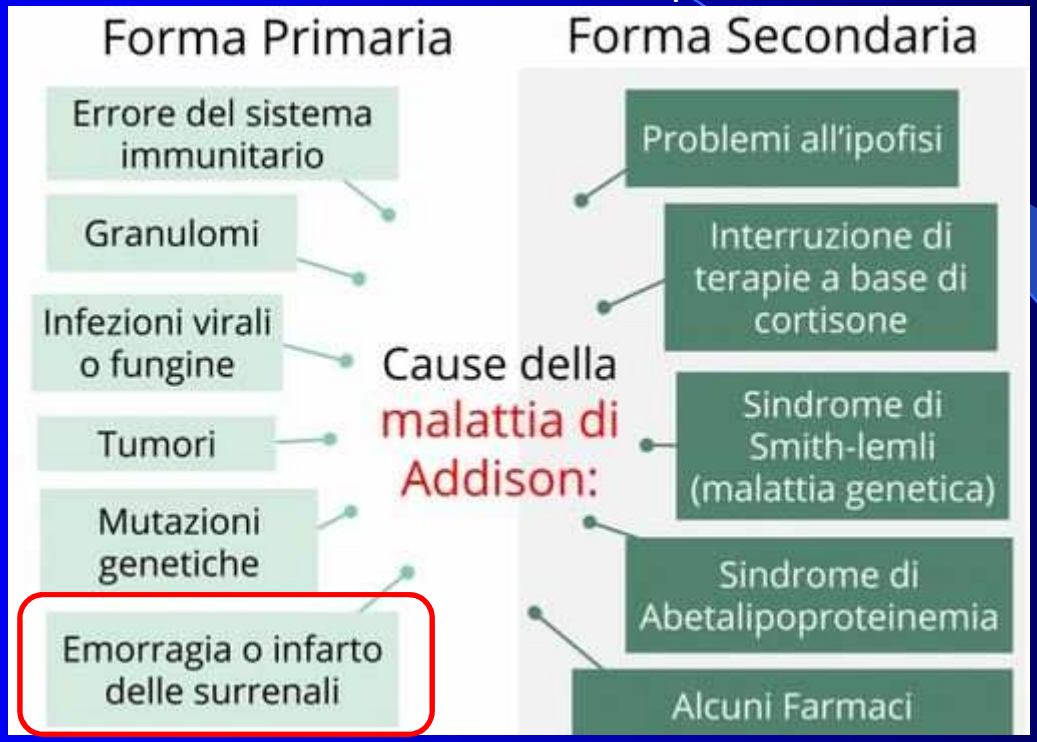


Sindrome di Waterhouse Friederichsen

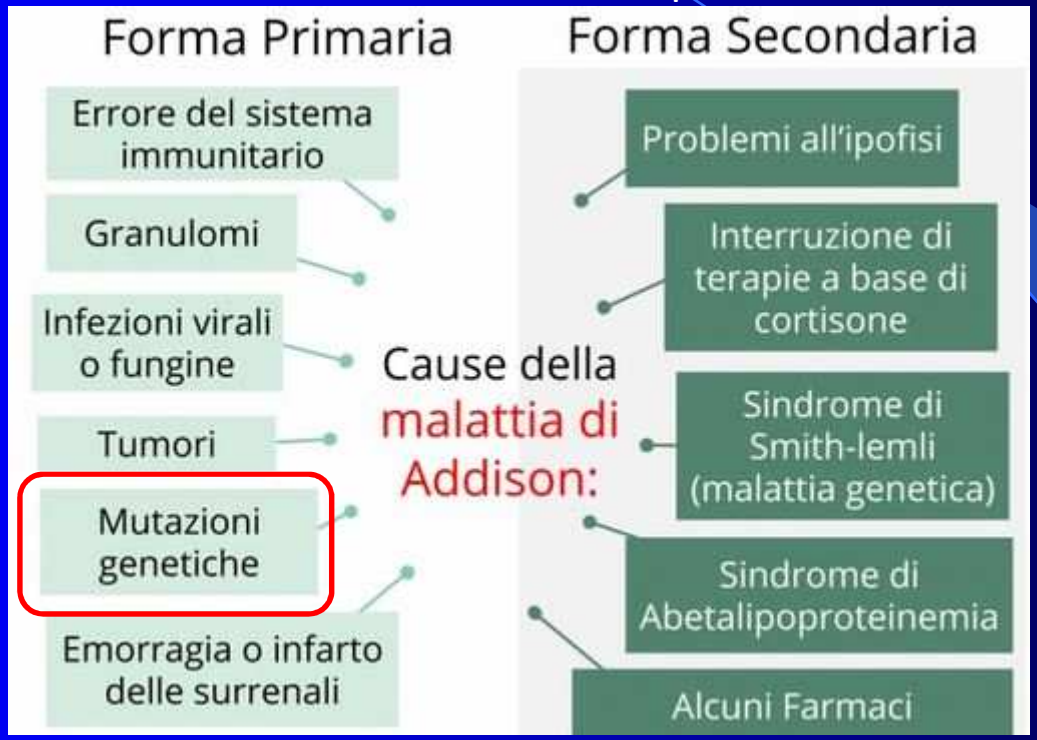
insufficienza surrenalica acuta emorragica correlata a setticemia

(Neisseria meningitidis, Pseudomonas aeruginosa, Hemophilus influenzae, Streptococchi)

INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

Insufficienza surrenalica primitiva



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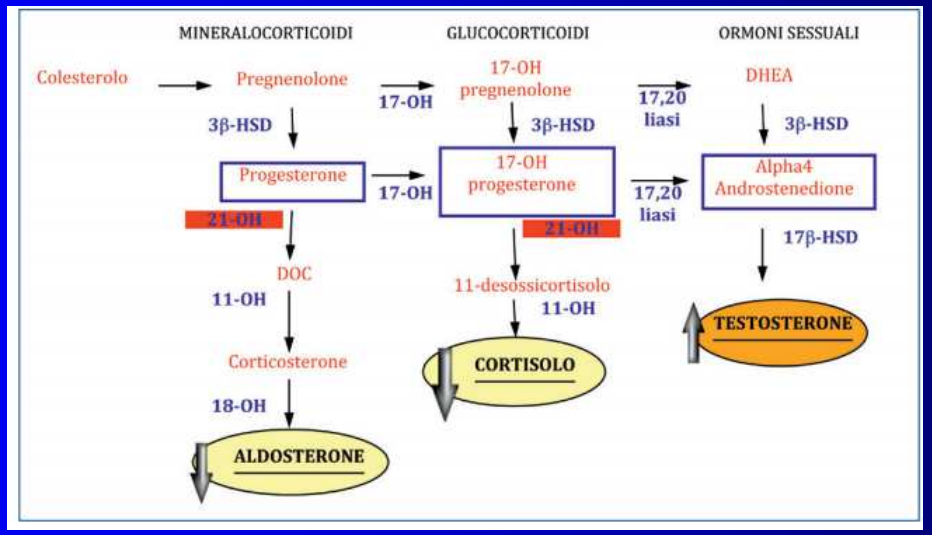
Congenital lipoid adrenal hyperplasia (StAR mutations)	XY sex reversal

La forma più frequente è il deficit di 21-idrossilasi



J Clin Endocrinol Metab, February 2016, 101(2):364–389

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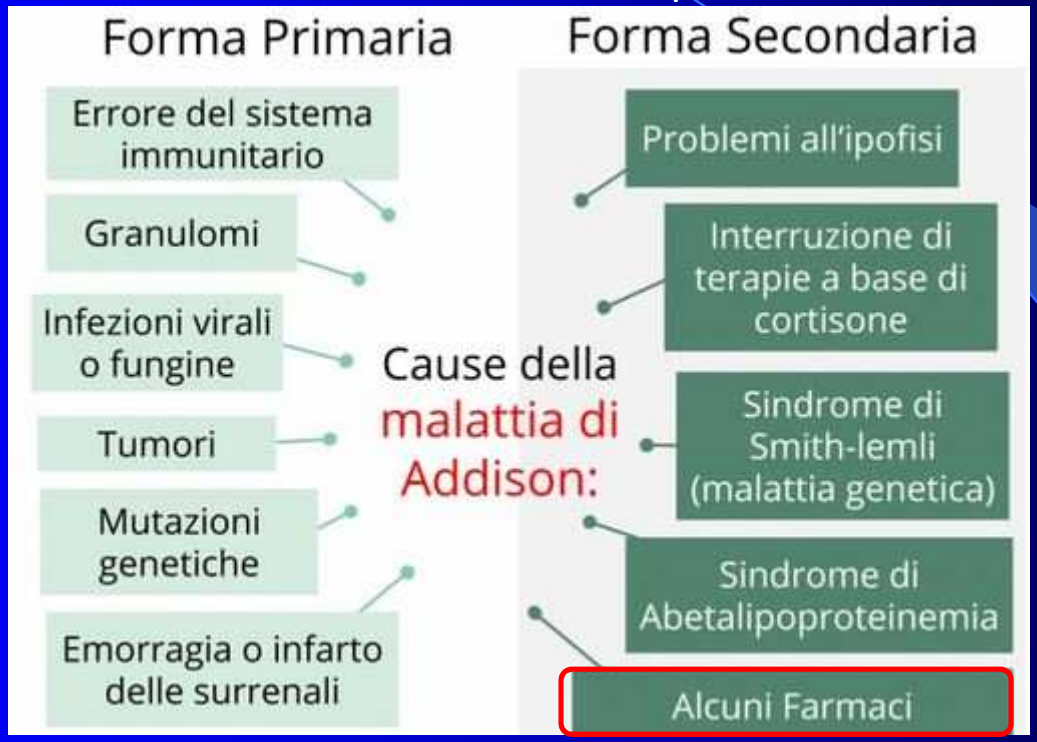
INQUADRAMENTO CLINICO

MALATTIA DI ADDISON

Insufficienza surrenalica primitiva



INQUADRAMENTO CLINICO

Anticoagulanti → Emorragia surrenalica

Ketoconazolo
Mitotane
Rifampicina
Abiraterone
Carbamazepina
Etomidate
Fenitoina
Inquinanti ambientali
→ Alterazione della sintesi o del metabolismo dei glucocorticoidi

Immune checkpoint inhibitors → Adrenalite autoimmune

Bornstein SR. Predisposing factors for adrenal insufficiency. N Engl J Med 2009; 360: 2328–2339

Konda et al. Curr Opin Endocrinol Diabetes Obes 2017; 24: 337–347

Barroso-Sousa et al. JAMA Oncol 2018; 4: 173–182

INQUADRAMENTO CLINICO

MANIFESTAZIONI CLINICHE

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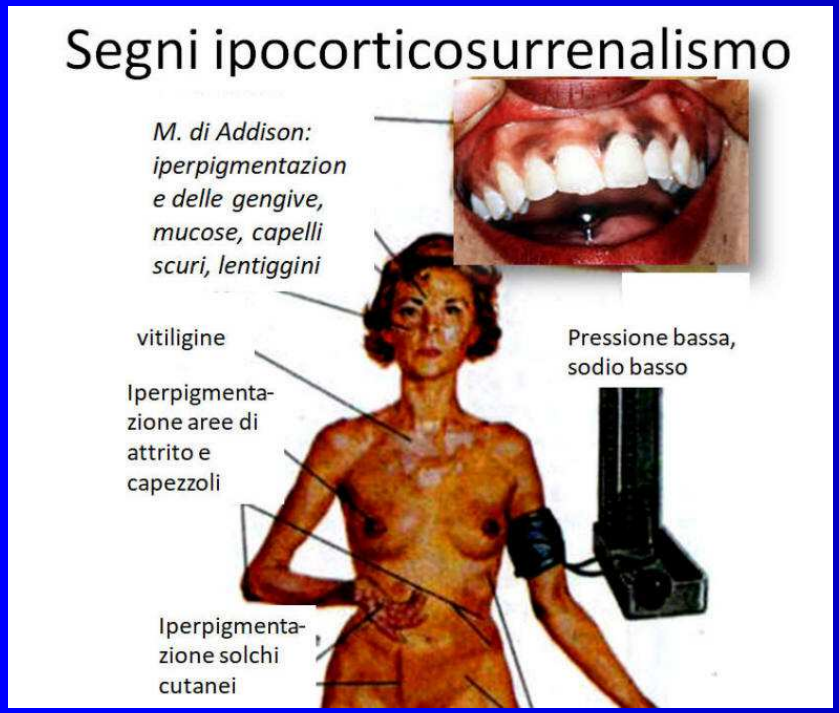
INQUADRAMENTO CLINICO

MANIFESTAZIONI CLINICHE



Ipoglicemia
Iperkaliemia
Iponatraemia
Deplezione di volume

Attenzione a pazienti con patologie autoimmuni (vitiligine, diabete mellito di tipo 1, gastrite autoimmune) o con malattie infettive (TBC, HIV, citomegalovirus, candidiasi, istoplasmosi)

Bornstein et al. J Clin Endocrinol Metab 2016; 101: 364–389

INQUADRAMENTO CLINICO

MANIFESTAZIONI CLINICHE

SPECIAL FEATURE

Clinical Practice Guideline

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

Symptoms	Signs	Routine Laboratory Tests
Adrenal insufficiency		
Fatigue	Hyperpigmentation (primary only), particularly of sun-exposed areas, skin creases, mucosal membranes, scars, areola of breast	Hyponatremia
Weight loss	Low blood pressure with increased postural drop	Hyperkalemia
Postural dizziness	Failure to thrive in children	Uncommon: hypoglycemia, hypercalcemia
Anorexia, abdominal discomfort		
Adrenal crisis		
Severe weakness		Hyponatremia
Syncope	Hypotension	Hyperkalemia
Abdominal pain, nausea, vomiting; may mimic acute abdomen	Abdominal tenderness/guarding	Hypoglycemia
Back pain	Reduced consciousness, delirium	Hypercalcemia
Confusion		

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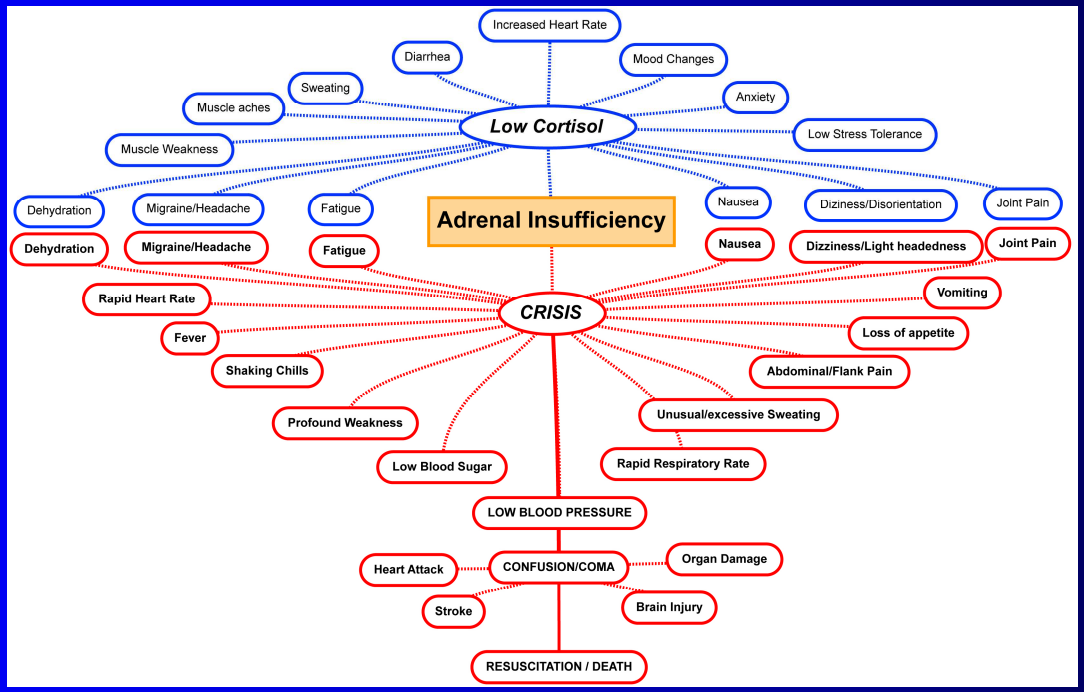
INQUADRAMENTO CLINICO

MANIFESTAZIONI CLINICHE

Insufficienza surrenalica acuta

EMERGENZA ENDOCRINA



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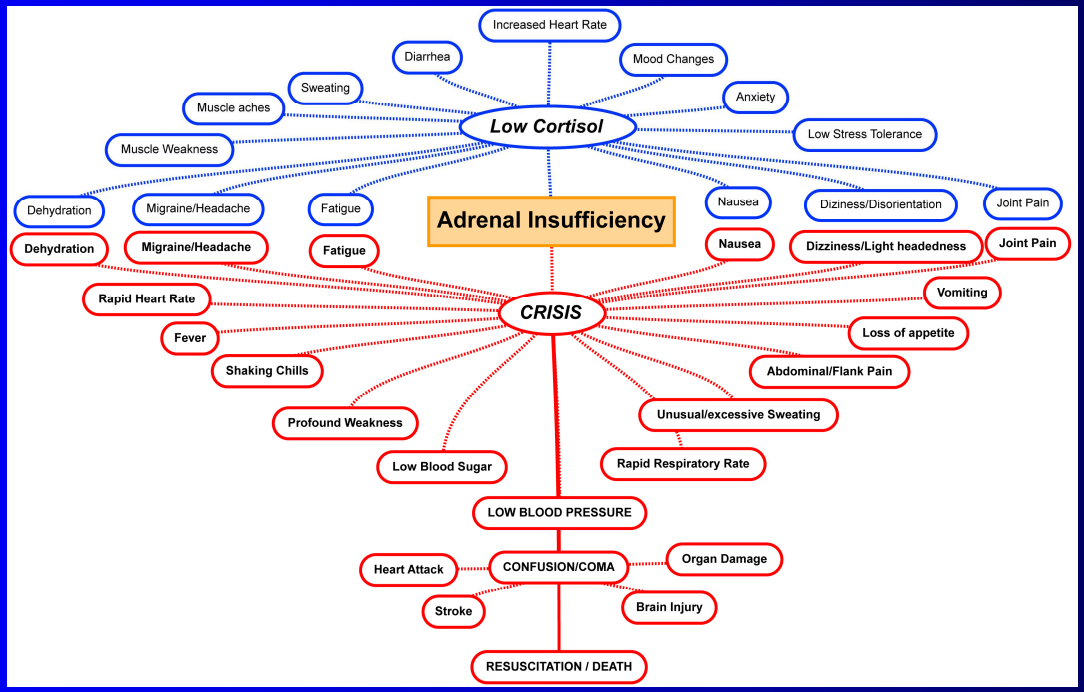
INQUADRAMENTO CLINICO

MANIFESTAZIONI CLINICHE

Insufficienza surrenalica acuta

EMERGENZA ENDOCRINA



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INQUADRAMENTO CLINICO

MALATTIA DI ADDISON


FATIGUE
MEN
MELATONIN
ALDOSTERONE
PARATHYROID
POTASSIUM
INSUFFICIENCY
GLUCAGON
PITUITARY
THYMUS
OVARIES
MOOD
POLYCYSTIC OVARY
ADRENAL
WOMEN
CORTISOL
HORMONES
SOMATOSTATIN
PANCREAS
ENDOCRINE
GROWTH
PROLACTIN
HYPOTHALAMUS
SYSTEM
TESTES
SYNDROME
PINEAL
ENDORPHINS
CLINICAL
THYROID
METABOLISM
NAUSEA
KIDNEYS
DISORDERS
ESTROGEN
FATIGUE
GLANDS
DIABETES
DEHYDRATION
ACROMEGALY
PRECOCIOUS
PUBERTY
CHILDREN

INQUADRAMENTO CLINICO

INQUADRAMENTO CLINICO