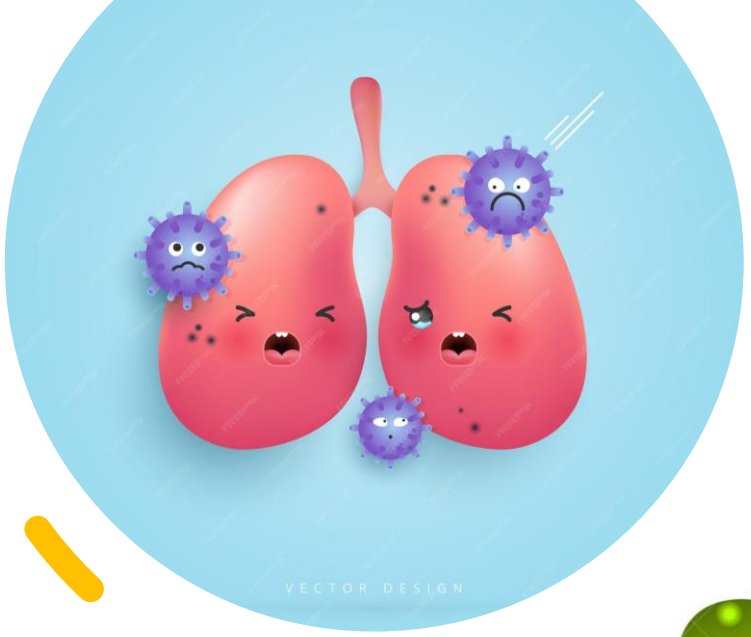
Il mio paziente fa infezione a ripetizione



Dott.ssa Gaia Mancuso
Immunologia Clinica
Ente Ospedaliero Cantonale

Agenda:

- Le infezioni ricorrenti sono una preoccupazione crescente nella pratica clinica.

- L’obiettivo di questo workshop è esplorare le cause, le diagnosi e le modalità di gestione per pazienti che sviluppano infezioni ripetute.

Valutazione clinica:

Natura delle infezioni:

- Frequenza
- Cronicità
- Gravità
- Riposta alla terapiaa
- Interessamento d’organo
- Patogeno

Età di insorgenza della malattia
Alterazioni della crescita
Storia personale di malattie linfoproliferative

Familiarità per:

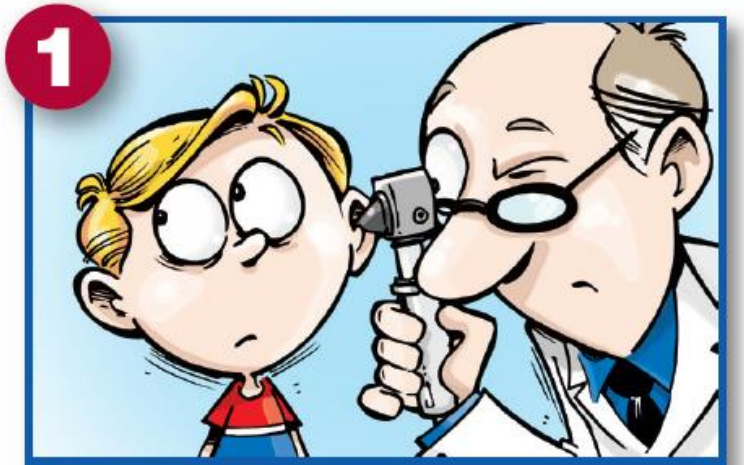
- Suscettibilità alle infezioni
- Malattie autoimmuni
- Malattie linfoproliferative

Valutazione Clinica

- anomalie anatomiche o segni e stigmate di disturbi sottostanti significativi (p.es., insufficienza venosa).
- indice di massa corporea (BMI)
- sequele di infezioni ricorrenti sotto forma di cicatrici (delle membrane timpaniche o della pelle), segni di malattia polmonare cronica (tosse cronica, riflesso del vomito assente, bastonate, crepitii o respiro sibilante per suggerire bronchiectasie)
- infezione in corso (segni di sinusite cronica, mughetto orale, verruche o infezioni da dermatofiti).
- linfoadenopatia e/o l'epatosplenomegalia

10 Warning Signs of Primary Immunodeficiency

1



Four or more new ear infections within one year.

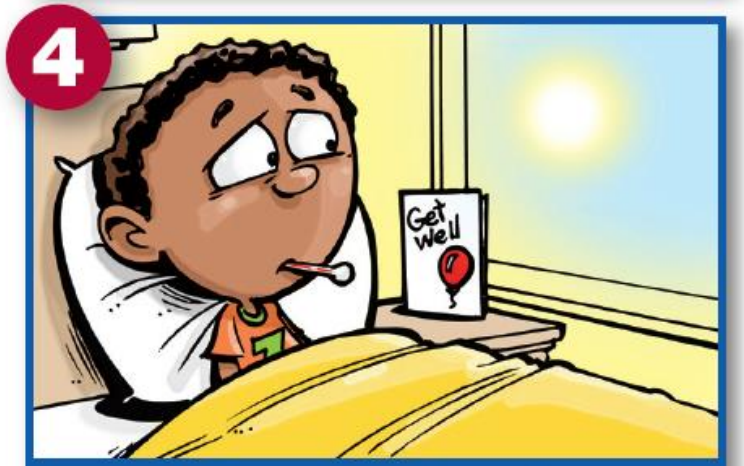
2

Two or more serious sinus infections within one year.

3

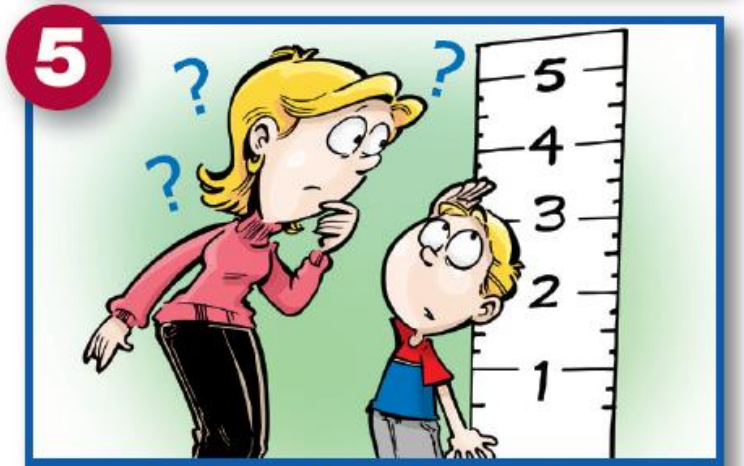
Two or more months on antibiotics with little effect.

4



Two or more pneumonias within one year.

5



Failure of an infant to gain weight or grow normally.

6

Recurrent, deep skin or organ abscesses.

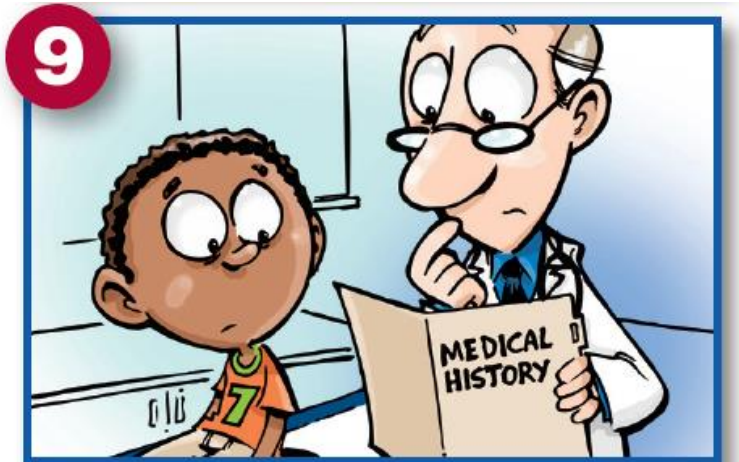
7

Persistent thrush in mouth or fungal infection on skin.

8

Need for intravenous antibiotics to clear infections.

9

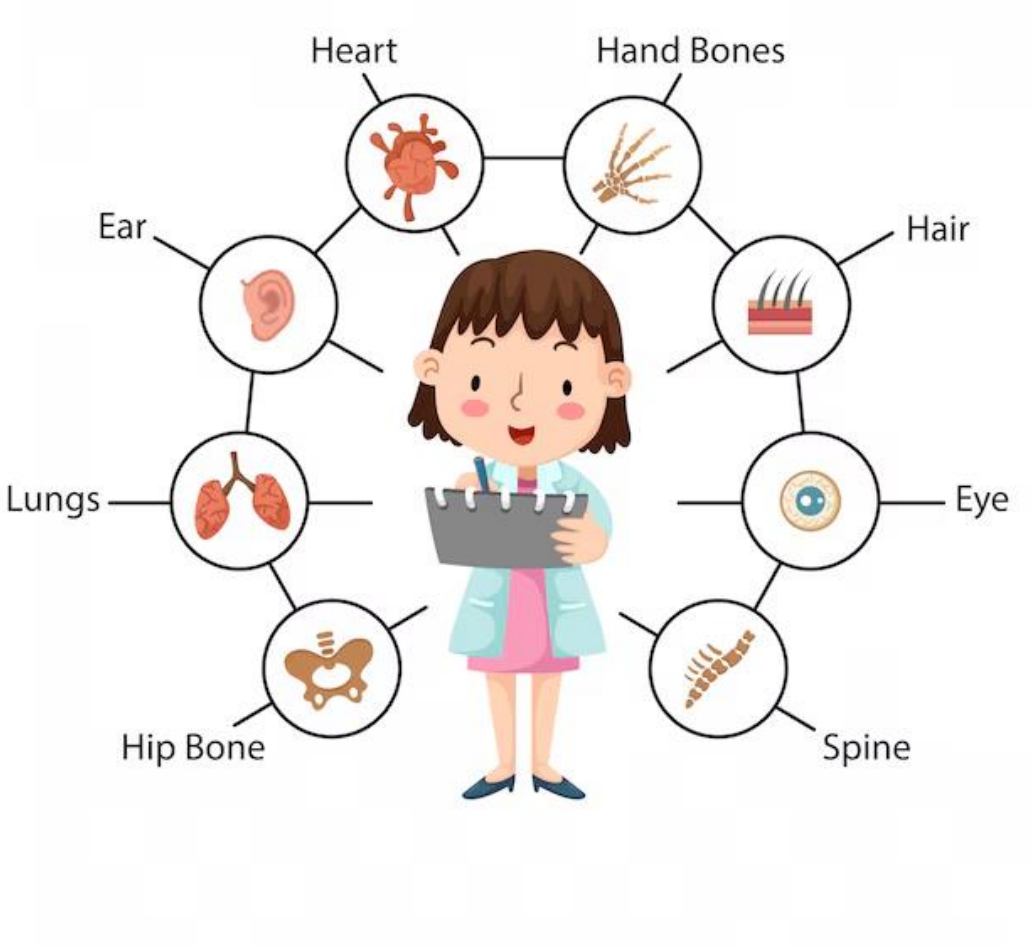


Two or more deep-seated infections including septicemia.

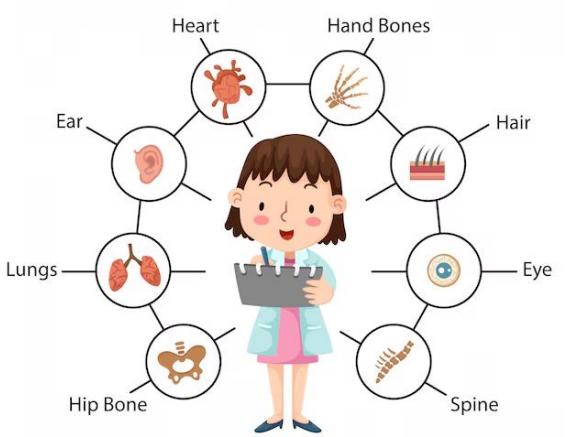
10

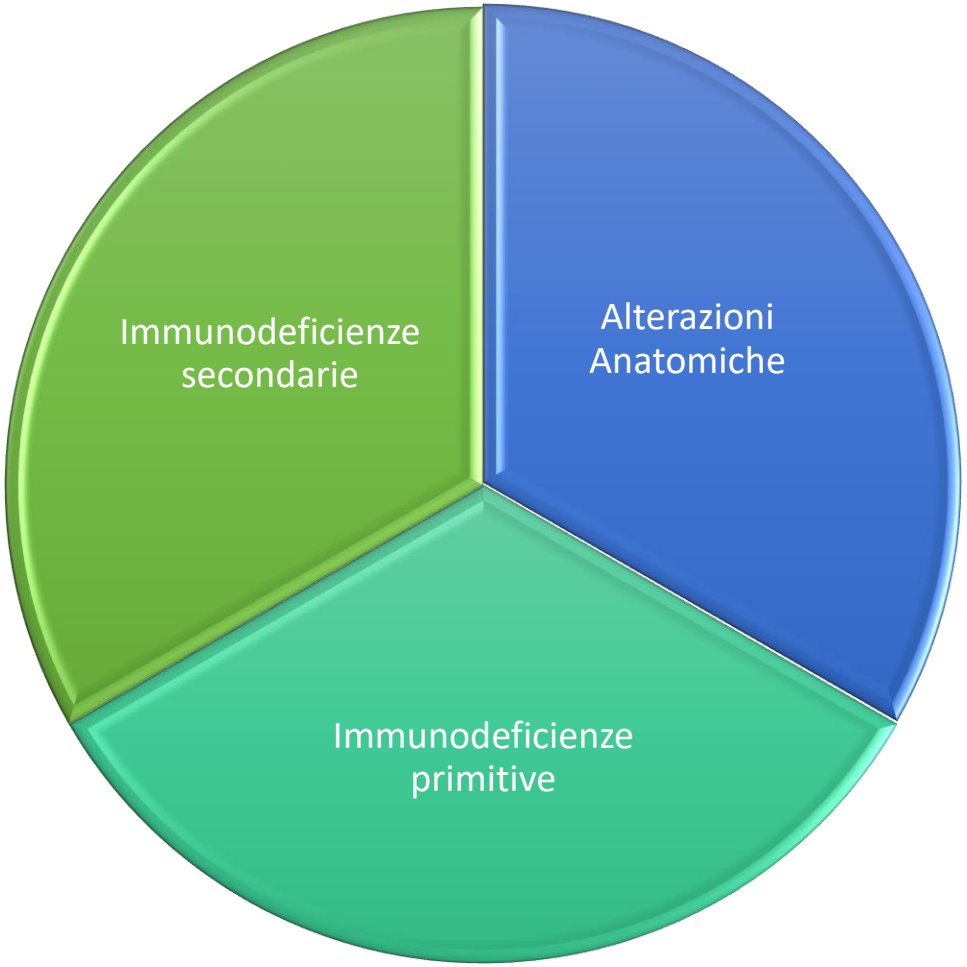
A family history of PI.

VALUTAZIONE CLINICA – Overview eziologie



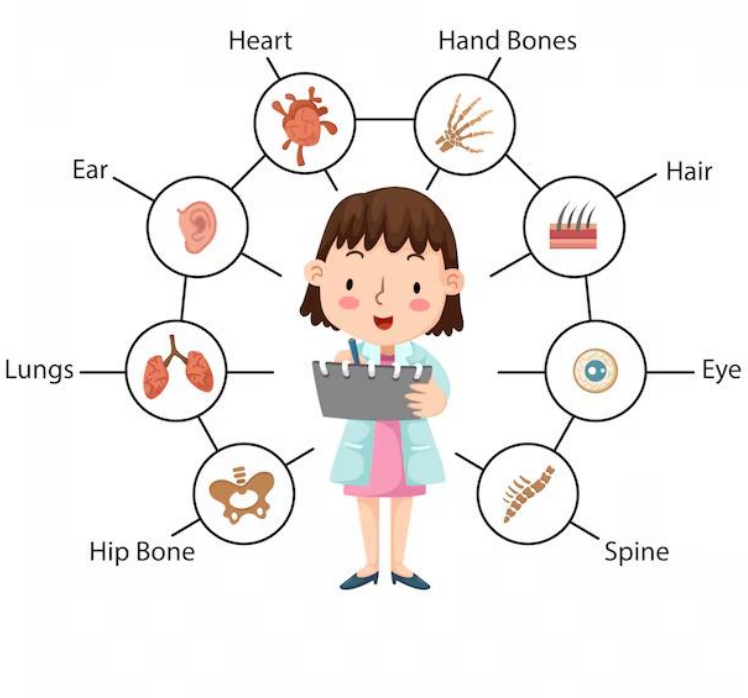
VALUTAZIONE CLINICA – Overview Eziologie

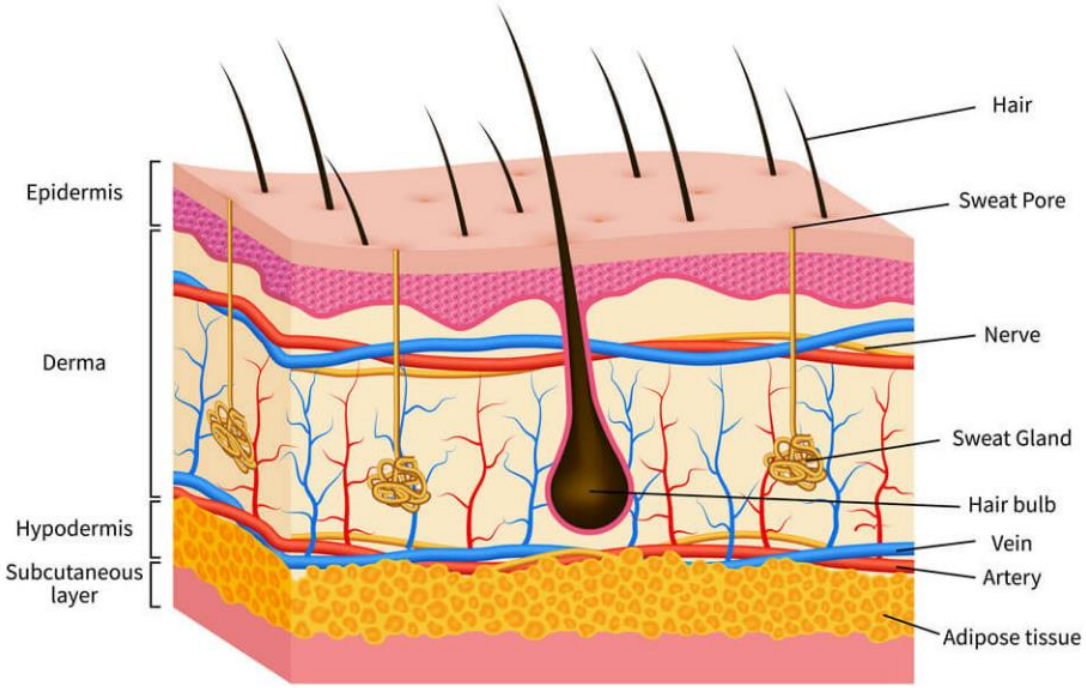




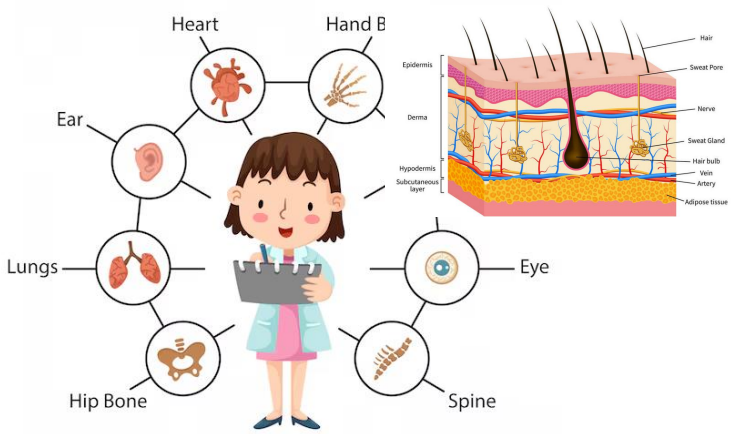
VALUTAZIONE CLINICA – Overview Eziologie – il sito d’infezione

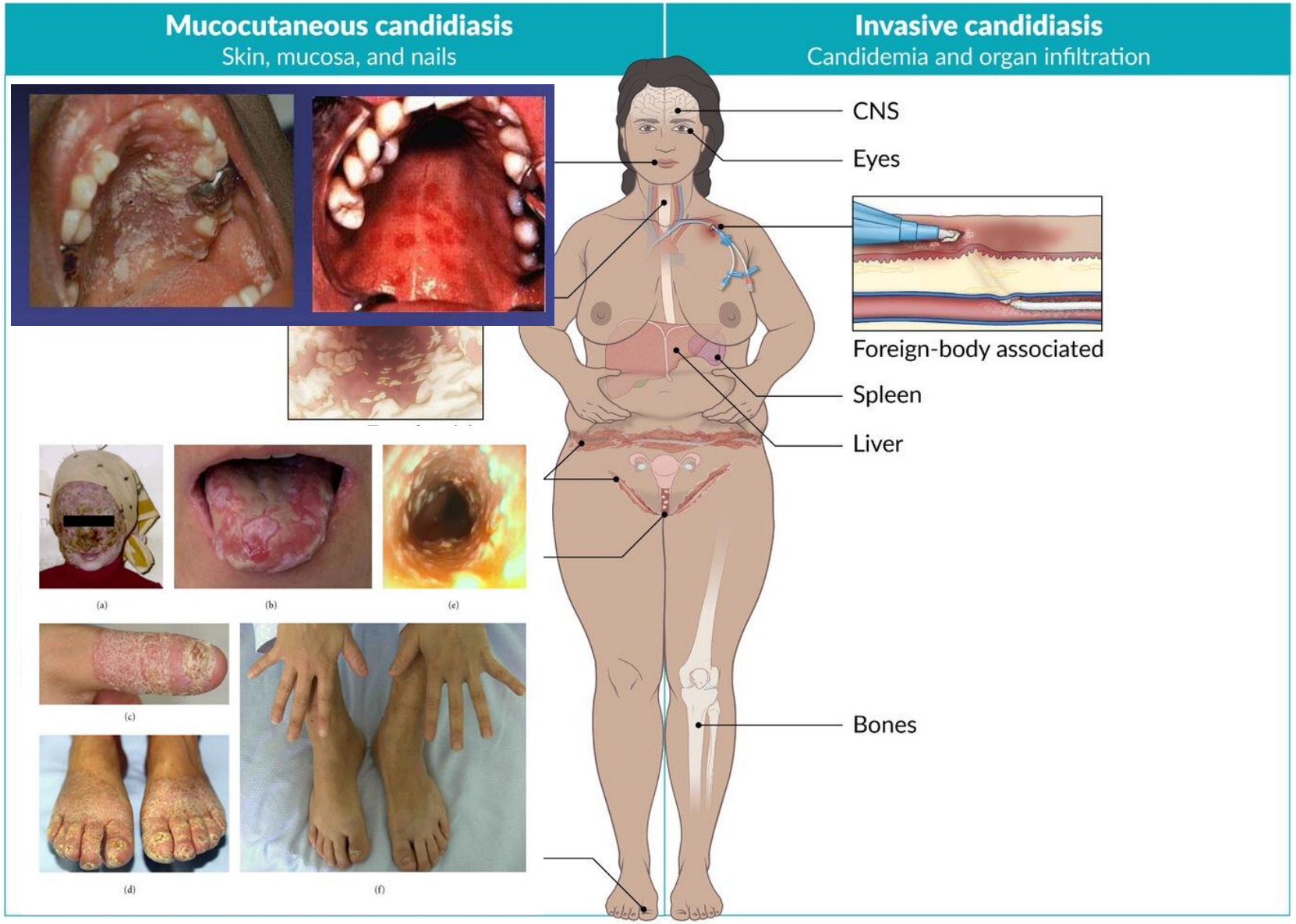
- Impetigine
- Cellulite
- Ascessi cutanei riconrrenti



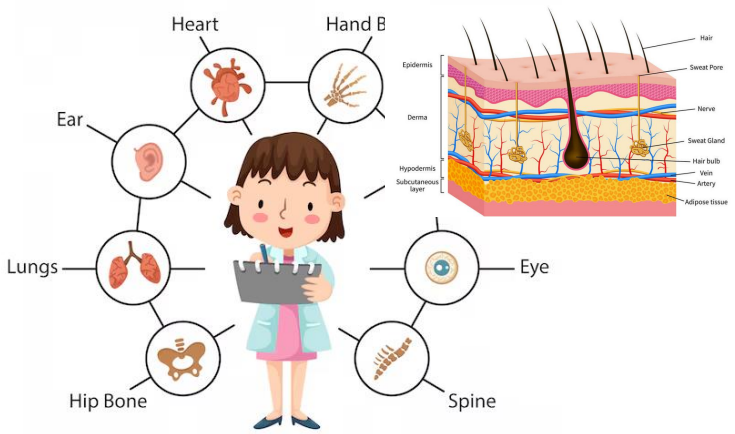


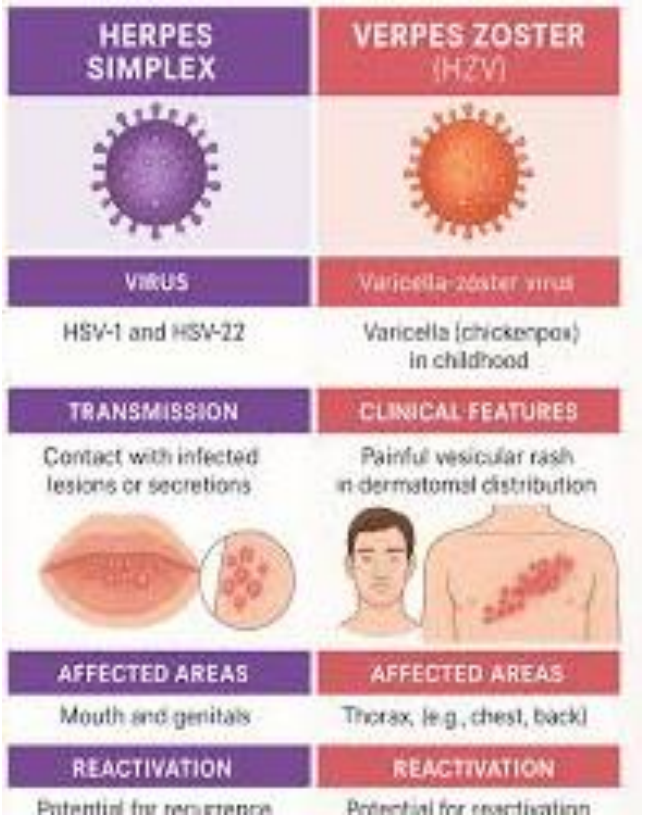
VALUTAZIONE CLINICA – Overview Eziologie – il sito d'infezione





VALUTAZIONE CLINICA – Overview Eziologie – il sito d'infezione

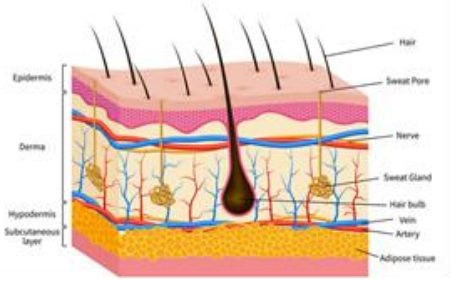




Nei pazienti con focolai ricorrenti o gravi, è importante confermare la diagnosi di herpes preferibilmente mediante immunofluorescenza diretta, coltura virale, diagnosi molecolare mediante PCR o sierologia.

La frequenza di recidiva:

- l'età al momento dell'infezione primaria,
- l'età al momento della recidiva (immaturità immunologica nell'infanzia, diminuzione della protezione immunitaria in età avanzata),
- variazioni del ceppo virale,
- fattori scatenanti dell'infiammazione nella distribuzione dei neuroni infettati in modo latente
- malattie dell'ospite sottostanti.



VALUTAZIONE CLINICA – Overview Eziologie – il sito d'infezione

ASCESSI

A. Ascessi ricorrenti nella stessa sede

Causati da difetti locali:

- **Cisti branchiale, cisti pilonidale, uracale**
- **Idrosadenite suppurativa**
- **Corpi estranei**

Non indicano immunodeficienza sistemica.

B. Ascessi associati a condizioni sistemiche

Malattia di Crohn:

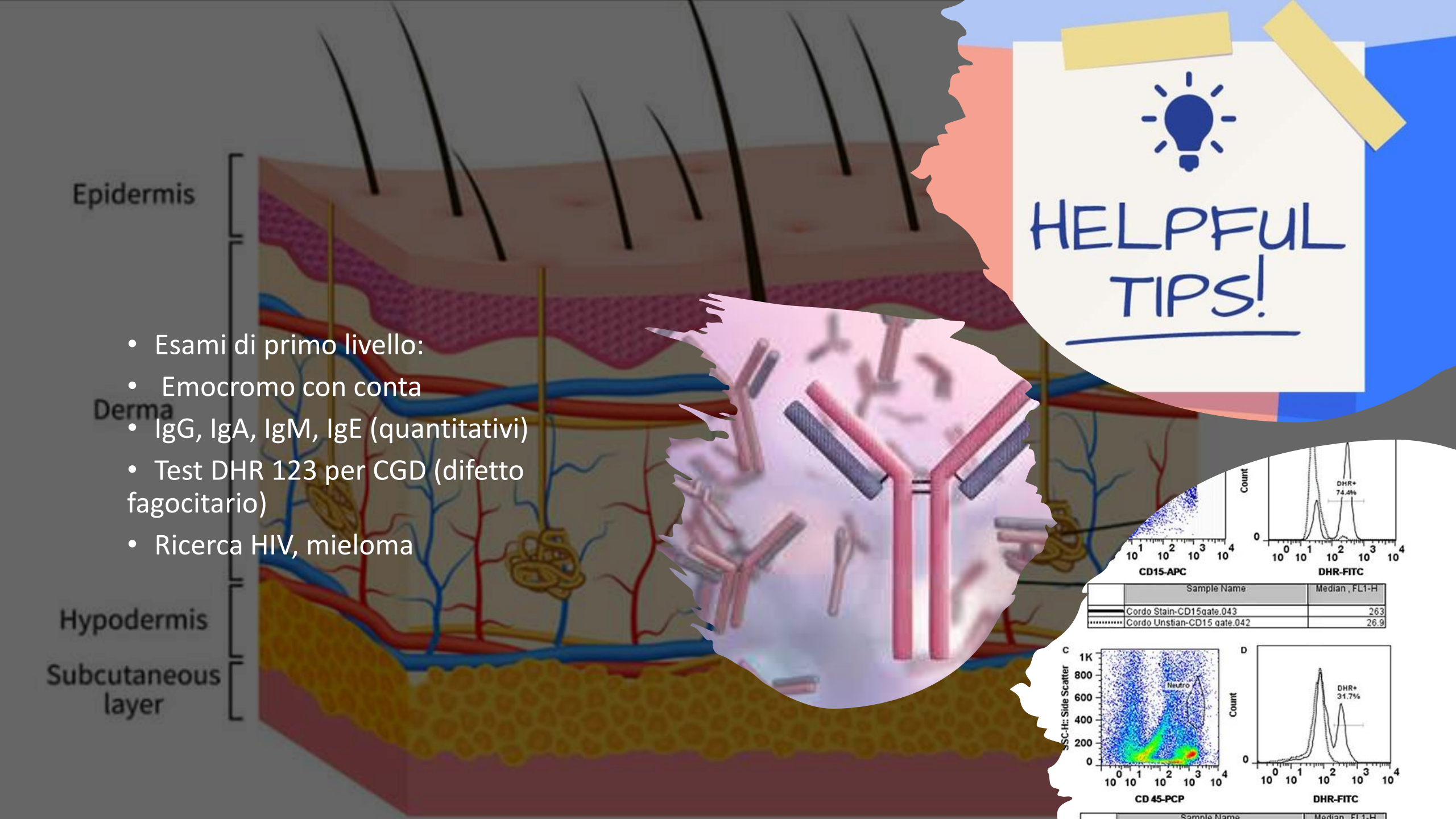
- Ascessi inguinali/perianali o intra-addominali.
- Immunodeficienze correlate: **CGD, carenze anticorpali, deficit XIAP**.

Condizioni immunosoppressive acquisite:

- Diabete
- HIV
- Altre (**mielofibrosi**)

Cause comportamentali:

- Abuso di droghe (iniezione sottocutanea/"skin-popping")
- **Sindrome di Munchausen**

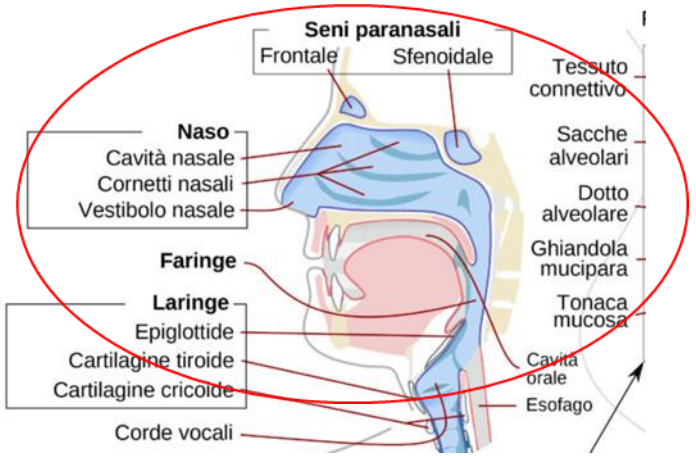


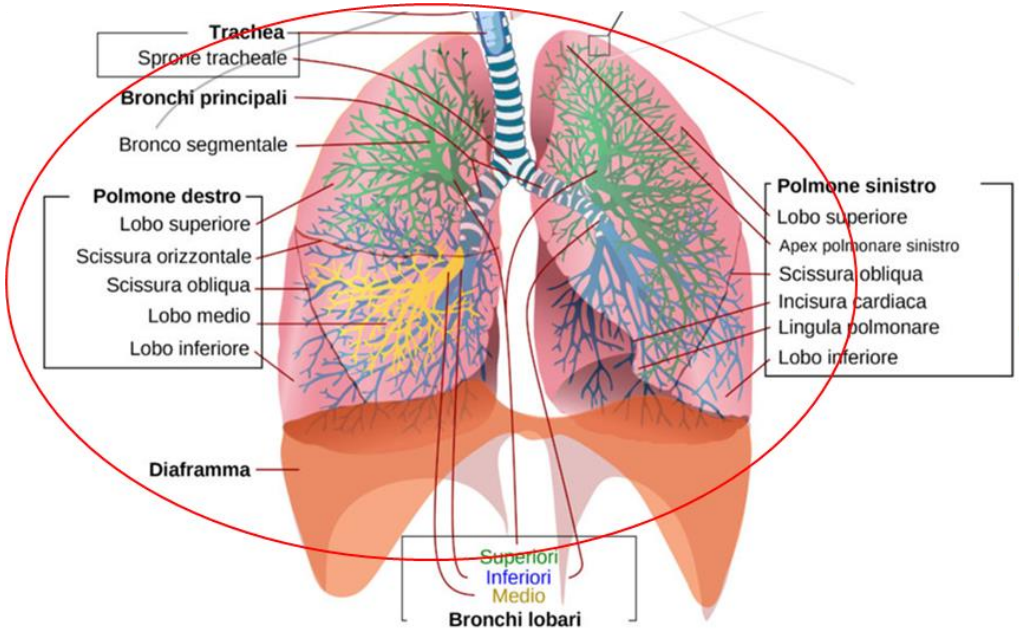
HELPFUL TIPS!

- Esami di primo livello:
- Emocromo con conta
- IgG, IgA, IgM, IgE (quantitativi)
- Test DHR 123 per CGD (difetto fagocitario)
- Ricerca HIV, mieloma

VALUTAZIONE CLINICA – Overview Eziologie – il sito d'infezione

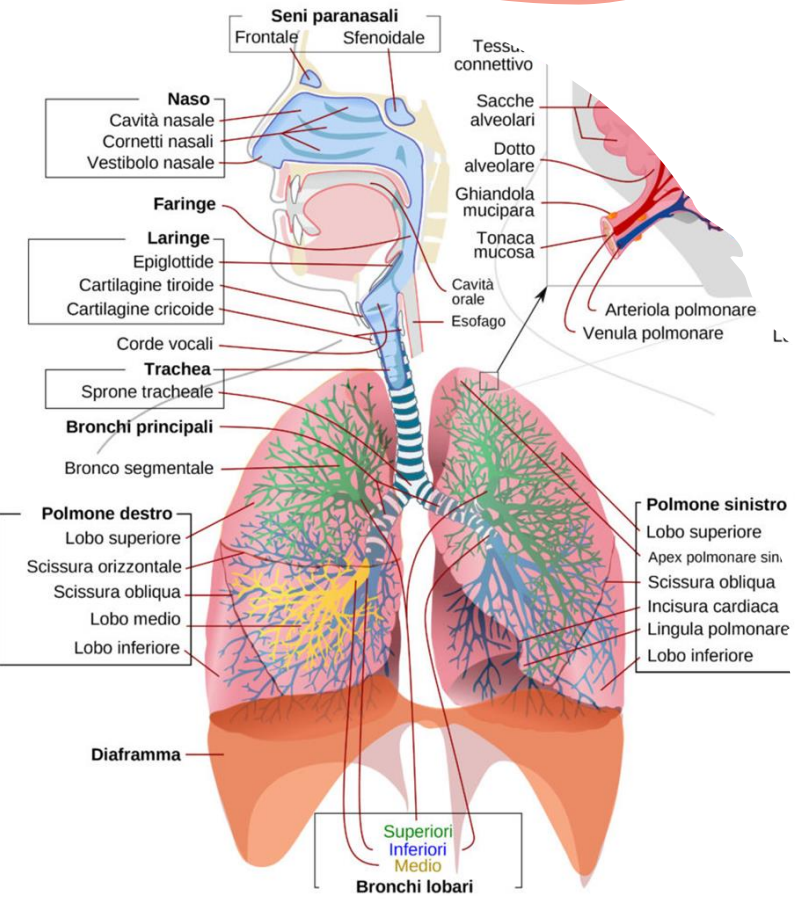
Sinusite
Faringite
Otite media





Polmonite

- Limitata ad una particolare regione anatomica
  - Anomalie estrinseche
  - Anomalie intrinseche
- Diversi lobi polmonari
  - Fibrosi Cistica, Sindrome delle cigli aimmonili
  - Immunodeficienza secondaria o primaria

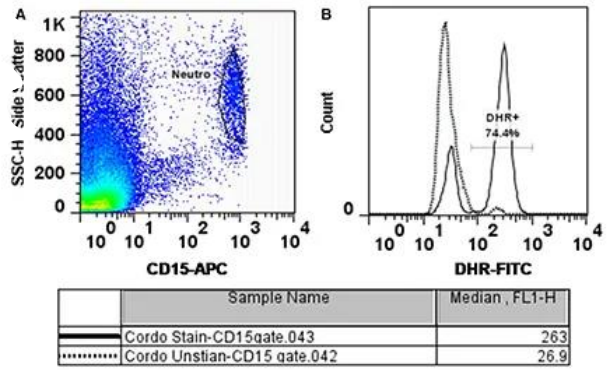


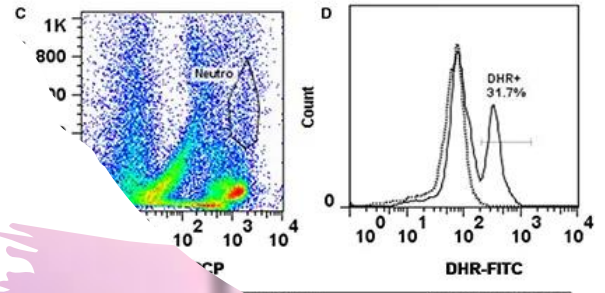
Esami di primo livello:

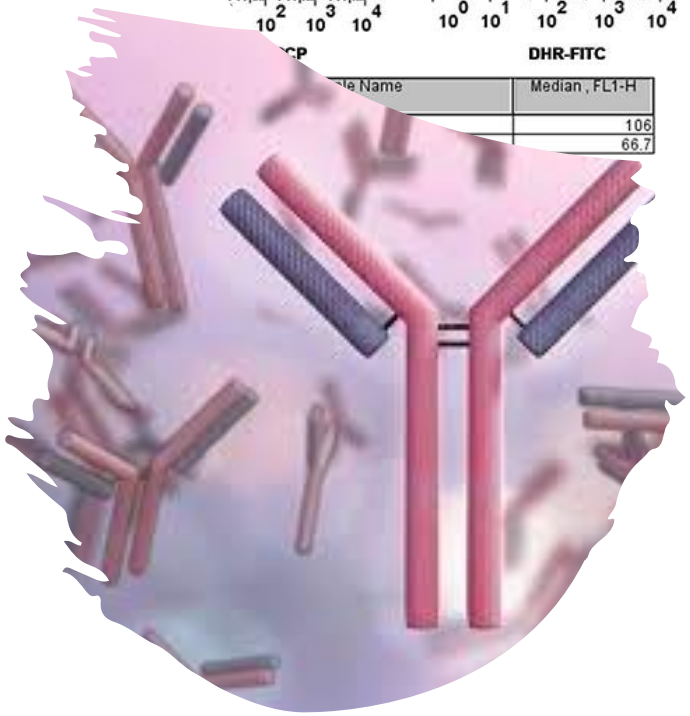
- IgG, IgA, IgM, IgE (quantitativi)
- Test DHR 123 per CGD (difetto fagocitario)
- Ricerca HIV, mieloma, malattie autoimmuni

Esami di secondo livello (se Ig normali):

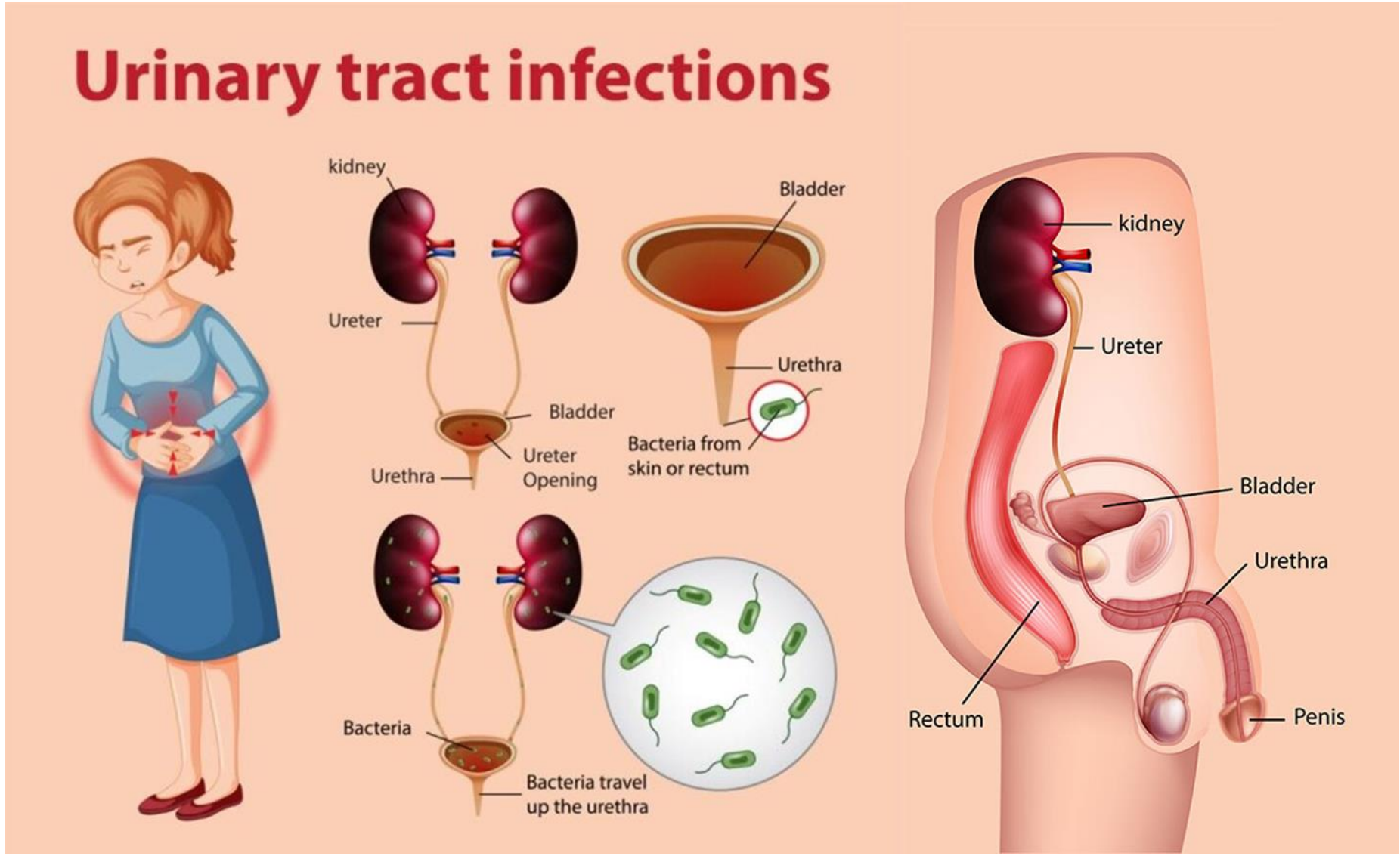
- Sottoclassi IgG (IgG1, IgG2, IgG3, IgG4)
- Anticorpi antipolisaccaridici (pre e post vaccino pneumococcico)



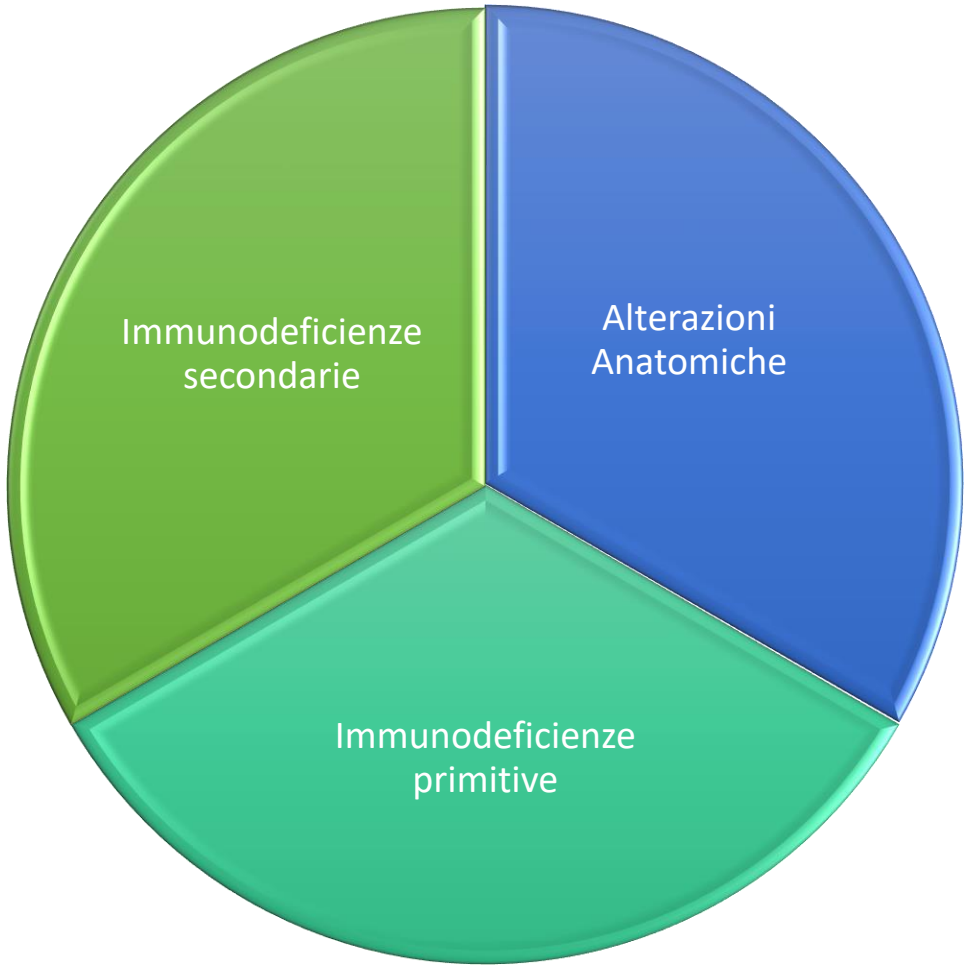


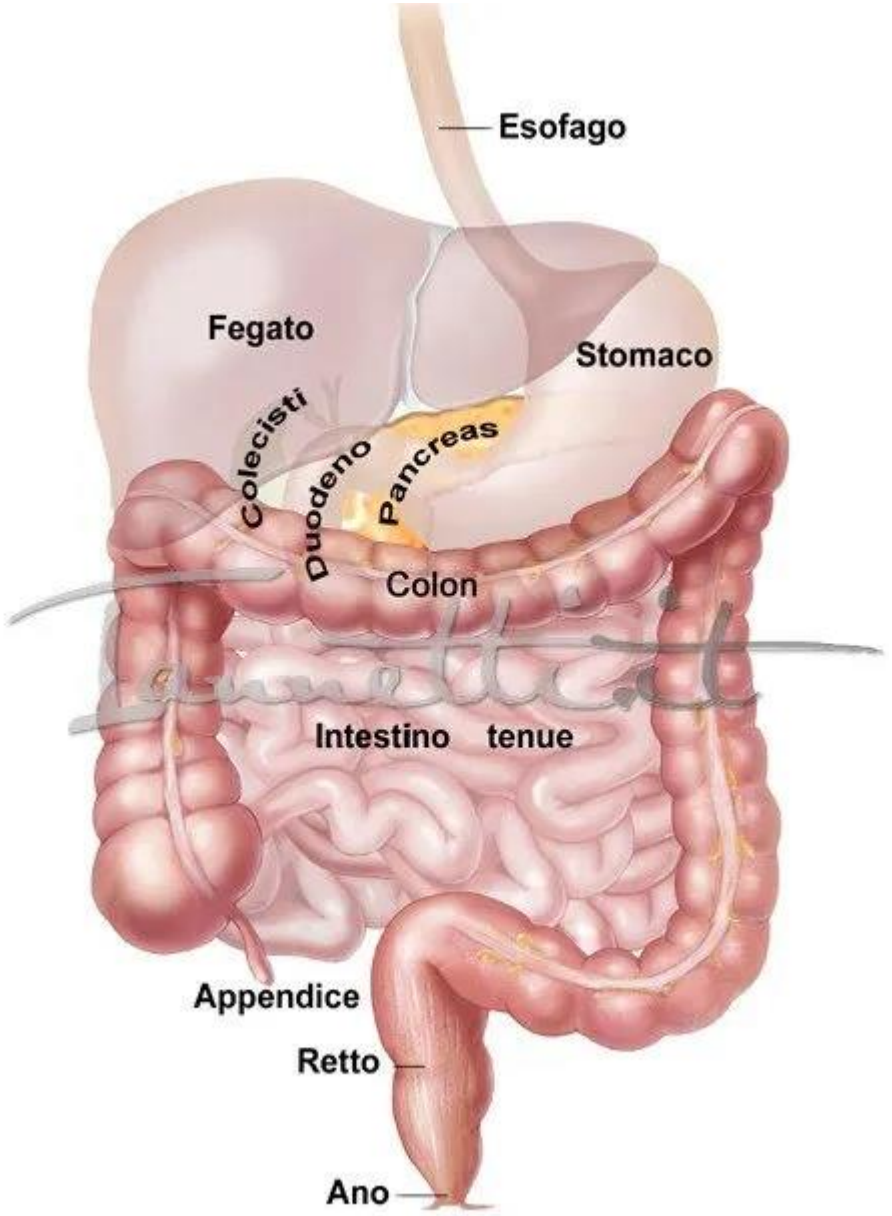


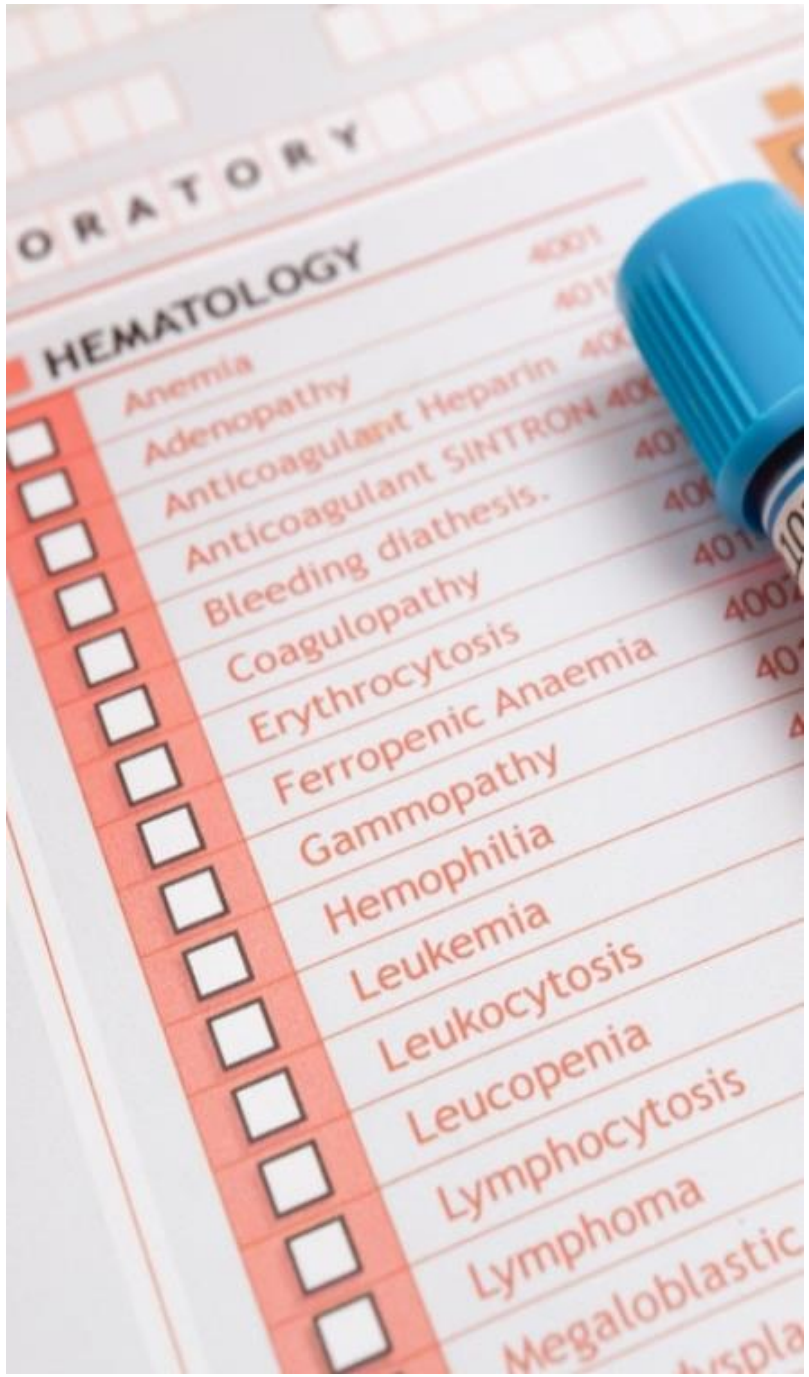
VALUTAZIONE CLINICA – Overview Eziologie – il sito d'infezione

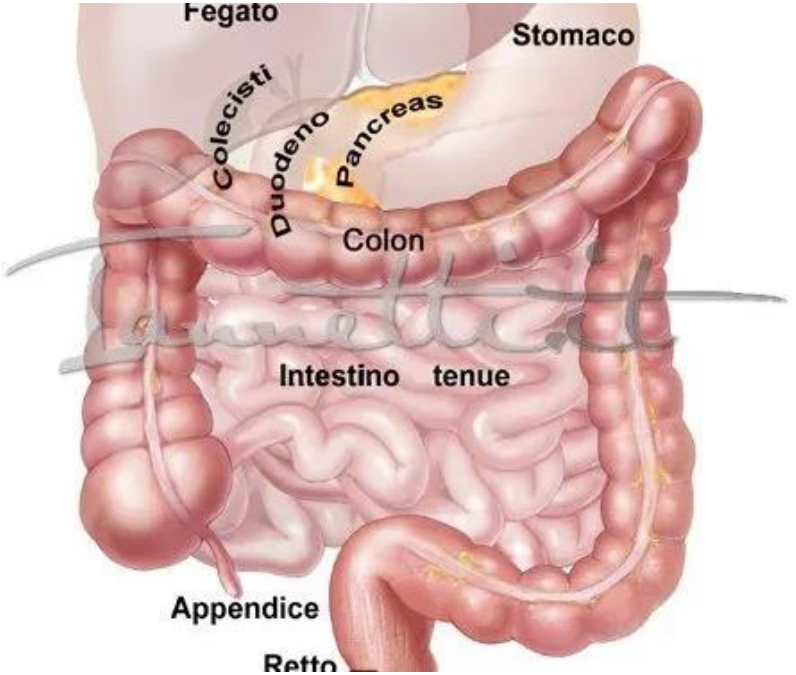


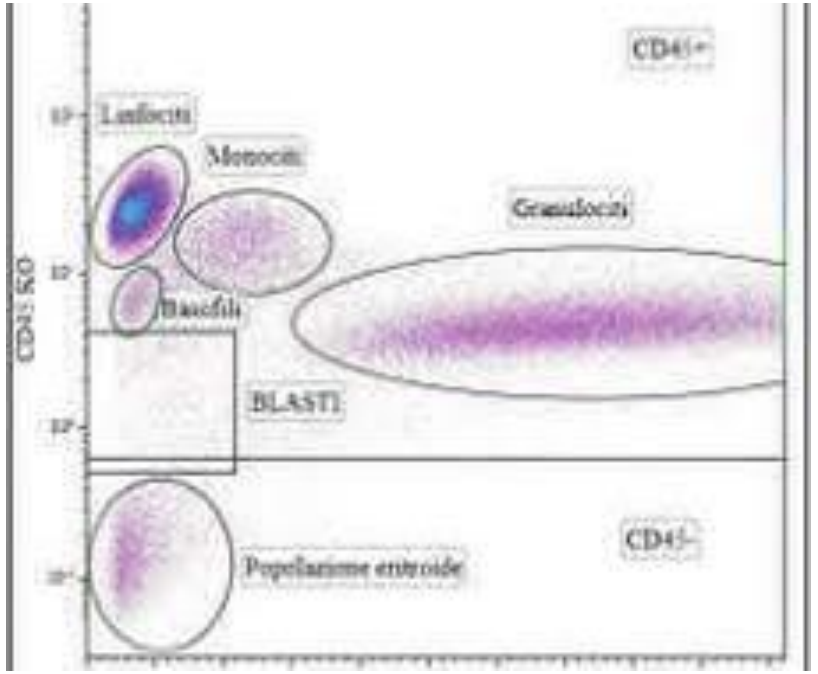
VALUTAZIONE CLINICA – Overview Eziologie – il sito d'infezione





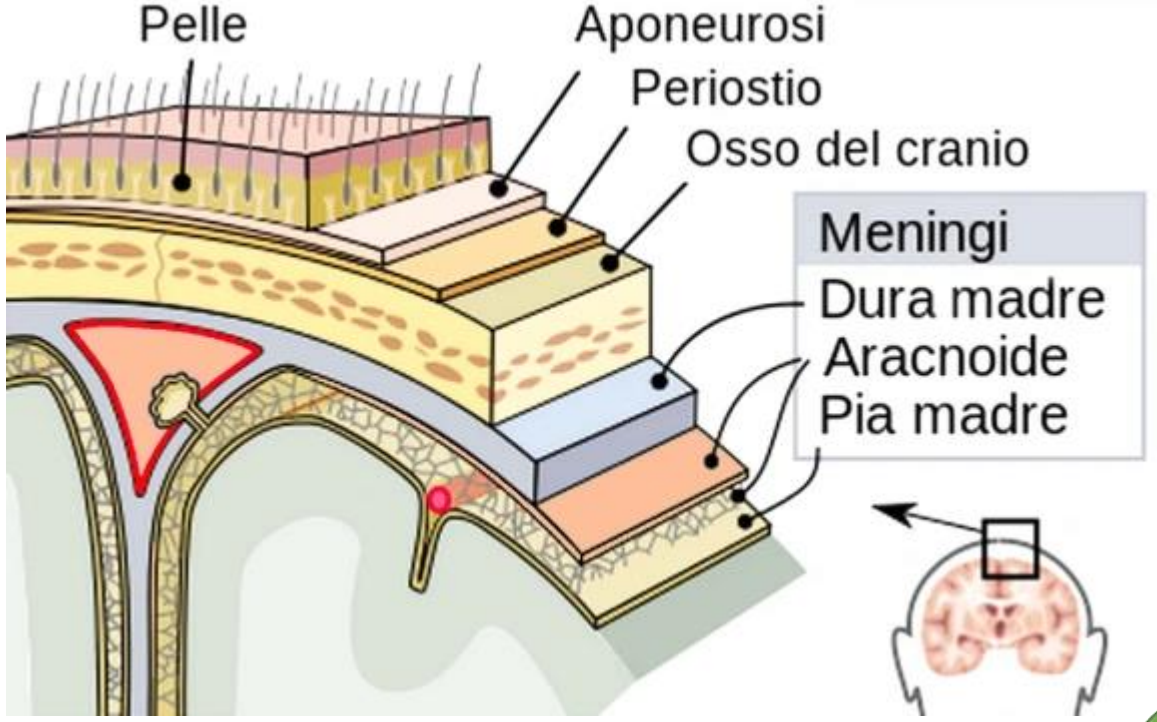

ORATORY
HEMATOLOGY
Anemia
Adenopathy
Anticoagulant Heparin
Anticoagulant SINTRON
Bleeding diathesis.
Coagulopathy
Erythrocytosis
Ferropenic Anaemia
Gammopathy
Hemophilia
Leukemia
Leukocytosis
Leucopenia
Lymphocytosis
Lymphoma
Megaloblastic


Fegato
Stomaco
Colecisti
Duodeno
Pancreas
Colon
Intestino tenue
Appendice
Retto

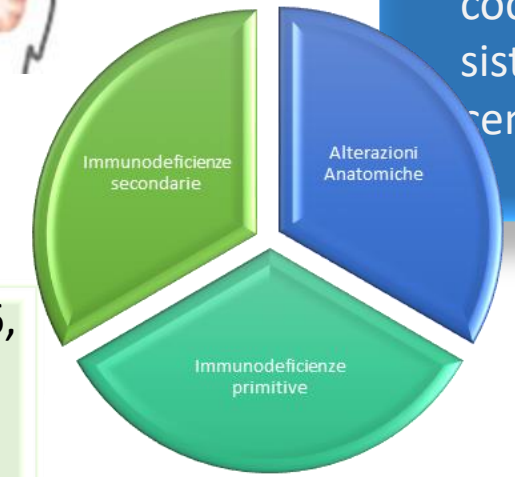

CD45+
Linfociti
Monociti
Granulociti
BLASTI
CD45-
Popolazione eterogenea


HELPFUL
TIPS!

VALUTAZIONE CLINICA – Overview Eziologie – il sito d'infezione

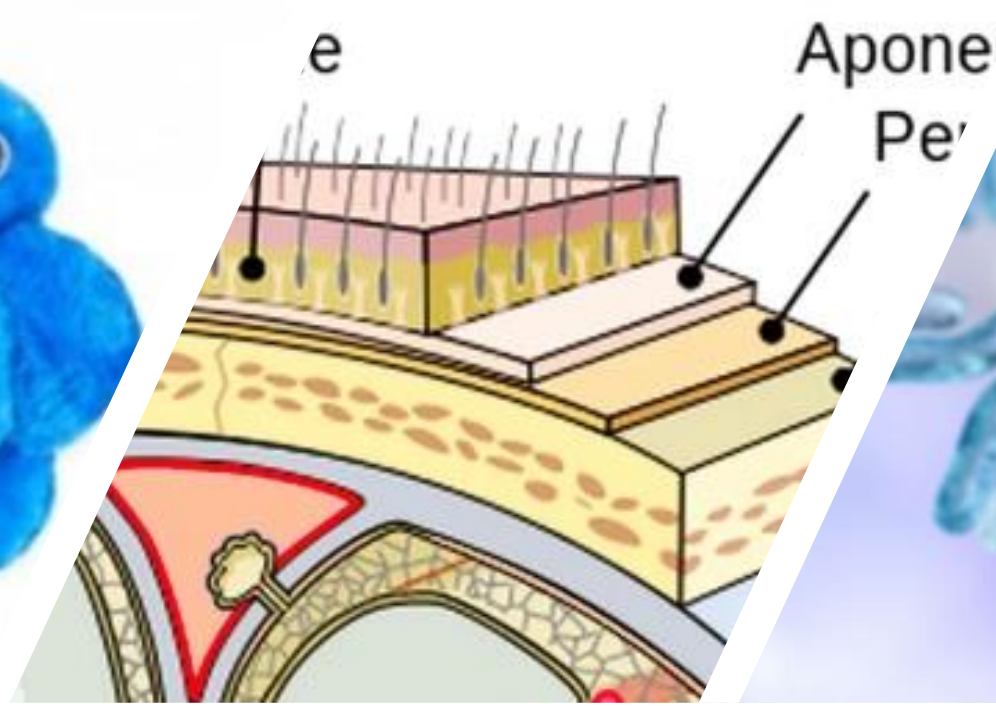


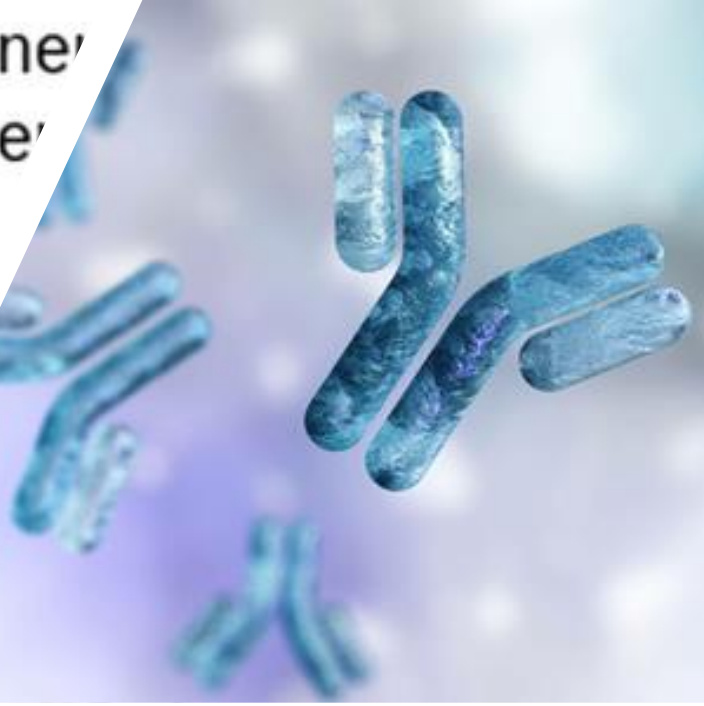
- Difetti della volta cranica congeniti o acquisiti (post-traumatici o post-neurochirurgici,
- Uso di dispositivi medici a permanenza (p.es., serbatoi di Ommaya, shunt ventricolari e impianti cocleari) inseriti nel sistema nervoso centrale.

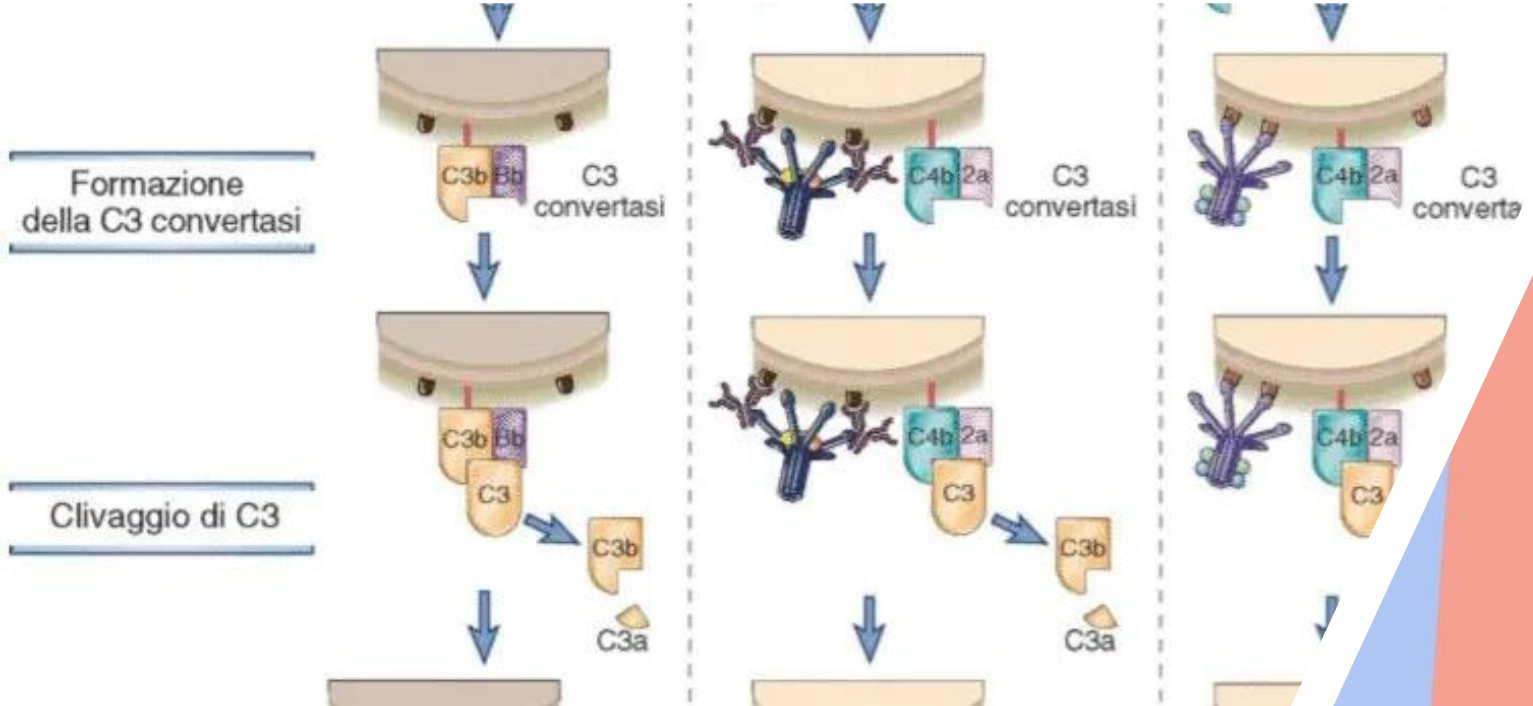


- Il deficit di uno o più componenti terminali del complemento (C5, C6, C7, C8, C9) congenito o a malattie acquisite
- Deficit di immunoglobuline o compromissione della funzione reticoloendoteliale derivante da splenectomia o emoglobinopatia


Strep

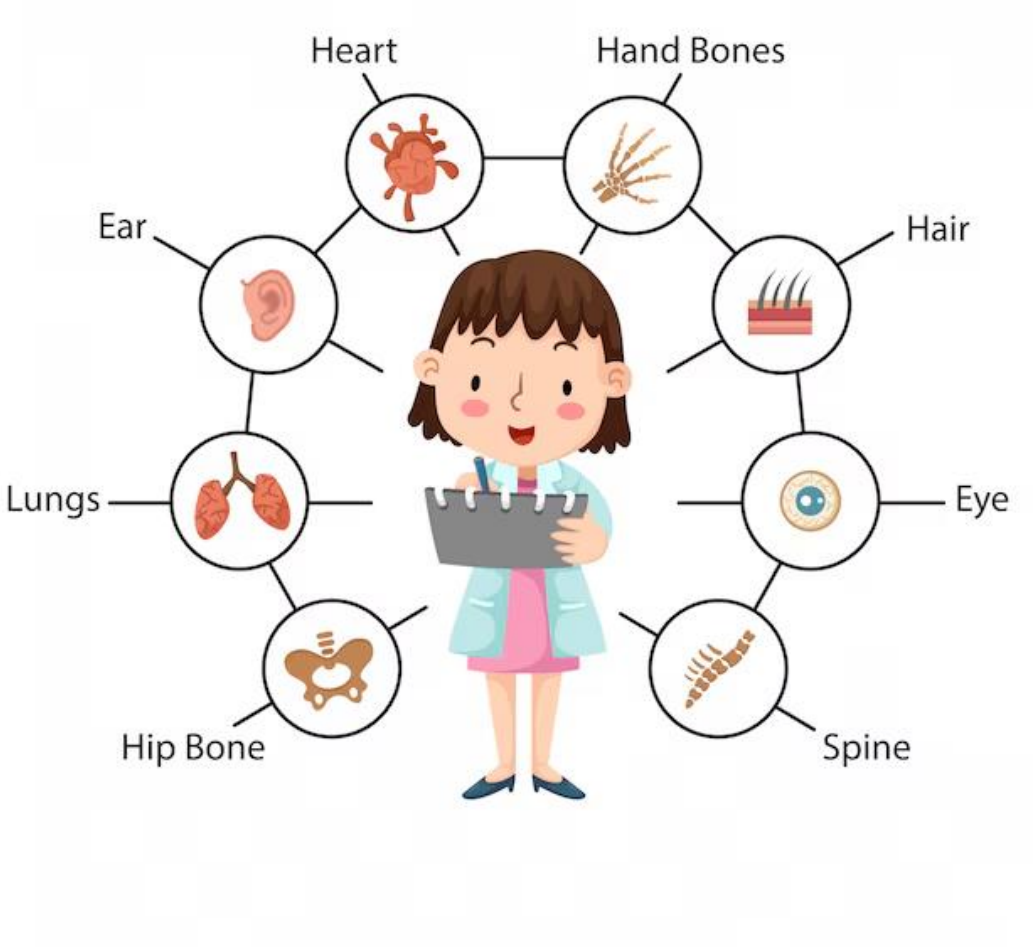





Formazione della C3 convertasi
Clivaggio di C3
C3b
Bb
C3 convertasi
C4b
2a
C3
C3a


HELPFUL TIPS!

VALUTAZIONE CLINICA – Overview Eziologie



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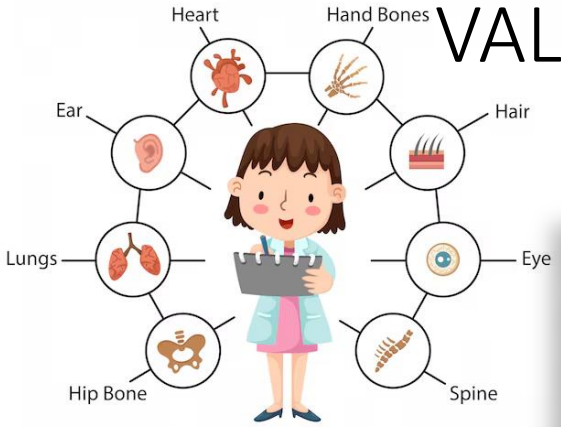
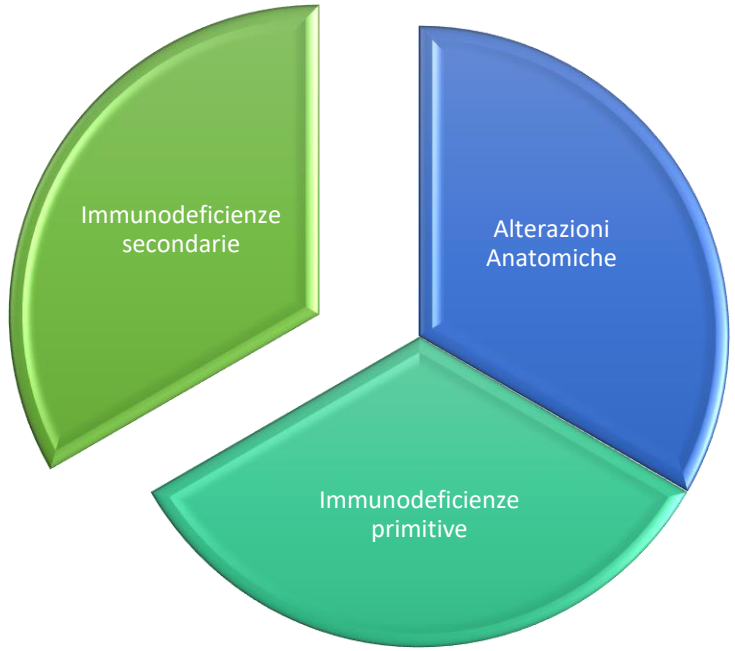
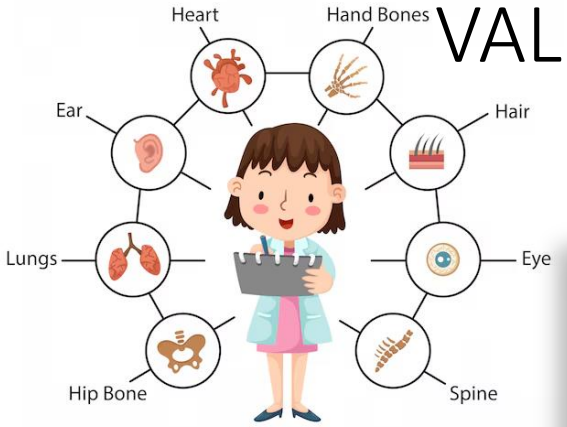


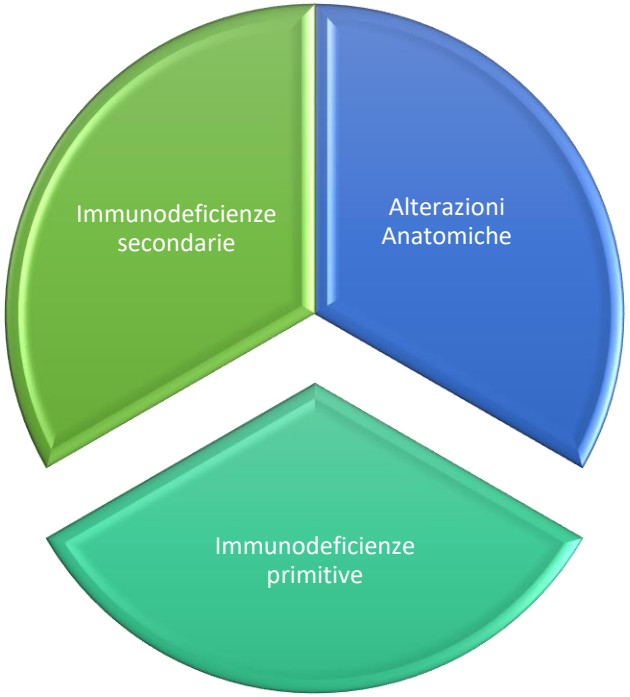
- Diabete mellito
- Infezione da virus dell'immunodeficienza umana (HIV)
- Cirrosi
- Sindrome nefrosica
- Altri stati di perdita di proteine, come enteropatie, grave malattia essudativa della pelle, comprese le ustioni, e la dialisi peritoneale
- Malnutrizione
- Emoglobinopatia
- Malattia neurologica
- Malattia autoimmune
- Splenectomia
- Malignità
- Radioterapia
- Agenti immunosoppressori, come glucocorticoidi, RTX,anti TNFalfa ed altri



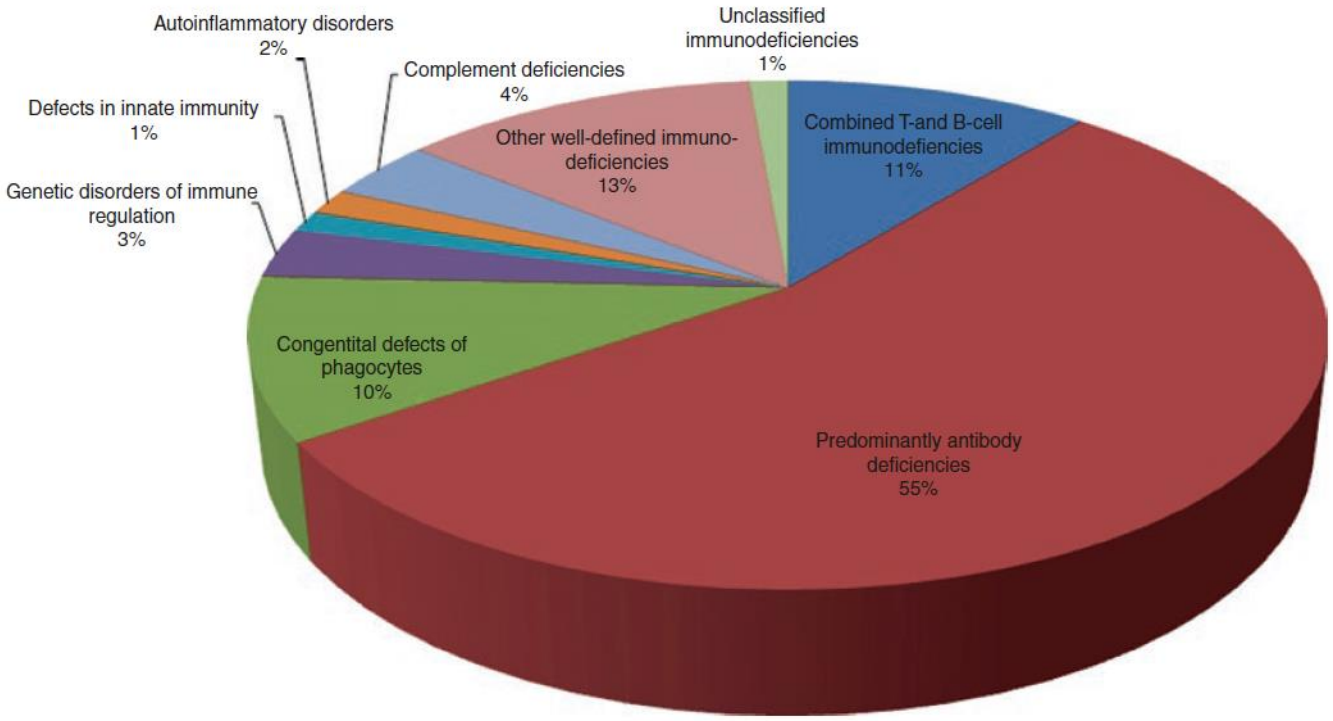
VALUTAZIONE CLINICA – Overview Eziologie

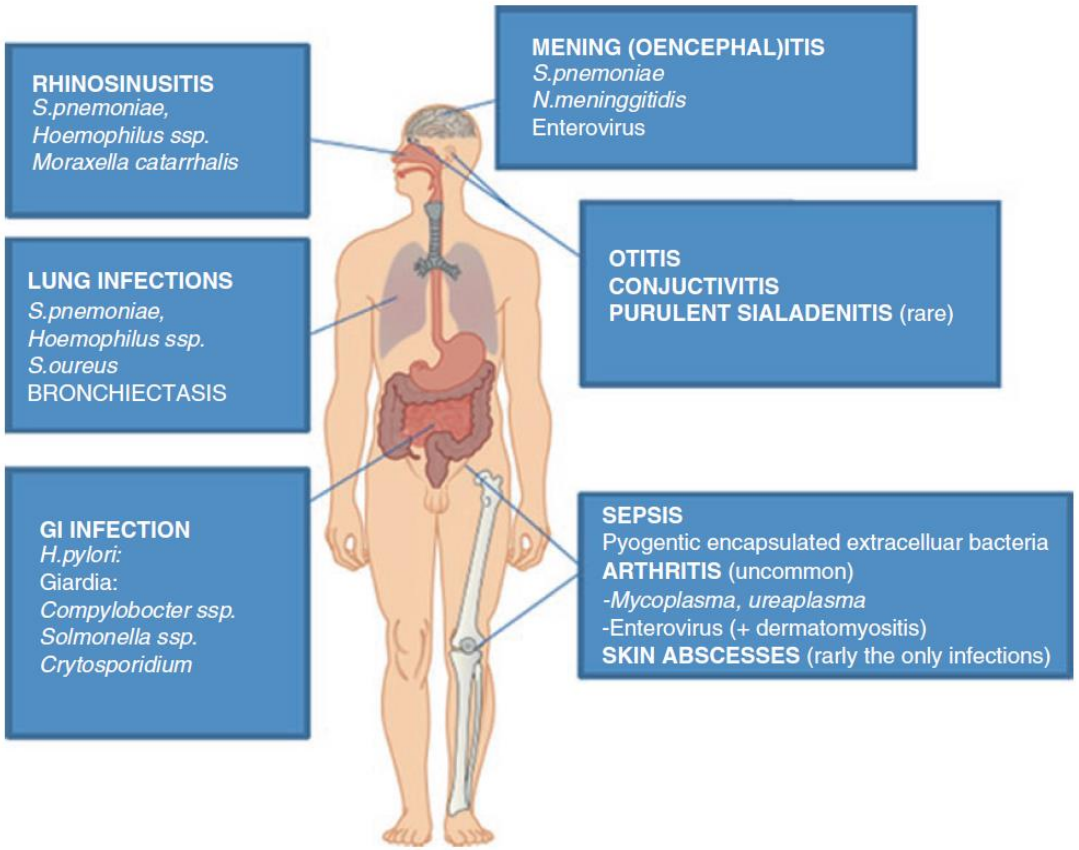


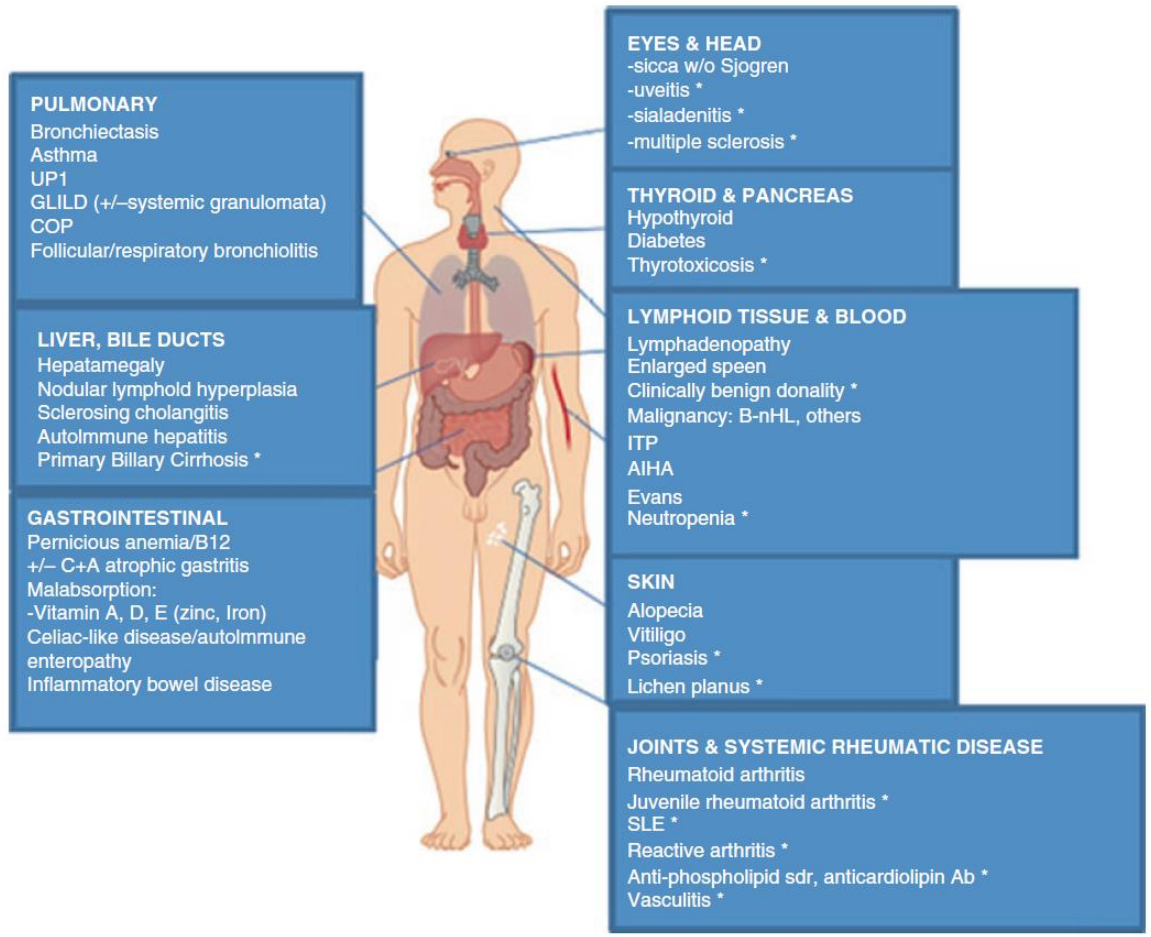
- Le immunodeficienze primarie, chiamate anche errori congeniti dell'immunità, non sono così rare come si pensava in precedenza. Uno studio pubblicato nel 2007 ha stimato la prevalenza di disturbi da immunodeficienza primaria ben definiti a 1 su circa 1200 persone negli Stati Uniti, che è 10 volte superiore alle stime precedenti.
- Sono stati identificati centinaia di disturbi specifici. Alcuni di questi disturbi, in particolare alcuni difetti anticorpali, sono di lieve o moderata gravità clinica (p.es., deficit di anticorpi specifici, deficit della sottoclasse delle immunoglobuline G [IgG], deficit selettivo di immunoglobuline A [IgA] e sfuggono regolarmente al rilevamento fino all'età adulta.



- Frequenze relative delle malattie da immunodeficienza primaria (Estratto dai dati dei report dei principali database, tra cui ESID (Società Europea per le Immunodeficienze), LASID (Società Latinoamericana per le Malattie da Immunodeficienza Primaria), USIDnet (rete statunitense per le Immunodeficienze), nonché da registri selezionati di Asia, Africa e Australia)

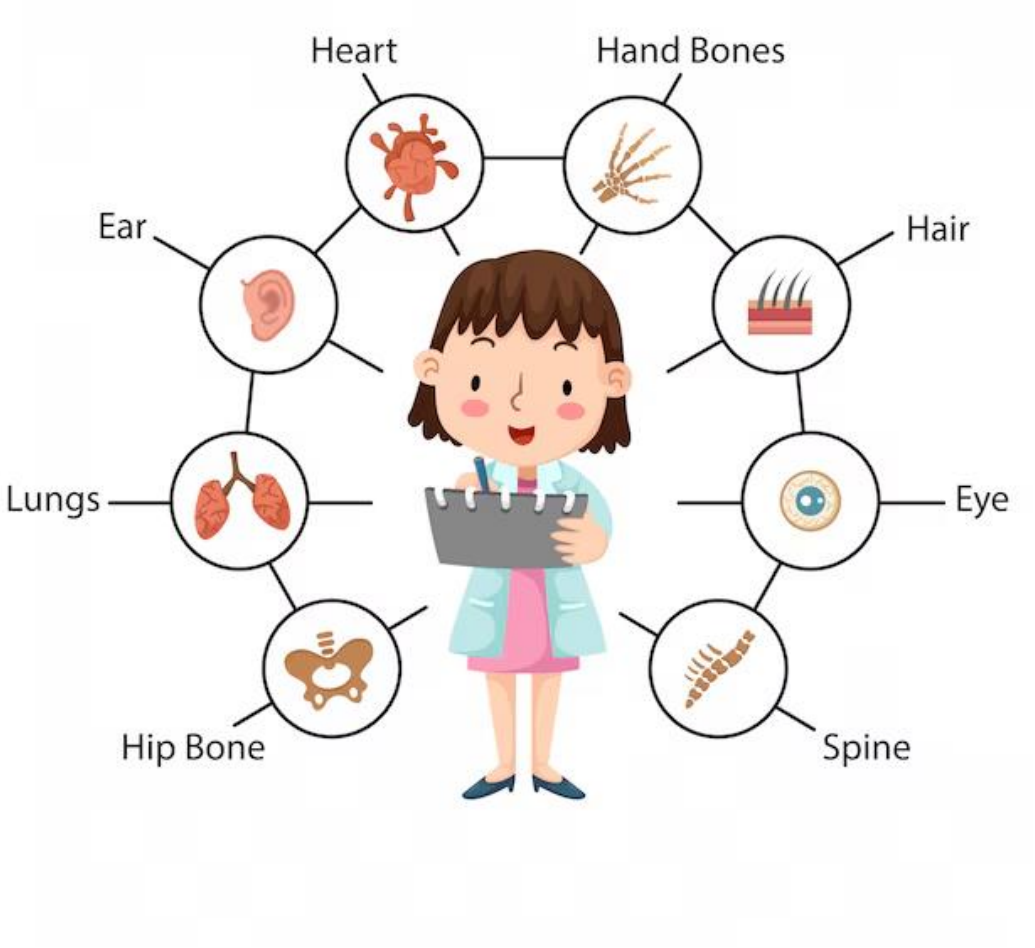




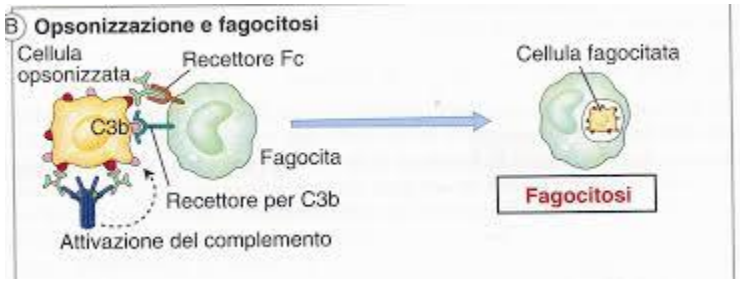


Infezioni...e non solo!

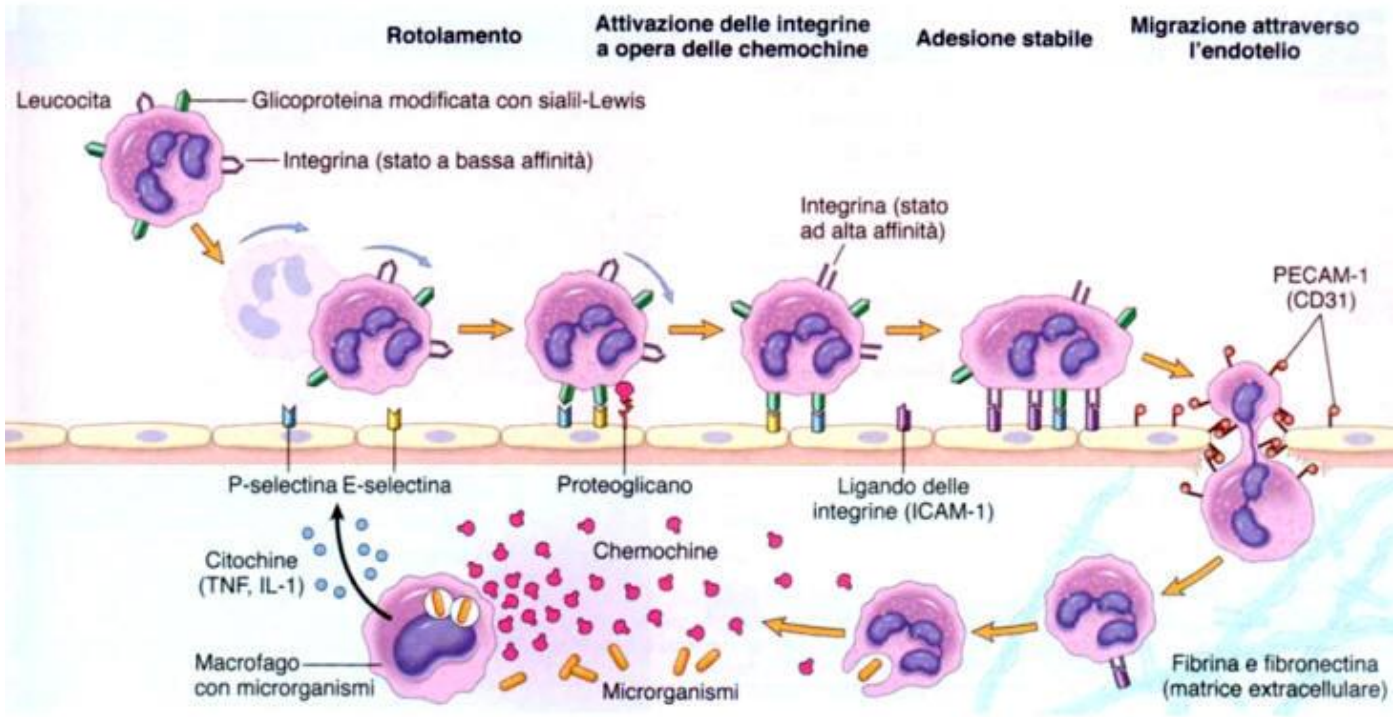
Pattern di malattia



Pattern di malattia

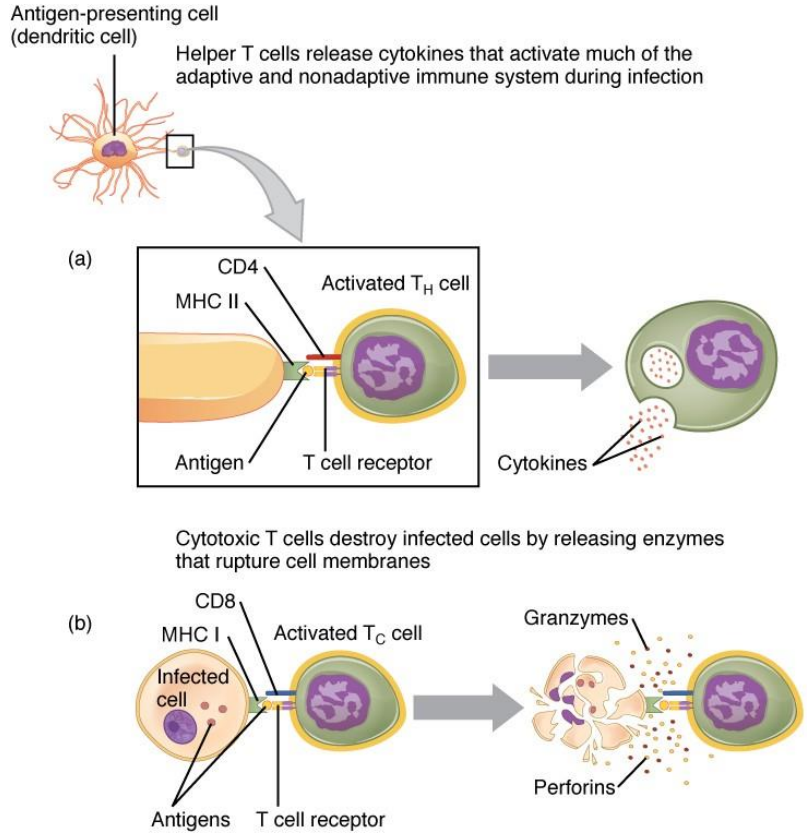


Difetti nelle immunoglobuline e/o nelle proteine del complemento — Infezioni sinopolmonari ricorrenti, infezioni gastrointestinali croniche, batteriemia e/o meningite sono associate a difetti nelle immunoglobuline e/o nelle proteine del complemento. Gli agenti patogeni comuni includono i batteri incapsulati, S. pneumoniae, H. influenzae di tipo b e N. meningitidis, nonché Giardia, Cryptosporidia e Campylobacter.



Processo di migrazione attraverso i vasi sanguigni. Qui sono raffigurati i neutrofili, le selectine, le chemochine, le integrine ecc.

Difetti dei granulociti (neutrofili) — Le infezioni invasive ricorrenti della pelle e dei tessuti molli, in particolare gli ascessi focali che richiedono incisione e drenaggio, sono associate a difetti dei granulociti (neutrofili). Gli organismi caratteristici sono gli organismi catalasi-positivi, come S. aureus, i bacilli gram-negativi, l'Aspergillus e la Nocardia.



Difetti nell'immunità cellulo-mediata - Le infezioni progressive con virus normalmente "benigni", patogeni intracellulari opportunistici o funghi suggeriscono un'immunità cellulo-mediata difettosa, in particolare difetti delle cellule T. I microrganismi tipici includono citomegalovirus, virus di Epstein-Barr o altri virus dell'herpes, micobatteri (sia M. tuberculosis che micobatteri non tubercolari) e funghi (Candida, Cryptococcus e Pneumocystis). I difetti delle cellule natural killer (NK) si presentano anche con infezioni da virus dell'herpes gravi e fulminanti, sebbene queste condizioni siano rare.

Approccio diagnostico

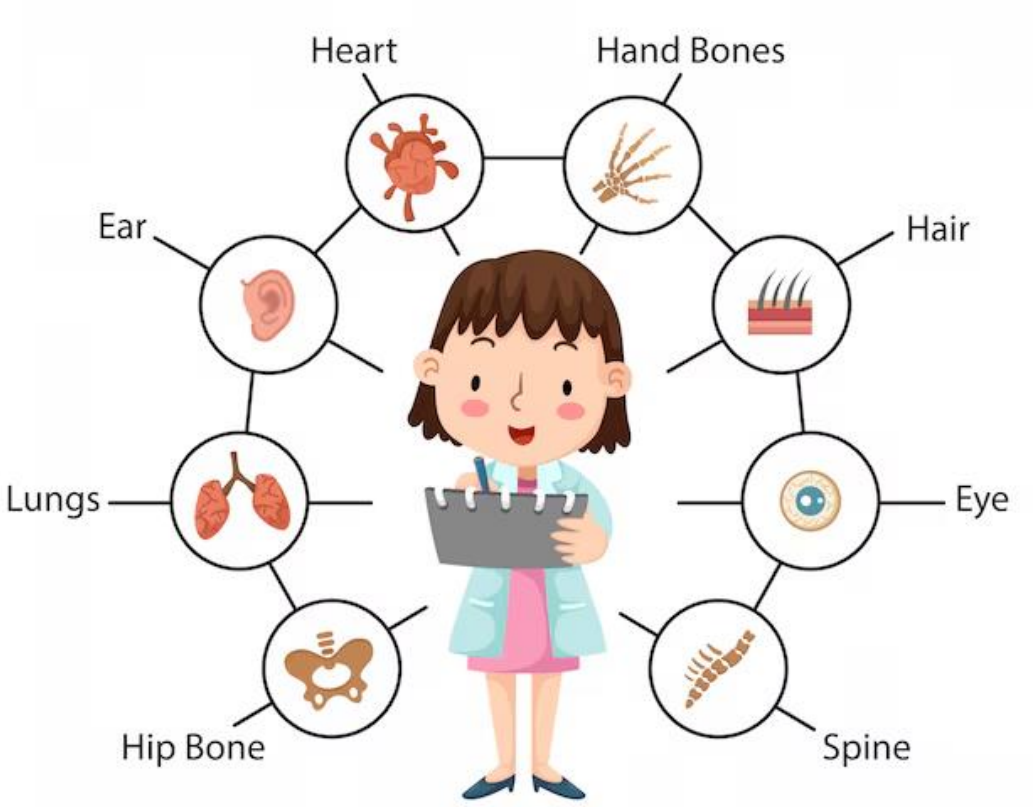


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Table 3. In-depth differential diagnosis of the clinical presentations.

Clinical presentations		Suspected category of immunodeficiency [3] (same order as IUIS tables; bold: most frequent)	Possible immunological diagnosis [3] (same order and designation as IUIS tables; bold: most frequent)
1	Recurrent ENT and airway infections (unexplained bronchiectasis)	Combined T and B cell immunodeficiencies	DOCK8
		Predominantly antibody deficiencies	Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells (Btk, μ heavy chain, λ5, Igα, Igβ, BLNK, thymoma with immunodeficiency) Severe reduction in at least two serum immunoglobulin isotypes with normal or low numbers of B cells (**CVIDs**, ICOS, CD19, **TACI**, BAFF-R) Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells (CD40L, CD40, AID, UNG) Isotype or light chain deficiencies with normal numbers of B cells (**Ig heavy chain**, κ chain, **isolated IgG subclass**, **IgA with IgG subclass**, **selective IgA**) **Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells** **Transient hypogammaglobulinaemia of infancy with normal numbers of B cells**
		Other well-defined immunodeficiency syndromes	PMS2; AR-HIES
		Congenital defects of phagocyte number, function, or both	P14; pulmonary alveolar proteinosis
		Defects in innate immunity	NEMO-ID; IRAK4; MyD88; warts, hypogammaglobulinaemia, infections, myelokathexis syndrome (WHIM)
		Complement deficiencies	Complement deficiency (C1q, C1r, C4, C2, C3, factor I, MBP, MASP2); immunodeficiency associated with ficolin 3 deficiency.
2	Failure to thrive from early infancy (intractable diarrhoea, severe eczema)	**Combined T and B cell immunodeficiencies**	T–B + SCID (γc, JAK3, IL7-Rα, CD45, CD3δ, CD3ε, CD3ζ, Coronin-1a); T–B – SCID (RAG1/2, DCLRE1C (Artemis), DNA PKcs, ADA, reticular dysgenesis); Omenn syndrome; DNA-ligase IV; Cernunnos; PNP; CD3γ; CD8; ZAP-70; Ca^{++} channel; MHC class I; MHC class II; winged helix (nude), FOXN1; CD25; STAT5b
		Other well-defined immunodeficiency syndromes	Thymic defects (**DiGeorge**, **22q11.2 deletion**, 10p deletion); immune-osseous dysplasias (cartilage hair hypoplasia, Schimke); Comel–Netherton
		Congenital defects of phagocyte number, function, or both	IFN-γ-receptor-1 (mainly recessive complete disorder).
		Diseases of immune dysregulation	IPEX
		Defects in innate immunity	NEMO-ID
3	Recurrent pyogenic infections (granulomatous inflammation, poor wound healing)	Other well-defined immunodeficiency syndromes	AD-HIES (Job syndrome) (STAT3)
		Congenital defects of phagocyte number, function, or both	Severe congenital neutropenias (ELA2, GFI1); Kostmann; neutropenia with cardiac and urogenital malformations (G6PC3); glycogen storage disease type 1b; cyclic neutropenia; X-linked neutropenia/myelodysplasia; P14; LAD1; LAD2; LAD3; rac2; β-actin; localized juvenile periodontitis; Papillon–Lefèvre syndrome; specific granule deficiency; Shwachman–Diamond syndrome; **CGD** (**X-linked**, CYBB; **autosomal**, CYBA, NCF1/2) G6PD, MPO
		Defects in innate immunity	NEMO-ID; warts, hypogammaglobulinaemia, infections, myelokathexis syndrome (WHIM)
		Complement deficiencies	Complement deficiency (C3, Factor I); immunodeficiency associated with ficolin 3 deficiency
4	Unusual infections or unusually severe course of infections (unexplained – periodic fever see 6)	Combined T and B cell immunodeficiencies	T-B + SCID (γc, JAK3, IL7-Rα, CD45, CD3δ, CD3ε, CD3ζ, Coronin-1A); T-B- SCID (RAG1/2, DCLRE1C (Artemis), DNA PKcs, ADA, reticular dysgenesis); Omenn syndrome; DNA-ligase IV; Cernunnos; CD40 ligand; CD40; PNP; CD3γ; CD8; ZAP-70; Ca ++ channel; MHC class I; MHC class II; winged helix (nude), FOXN1; CD25; STAT5b; ITK; DOCK8.
		Other well-defined immunodeficiency syndromes	Wiskott-Aldrich syndrome; immunodeficiency with centromeric instability and facial anomalies (ICF); thymic defects (**DiGeorge**, **22q11.2 deletion**, 10p deletion); immune-osseous dysplasias (cartilage hair hypoplasia, Schimke); Comel-Netherton; HIES; hepatic venoocclusive disease with immunodeficiency (VODI); XL-dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome).
		Diseases of immune dysregulation	FHL; XLP.
		Defects in innate immunity	NEMO-ID; warts, hypogammaglobulinaemia, infections, myelokathexis syndrome (WHIM).

Table 3. *Continued*

Clinical presentations		Suspected category of immunodeficiency [3] (same order as IUIS tables; bold: most frequent)	Possible immunological diagnosis [3] (same order and designation as IUIS tables; bold: most frequent)
5	Recurrent infections with the same type of pathogen	Other well-defined immunodeficiency syndromes	AD-HIES (Job syndrome); AR-HIES; chronic mucocutaneous candidiasis.
		Congenital defects of phagocyte number, function, or both	IL-12 and IL-23 receptor β1 chain; IL-12p40; IFN-γ-receptor1/2; AD hyper-IgE; hyper-IgE (STAT3, TYK2); MPO
		Defects in innate immunity	Epidermodysplasia verruciformis; herpes simplex encephalitis (HSE); trypanosomiasis (APOL-1)
		Complement deficiencies	Complement deficiency (C2, C3, C5, C6, C7, C8, C9, properdin)
6	Autoimmune or chronic inflammatory disease; lymphoproliferation	Combined T and B cell immunodeficiencies	Omenn syndrome; CD25; STAT5b; ITK
		Predominantly antibody deficiencies	**CVIDs**
		Other well-defined immunodeficiency syndromes	Wiskott–Aldrich syndrome; Nijmegen breakage syndrome; PMS2
		Diseases of immune dysregulation	Immunodeficiency with hypopigmentation (Chediak–Higashi syndrome, Griscelli syndrome type 2, Hermanski–Pudlak syndrome type 2); familial haemophagocytic lymphohistiocytosis (FHL) syndromes (Perforin, UNC13D, Syntaxin11, STXBP2); lymphoproliferative syndromes (XLP1 (SH2D1A), XLP2 (XIAP), ITK); syndromes with autoimmunity, autoimmune lymphoproliferative syndrome (ALPS) (CD95, CD95L, caspase 8, caspase 10, activating N-ras defect); APECED; IPEX.
		Congenital defects of phagocyte number, function, or both	X-linked neutropenia/myelodysplasia; pulmonary alveolar proteinosis
		Autoinflammatory disorders	**FMF**; TRAPS, hyper-IgD syndrome; Muckle–Wells syndrome; familial cold autoinflammatory syndrome; neonatal onset multi-system inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA); pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome; Blau syndrome; chronic recurrent multi-focal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome); deficiency of the IL-1 receptor antagonist (DIRA)
		Complement deficiencies	Complement component deficiency (**C1q**, C1r, C1s, **C4**, C2, C3, C5, C6, C7, C8, C9; **PNH** (CD55/CD59 deficiency)
7	Characteristic combinations of clinical features (eponymous syndromes)	Combined T and B cell immunodeficiencies	Omenn syndrome; DNA-ligase IV; Cernunnos; PNP; winged helix (nude), FOXN1
		Other well-defined immunodeficiency syndromes	**Ataxia telangiectasia**; ataxia telangiectasia-like disease (ATLD); Nijmegen breakage syndrome; Bloom syndrome; immunodeficiency with centromeric instability and facial anomalies (ICF); **Di-George syndrome**; immune-osseous dysplasias (cartilage hair hypoplasia, Schimke, Comel–Netherton); XL-dyskeratosis congenita (Hoyeraal–Hreidarsson syndrome)
		Diseases of immune dysregulation	Immunodeficiency with hypopigmentation (Chediak–Higashi syndrome, Griscelli syndrome type 2, Hermanski–Pudlak syndrome type 2).
		Congenital defects of phagocyte number, function, or both	P14; LAD2; β-actin; Shwachman–Diamond
		Defects in innate immunity	NEMO-ID
		Autoinflammatory disorders	NOMID / CINCA, Blau, Majeed syndromes
8	Angioedema	Complement deficiencies	**C1-inhibitordeficiency**.

This table contains additional information for those interested; this information is not needed for the initial diagnostic evaluation process. For explanations concerning the various immunological disorders the reader is referred to the original IUIS 2009 publication [2] and its references; the word 'deficiency' has in most cases been omitted in column 3. AD: autosomal dominant; AR: autosomal recessive; CD: cluster of differentiation; IFN: interferon; Ig: immunoglobulin; IL: interleukin; IUIS: International Union of Immunological Societies; L: ligand; LAD: leucocyte adhesion deficiency; PID: primary immunodeficiency disease; PNH: paroxysmal nocturnal haemoglobinuria; R: receptor; SCT: stem cell transplantation.

Test di Laboratorio

Laboratory investigations in primary immunodeficiencies

	Neutrophils investigations for phagocyte disorders	Lymphocytes investigations for cellular defects	Immunoglobulins investigations for humoral defects	Complement Investigations for complement defects
Routine	***Full blood count*** May reveal neutropenias (congenital/cyclic) or neutrophilias (LAD). Serial counts may be necessary	***Full blood count*** Lymphocyte count <2 x10^9/litre in a child <6 months is SCID until proven otherwise	***Immunoglobulin levels*** Hypogammaglobulinaemia is associated with many PIDs and confers susceptibility to infection. Hyper-IgM, hyper-IgE and hyper-IgD syndromes may also be diagnosed based on elevations of their respective immunoglobulins	***C3, C4 levels*** Normal in terminal complement cascade defects. An isolated low C4 is associated with HAE
	Respiratory burst function Defective in CGD; assessed using DHR test (flow cytometry)	***Lymphocyte subsets*** Flow cytometric assessment of numbers of circulating T, B and NK lymphocytes Multiple disease associations: e.g. absent B lymphocytes in XLA, absent T lymphocytes in SCID, increased CD4–CD8– T cells in ALPS	***Pathogen-specific antibodies*** Antibodies to specific pathogens may be assessed before and after vaccination to assess B lymphocyte function	***Haemolytic complement activity (CH50, AH50)*** *In vitro* assays examining the classical and alternative complement cascades. Both CH50 and AH50 are absent in terminal complement defects
Specialized immunology	***Migration, phagocytosis and killing*** Defects associated with very rare PIDs; assessed using highly specialized *in vitro* tests	***Proliferative function*** *In vitro* tests measure lymphocyte proliferation to non-specific (mitogen) and specific stimuli (antigen) to look for specific defects ***Thymic output*** Molecular analysis of TRECs is helpful in defining thymic function (absent in SCID)	***Anticytokine antibodies*** Rare PIDs are associated with the presence of antibodies against cytokines (e.g. anti-IL-17 in CMC, anti-IFN-γ in certain mycobacterial infections)	***Quantification of individual components of complement cascade*** Radial immunodiffusion assays can detect deficiencies in individual complement proteins
Genetics	***Sanger sequencing and genomics investigations*** A diagnosis of suspected immunodeficiency may be confirmed by Sanger sequencing a target gene to confirm a mutation. If, after exhaustive immunological investigations, a specific diagnosis can not be reached, genomic techniques including whole-exome sequencing and whole-genome sequencing may be employed.			

Simple haematological and biochemical investigations are usually sufficient to reveal most primary immunodeficiencies. Specialist immunological investigations may be targeted at cellular or molecular components of the immune system, based on clinical suspicion. Suspected single gene defects may be confirmed by Sanger sequencing and genomics approaches are undertaken only when all other avenues of investigation have failed to yield a diagnosis.

CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; DHR, dihydrorhodamine; HAE, hereditary angioedema; Ig, immunoglobulin; SCID, severe combined immunodeficiency; TREC, T cell receptor excision circle.

Il mio paziente fa infezione a ripetizione

- La chiave per individuare una PID è considerare la possibilità.
- Le PID si presentano quasi sempre con una o più delle otto presentazioni cliniche; queste possono essere utilizzate come punto di partenza per impostare il protocollo diagnostico appropriato.
- Il riconoscimento tempestivo della carenza di anticorpi previene futuri danni d'organo.
- Se si sospetta una PID o se è presente in famiglia, ritardare la vaccinazione con virus vivi attenuati e non rimandare gli esami immunologici.
- Utilizzare valori di riferimento corrispondenti all'età per evitare interpretazioni errate dei risultati dei test immunologici.

Il mio paziente fa infezione a ripetizione

Riferimenti utili

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Grazie per la vostra attenzione!

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