INFECTIONS IN THE COMPROMISED HOST

IMMUNODEFICIENCIES

caused by quantitative and/or functional changes in the different mechanisms involved in both the **INNATE** and the **ADAPTIVE immune response**

They are classified as:

- **PRIMARY IMMUNODEFICIENCY**
  inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood. They are rare, and vary in severity depending upon the type of defect

- **SECONDARY IMMUNODEFICIENCY**
  acquired immunodeficiency as a result of disease, environmental factors (e.g. HIV, malnutrition) or medical treatment (e.g. chemotherapy)

Factors affecting innate systems	
Primary	Complement deficiencies, phagocyte cell deficiencies
Secondary	Burns, trauma, major surgery, catheterization, foreign bodies (e.g. shunts, prostheses), obstruction
Factors affecting adaptive systems	
Primary	T-cell defects, B-cell deficiencies, severe combined immunodeficiency
Secondary	Malnutrition, infectious diseases, neoplasia, irradiation, chemotherapy, splenectomy

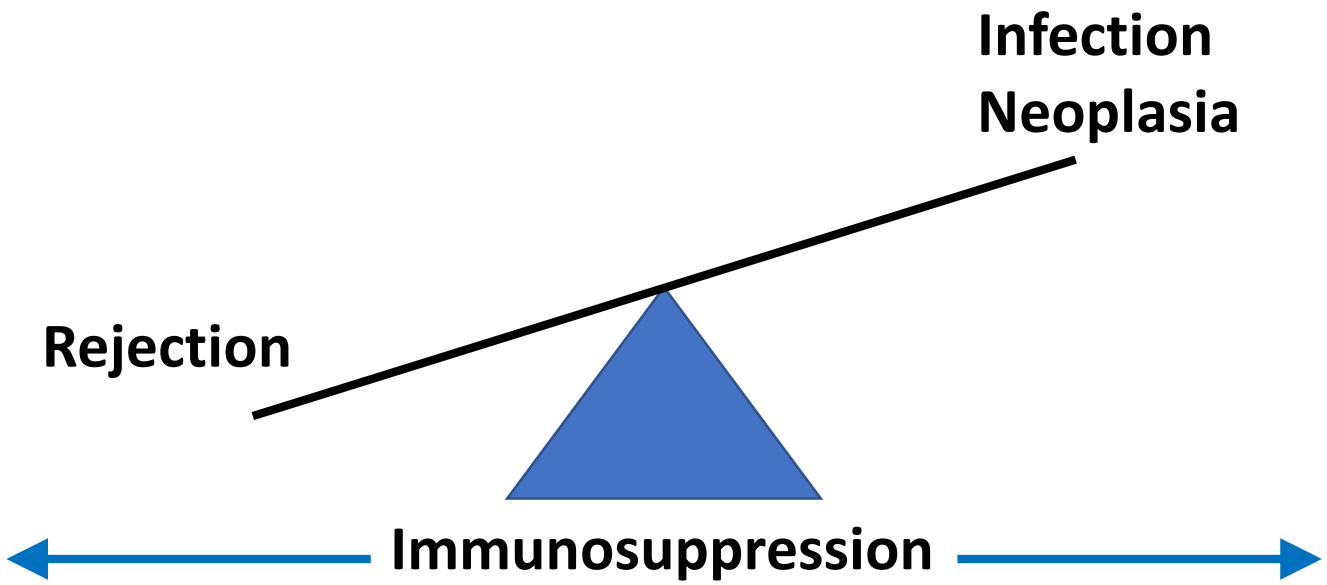
SECONDARY defects of ADAPTIVE immunity

Immunosuppression caused by **TREATMENT FOR NEOPLASTIC DISEASE**

- Cytotoxic agents
- Corticosteroids
- Radiotherapy

Immunosuppression caused by **IMMUNOSUPPRESSANTS** (or **ANTI-REJECTION DRUGS**)

Drugs that lower the body's ability to reject a transplanted organ



IMMUNODEFICIENCIES

result in the body being unable to effectively resolve infections or disease

Immunocompromised people can become infected **with any pathogen able to infect immunocompetent individuals** as well as those **opportunist pathogens** that do not cause disease in a healthy person.

Immunodeficient individuals are at high risk of **recurrent** and **reactivating infection.**

- Infections may be lethal when the host defences are lowered
- Different types of immune defect predispose to infection with different pathogens depending upon the critical mechanisms operating in the defence against each microorganism

Examples of opportunistic pathogens in immunocompromised hosts

Gram-positive
Staphylococcus aureus
Coagulase-negative staphylococci
Streptococci
Listeria spp.
Nocardia asteroides
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Gram-negative
Enterobacteriaceae
Pseudomonas aeruginosa
Legionella spp.
Bacteroides spp.
Fungi
Candida spp.
Aspergillus spp.
Cryptococcus neoformans
Histoplasma capsulatum
Pneumocystis jirovecii[a]
Parasites
Toxoplasma gondii
Strongyloides stercoralis
Viruses
Herpesviruses, e.g. HSV, CMV, VZV, EBV, HHV-6, HHV-7, HHV-8
Hepatitis B
Hepatitis C
Polyomaviruses, e.g. BKV, JCV
Adenoviruses
HIV

OPPORTUNIST PATHOGENS - VIRUSES

Viral infections are more common and severe in immunodeficient patients than in immunocompetent patients, particularly **reactivation of latent infections** (e.g. HSV, CMV, JCV)

Viral reactivation is a significant problem in **TRANSPLANT RECIPIENTS**

Pre-transplantation baseline serology is carried out to determine both the donor and recipient status for a number of virus infections, including:

HTLV	**CMV**
HBV	**EBV**
HCV	**HSV**

The potential for primary infection, re-infection or reactivation when immunosuppressed is thus known

Suppression of specific virus infections using **antiviral agents** is part of the management of the recipient in conjunction with regular **virological surveillance post-transplantation**

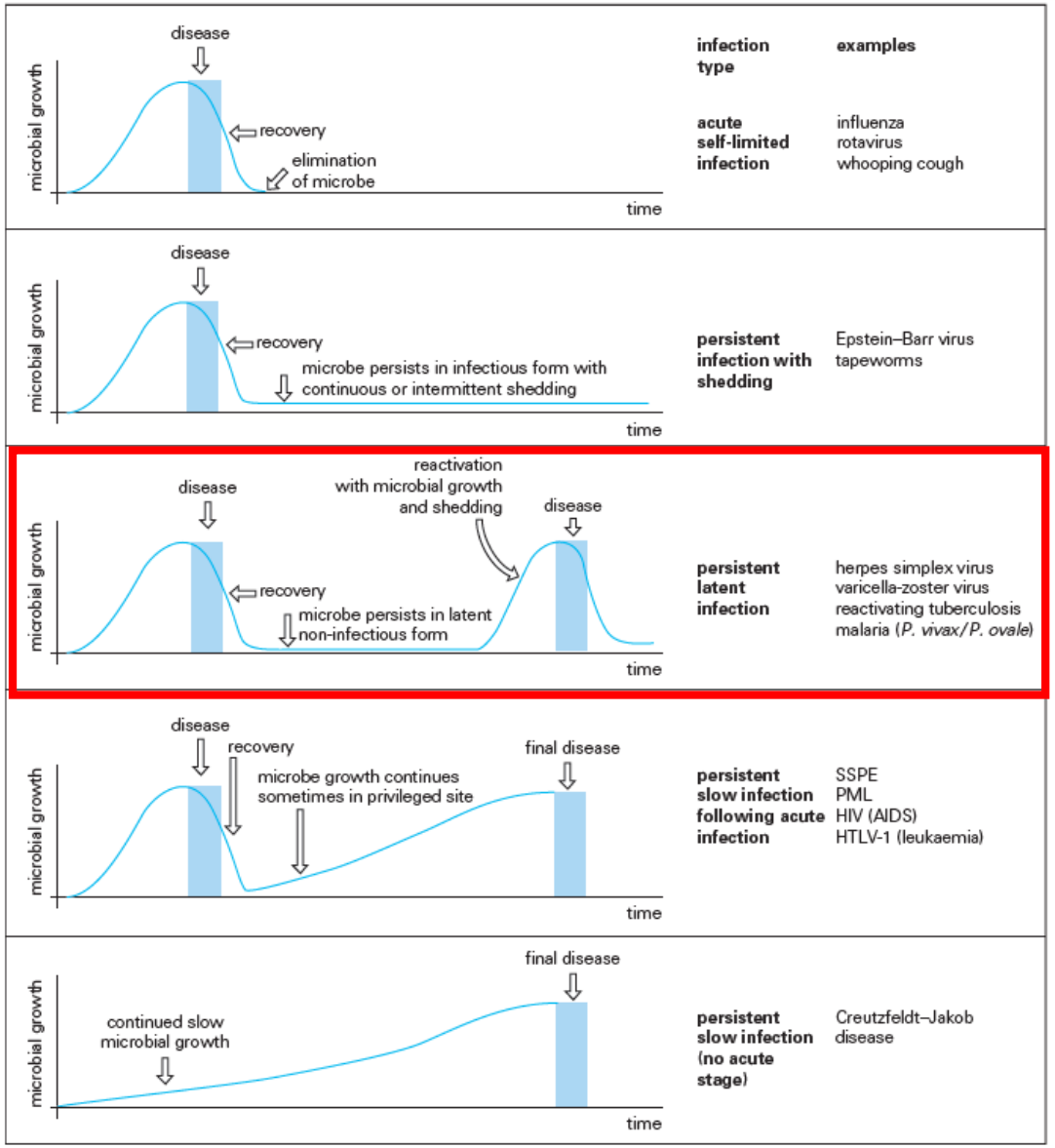


Figure 17.12 Patterns of acute and persistent infections. For some pathogens (e.g. cytomegalovirus), the distinction between persistence in infectious form and true latency is not clear. HIV, human immunodeficiency virus; HTLV-1, human T-cell leukaemia virus 1; PML, progressive multifocal leukoencephalopathy; SSPE, subacute sclerosing panencephalitis.

Cytomegalovirus

Direct effects of CMV infection

CMV Viral Syndrome
- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia

Tissue Invasive Disease
- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

Indirect effects of CMV infection

Probably due to CMV **immunomodulatory activity**
- Increased rate of opportunistic infections
- Cardiovascular disease
- Increased allograft rejection in solid-organ transplant recipients
- Increased graft-versus-host disease in HSCT recipients
- Increased mortality in HSCT recipients

Average Rate of CMV infection and CMV disease by graft type

Graft	CMV infection rate	CMV disease rate
Kidney	8-32%	8%
Heart, heart/lung	9-35%	25%
Liver	22-29%	29%
Pancreas, pancreas/kidney	50%	50%
HSCT transplant	7-37%	2-14%
(HSCT autologous transplant)	(12%)	

Rates for CMV infection (defined as evidence of CMV replication regardless of symptoms and differing from latent CMV) and CMV disease (defined as evidence of CMV infection with related symptoms) vary mostly **depending on transplanted organ and on serostatus and age of donor and recipient**

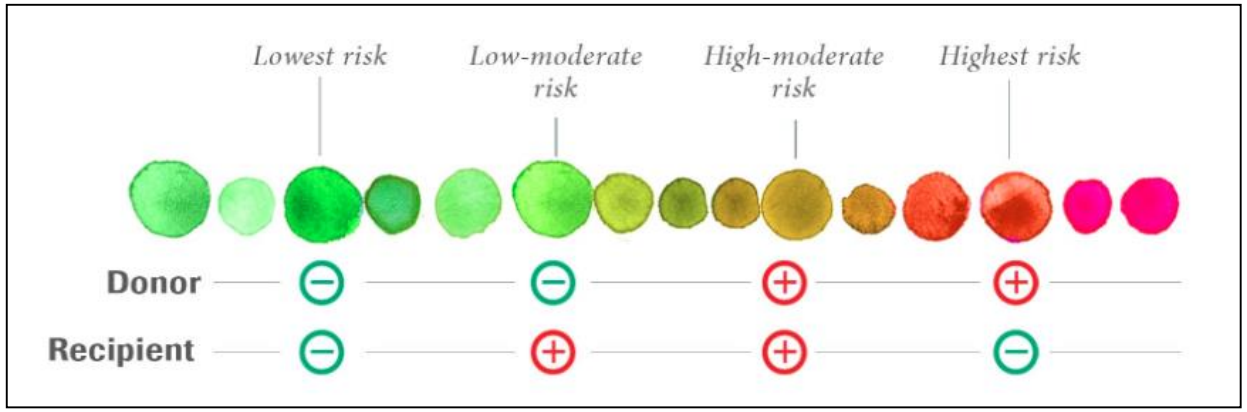
Grossi PA, et al (2019)

Cytomegalovirus

Pre-transplantation serology

IgG antibody is used to define the serological relationship between the donor and the recipient (D/R):

POST-TRANSPLANT RISK



- In **solid organ transplantation** (SOT), the greatest risk factor for CMV disease is a **serological mismatch** between the donor and the recipient (the recipient is CMV seronegative and the donor is seropositive) (D+/R-)
- In **allogeneic hematopoietic stem cell transplantation** (allo-HSCT) the main burden of morbidity arises from the reactivation of **latent infection** in R^+ patients

Cytomegalovirus

Table 1 - Definitions: CMV syndrome and disease affecting different organs (19–22).

Disease	Presumed diagnosis	Confirmation
CMV syndrome	The presence of one or more of these signs: fever > 2 days, malaise, leukopenia, > 5% atypical lymphocytes, thrombocytopenia, and increased aminotransferases (> 2-fold, except in liver transplantation) plus evidence of active CMV infection	Clinical and laboratory evidence of CMV infection without confirmation of other etiology
Pneumonia	The presence of signs and symptoms of pneumonia (fever, cough, dyspnea, hypoxemia, X-ray changes) plus evidence of CMV infection in the blood and/or bronchoalveolar lavage	Lung disease manifestations plus the presence of CMV in lung tissue based on immunohistochemistry with or without evidence of active CMV infection in the blood or bronchoalveolar lavage
Gastrointestinal disease (esophagitis, gastritis, enterocolitis, colitis)	The presence of signs and symptoms of gastrointestinal compromise plus endoscopic signs of mucosal lesions and evidence of active CMV infection in the blood	Gastrointestinal manifestations plus the detection of CMV in gastrointestinal tissues by immunohistochemistry
Hepatitis	An increase in liver enzymes and bilirubin levels (> 2-fold) in the absence of other known causes plus evidence of CMV in the blood	The presence of increased liver enzymes and bilirubin levels plus the presence of CMV in liver tissue, as determined by immunohistochemistry; note that the presence of hepatitis and CMV in the blood, without histological confirmation of CMV in liver tissue, does not allow for the diagnosis of hepatic invasive disease
Central nervous system disease	Neurological signs and symptoms in the absence of other known causes plus evidence of CMV (as detected by RT-PCR) in the cerebrospinal fluid	Neurological signs and symptoms plus evidence of CMV in brain tissue, as detected by immunohistochemistry
Retinitis	Not applicable	Typical CMV lesions on the retina, as confirmed by an ophthalmologist
Invasive disease in other organs (e.g., nephritis, myocarditis, pancreatitis)	The presence of organ dysfunction in the absence of other known causes plus evidence of CMV in the blood	The presence of organ dysfunction plus the presence of CMV in the target organ tissue, as detected by immunohistochemistry

Evidence of active CMV in the blood: positivity of antigenemia or RT-PCR testing.

Azevedo LS et al, 2015

P. Frange, M. Leruez-Ville / Médecine et maladies infectieuses 48 (2018) 495–502

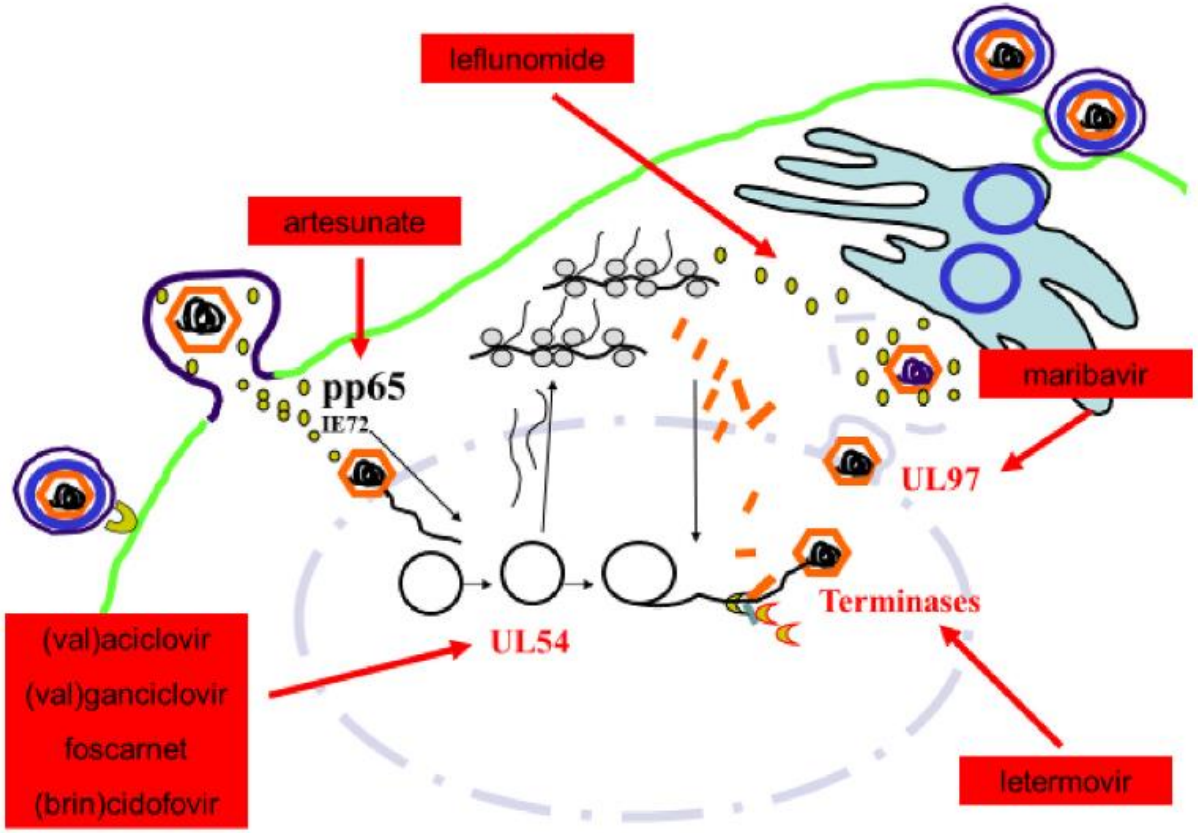


Fig. 1. Flow chart of CMV life cycle and targets of available antivirals or antivirals in development.
Représentation schématique du cycle viral du cytomégalovirus et des cibles d'actions des antiviraux disponibles ou en développement.

Ganciclovir is a nucleoside analogue that inhibits DNA synthesis in the same manner as acyclovir.

Valganciclovir is a prodrug of ganciclovir that is activated in the gut and liver to ganciclovir.

Foscarnet is a DNA chain inhibitor of phosphorylation. It has been used to treat resistant HSV and ganciclovir-resistant viruses. It is an effective antiviral.

Maribavir is a benzimidazole nucleoside and prevents viral DNA synthesis, as well as capsid nuclear egress.

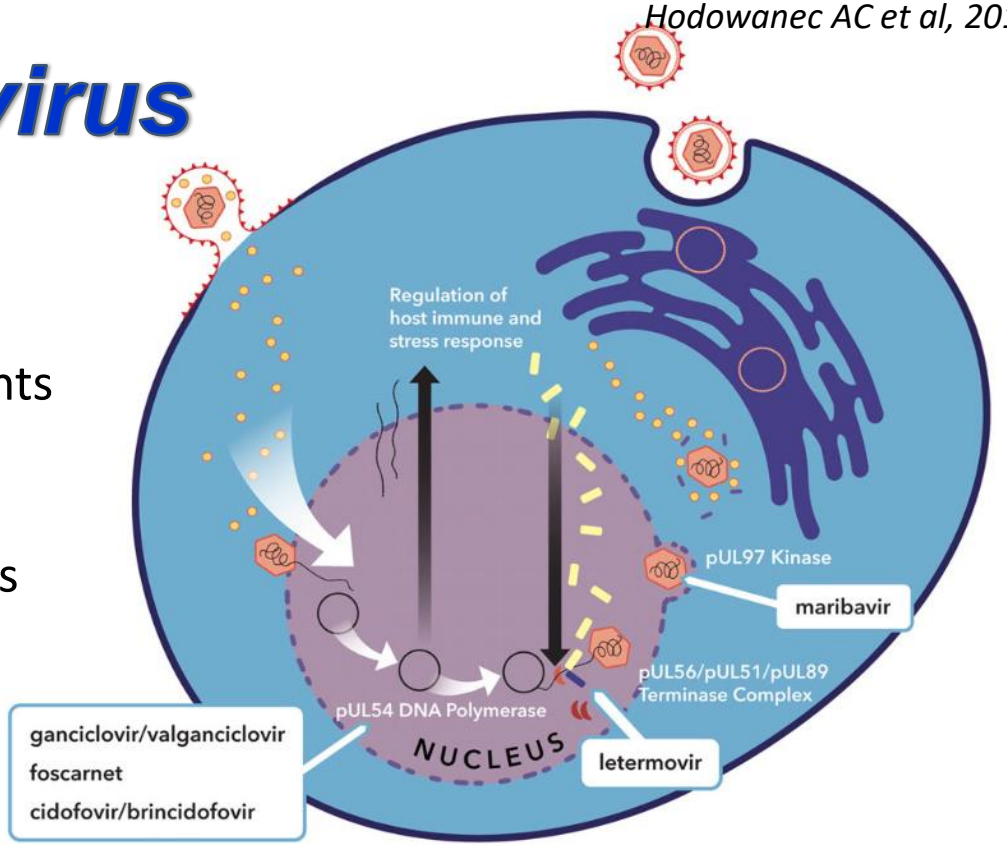
Letermovir is an anti-CMV drug that was approved by the FDA in November 2017. It inhibits the CMV DNA terminase complex (pUL51, pUL56, and pUL89), which is required for viral DNA processing and packaging by affecting the production of proper unit length genomes and interfering with virion maturation.

Hodowanec AC et al, 2019

Cytomegalovirus

Prevention of CMV disease can be accomplished by:

- administering **PROPHYLACTIC ANTIVIRAL THERAPY** to patients **without evidence of active CMV infection**
- administering **ANTIVIRAL PRE-EMPTIVE THERAPY** to subjects **with evidence** of **active CMV infection**

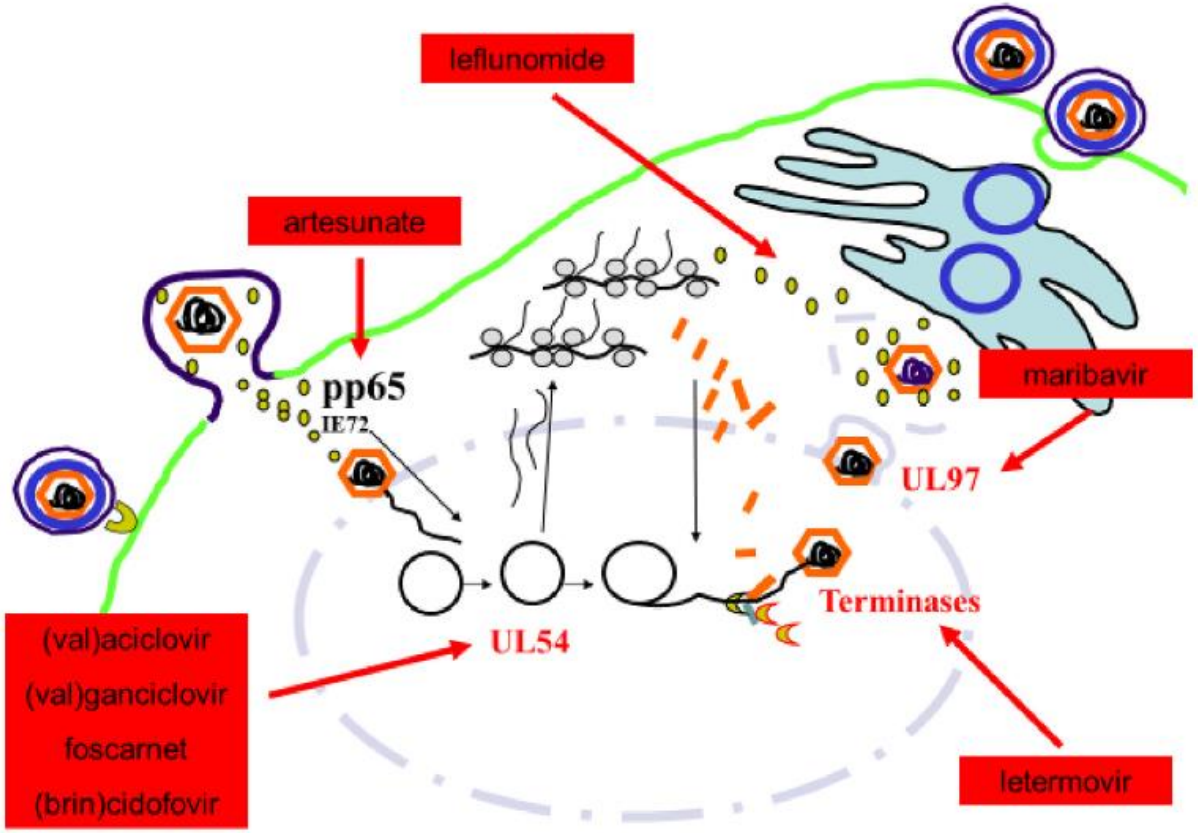


In both approaches, **CMV DNA monitoring** is carried out on blood samples on a regular basis post-transplantation

A primary CMV infection is usually detected around 4 weeks, compared with reactivation at around 6–8 weeks, post-transplantation respectively

QUANTITATIVE ASSESSMENT OF CMV CELL-MEDIATED IMMUNITY RECONSTITUTION may assist in risk stratification and enable an individualized approach for initiation or discontinuation of prophylaxis and preemptive therapy

P. Frange, M. Leruez-Ville / Médecine et maladies infectieuses 48 (2018) 495–502



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Cytomegalovirus

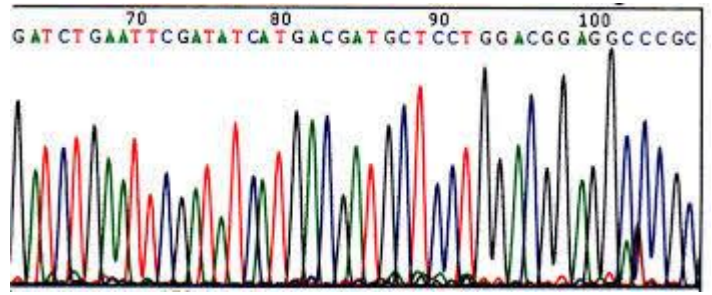
ANTIVIRAL DRUG RESISTANCE TEST

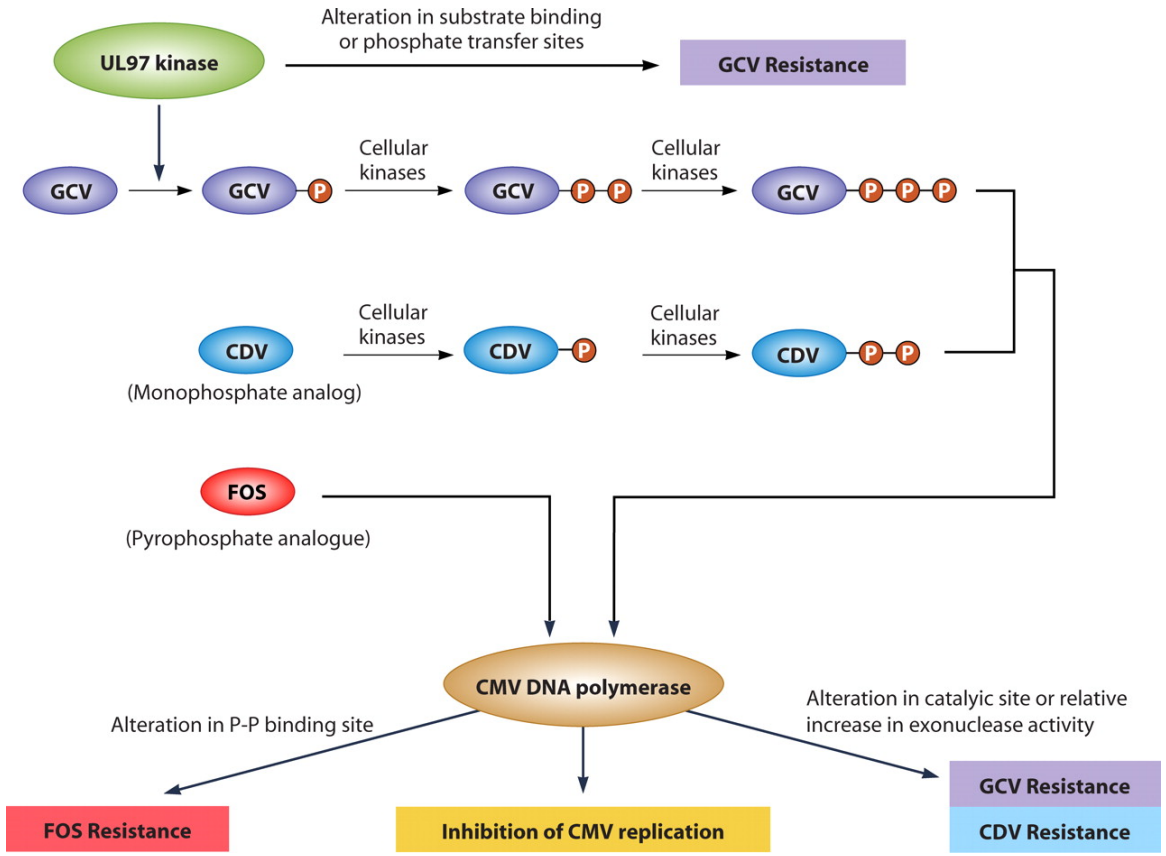
- Sequencing

Resistance should be suspected in patients who fail to achieve a significant reduction in CMV DNAemia following at least 2 weeks of full-dose CMV antiviral therapy, particularly in those who have previously received a CMV antiviral agent for at least 6 weeks

The most common location for amino acid substitutions associated with drug resistance to ganciclovir/valganciclovir is the viral **pUL97**

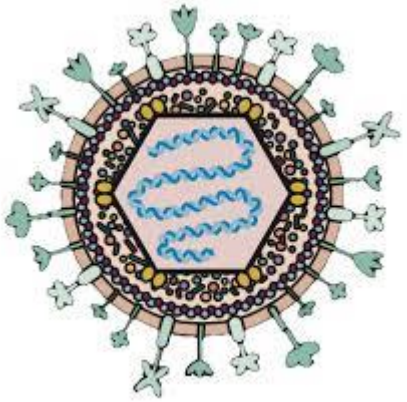
The next most common site for resistance substitutions is the **pUL54** (CMV DNA polymerase). pUL54 substitutions typically occur after substitutions in pUL97 have already been established.
Ganciclovir, valganciclovir, foscarnet, and cidofovir all target CMV DNA polymerase. Therefore, substitutions involving pUL54 may confer resistance to any or all these agents.





OPPORTUNIST PATHOGENS - VIRUSES

HSV



Recurrent HSV-1/HSV-2 infection is a major cause of morbidity and occasionally mortality in the immunocompromised patients, who experience **frequent, persistent and severe recurrences**

CLINICAL MANIFESTATIONS:

Herpetic lesions involving lips, oesophagus and other parts of the gastrointestinal tract
Pneumonitis
Hepatitis
Encephalitis

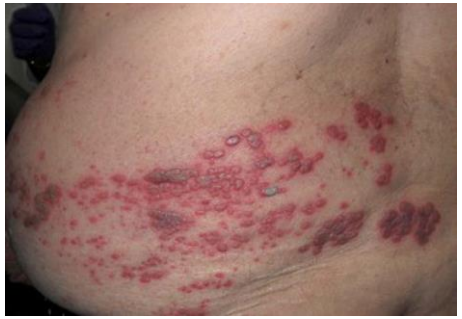
- HSV infection transmitted by means of **transplanted corneas** to HSV-seronegative recipients can result in serious HSV disease

Typically, reactivated localized HSV infections occur within the first few weeks of transplantation, while the more serious HSV systemic disease or encephalitis occurs rarely in transplant recipients

VZV

- **Herpes zoster** may occur within a few months post-transplantation, affecting the skin dermatome supplied by the involved nerve. The distribution may be multidermatomal and dissemination can occur to other sites

- **Young pediatric transplant recipients** without preexisting immunity to VZV are at risk for developing primary VZV infections after exposure to chicken pox



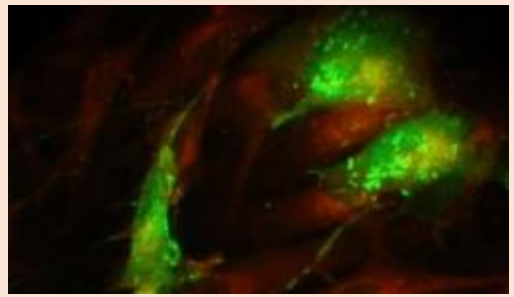
Diagnosis

HSV

- Culture of infectious virus from lesion fluids or mucosae
- Direct staining of cells or viral isolates with fluorescent-dye-conjugated monoclonal antibodies specific for HSV-1 and HSV-2 antigens
- Molecularly based techniques are critical for diagnosis of HSV encephalitis and are also useful for detecting corneal infections, but they are not routinely used for the detection of mucocutaneous HSV infection

VZV

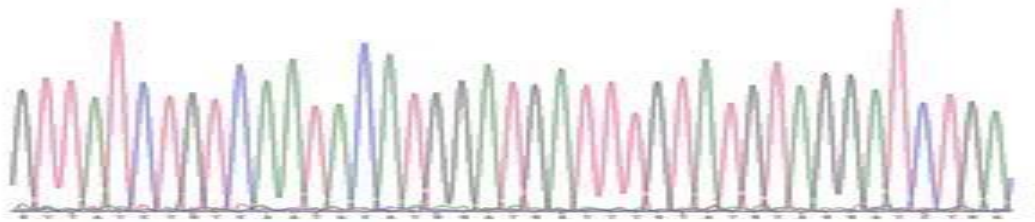
- Routinely diagnosed by clinical presentation
- To confirm the diagnosis, virus can be identified from the lesions by immunofluorescent staining with monoclonal antibody (IFA)



Antiviral prophylaxis is **ACICLOVIR** given at a low dose and is effective in preventing HSV and VZV reactivation that may occur in the immediate post-transplantation period

→ Infections are increasingly caused by **ANTIVIRAL-DRUG-RESISTANT MUTANTS** that evolve under pressure of prophylactic as well as therapeutic drug regimens

GENOME SEQUENCE ANALYSIS TO DETERMINE THE ANTIVIRAL SUSCEPTIBILITY



HHV-6 and HHV-7

Infection, re-infection or reactivation has been reported in transplant recipients, in particular with neurological conditions including **ENCEPHALITIS**

HHV-8

associated with the development of **Kaposi's sarcoma** (KS),
a multicentric tumour that involves massive proliferation of endothelial cells.

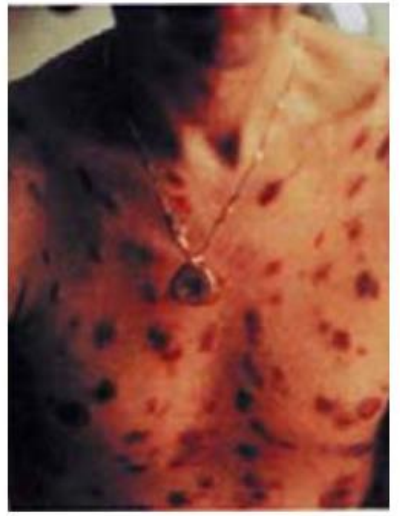
- **KS is 300 times more common among patients with AIDS than among other immunosuppressed groups**

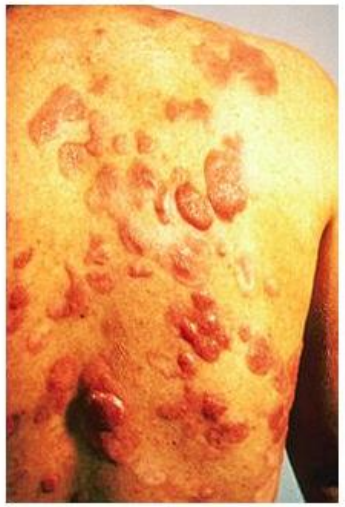
HHV-8 is also associated with other lymphomatous conditions, namely **multicentric Castleman's disease** and **primary effusion lymphoma**.

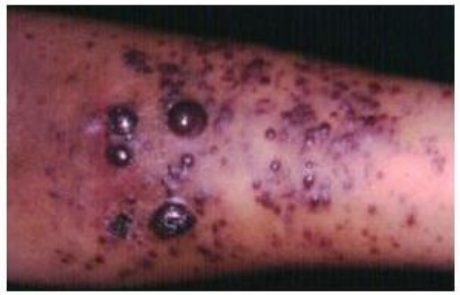
Diagnosis

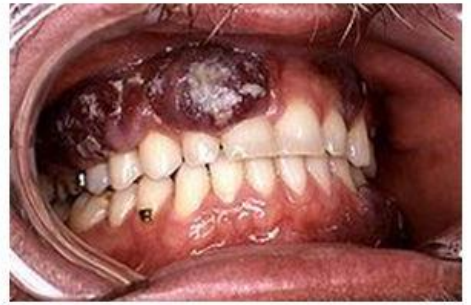
DNA detection by molecular methods

KS cutaneous lesions









EBV

Infection in the immunocompromised host is accompanied by the risk of developing lymphoproliferative diseases:

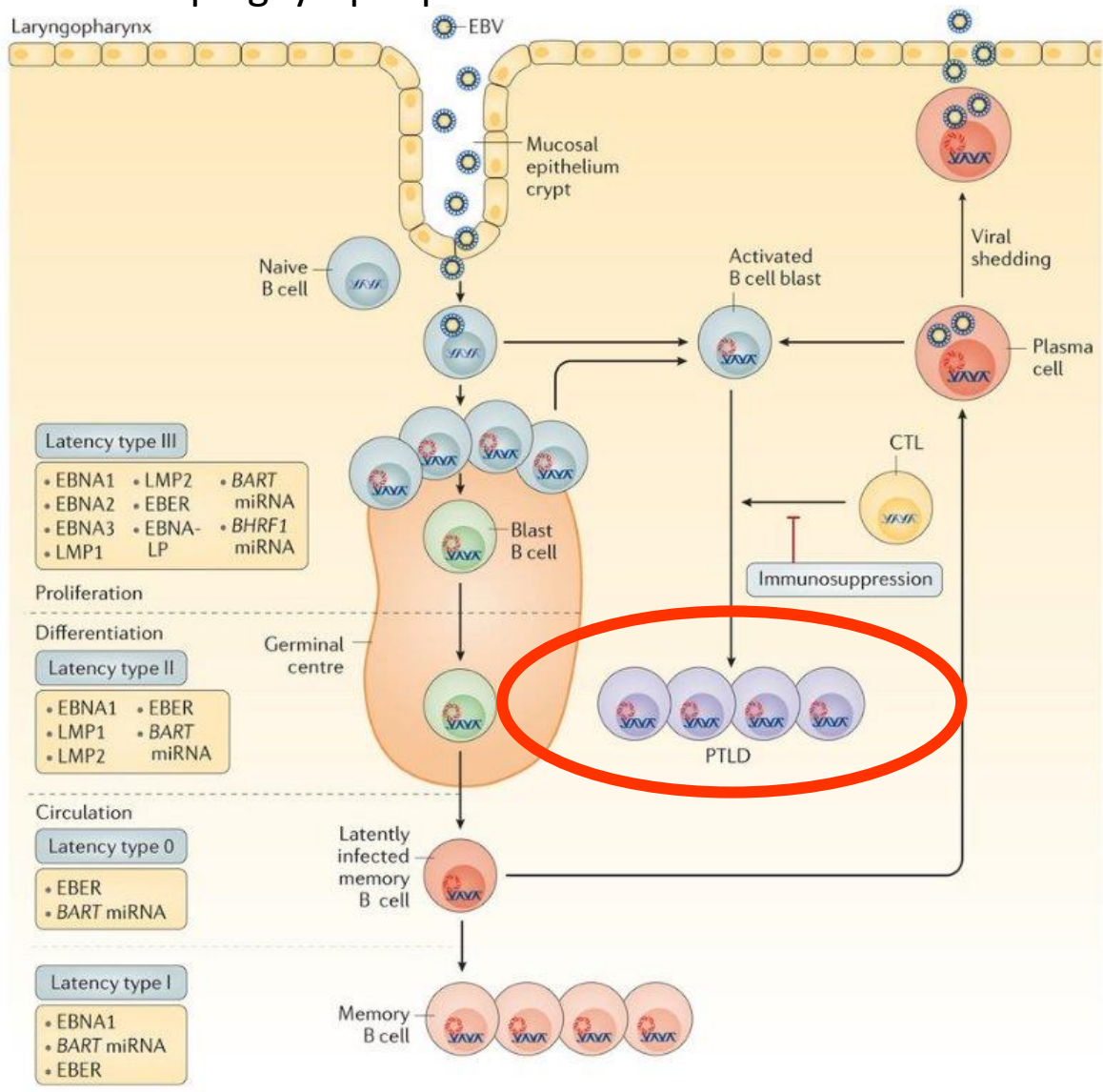
- Hodgkin's disease, non-Hodgkin's lymphomas in individuals with HIV infection
- Smooth muscle tumours in immunosuppressed children
- Post-transplantation lymphoproliferative disease (PTLD)

PTLD

- Prolonged fever, lymphadenopathy, intermittent tonsillar enlargement, progressive reduction in cellular lineages on complete blood count
- Hepatitis, colitis, pneumonia, nephritis, and cerebritis

Without an effective CTL response due to immunosuppression, the EBV-infected B lymphocytes may proliferate in an uncontrolled fashion → B-cell hyperplasia with CD20-positive lymphocytes resulting in:

- **Polyclonal PTLD**: may form tumor masses and present with symptoms due to a mass effect
- **Monoclonal PTLD**: cells present chromosomal abnormalities, tend to form a disseminated malignant lymphoma with a high mortality rate



Dharnidharka et al, 2016

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PTLD RISK FACTORS

- Post-transplantation primary EBV infection
- Mismatched donor and recipient EBV and CMV status
- CMV disease
- Intensity and type of immunosuppressive therapy

-Host origin infection in >90% of cases in SOT recipients
- Donor origin infection in HSCT recipients

Frequency: 0.5 to 23% in SOT recipients

As the two peaks of primary EBV infection are in children and adolescents, the incidence of PTLD is **higher in paediatric transplant recipients**

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PTLD

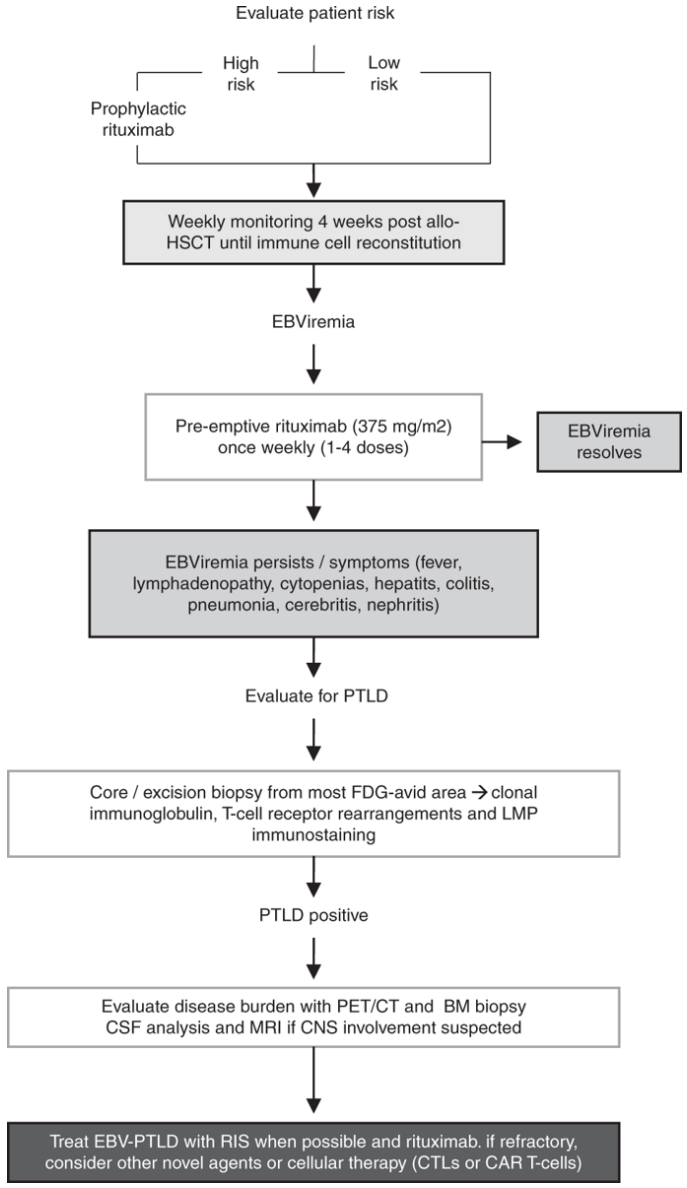
DIAGNOSIS

Once PTLD is suspected based on the clinical picture or rising peripheral blood EBV DNA levels, a tissue biopsy is required to confirm the diagnosis of PTLD and differentiate it from other entities

EBV DNA for:

- ➢ Prediction of lymphoproliferative disease
- ➢ Monitoring the progress of therapeutic interventions

Strict implementation of monitoring EBV DNAemia and pre-emptive therapy with novel drugs such as rituximab have managed to improve mortality due to PTLD from 84% before the year 2000 to 30% in 2013



Al Hamed R et al, 2019

Respiratory virus infections

Immunocompromised patients, especially transplant recipients, are at increased risk of pneumonia and death if they develop respiratory tract infections with viruses such as:

- Respiratory syncytial virus (RSV)
- Influenza
- Parainfluenza
- Adenoviruses

Preventive measures include early diagnosis of an upper respiratory tract infection using SENSITIVE TESTS such as **VIRAL GENOME DETECTION**

Multiplex PCR syndromic testing

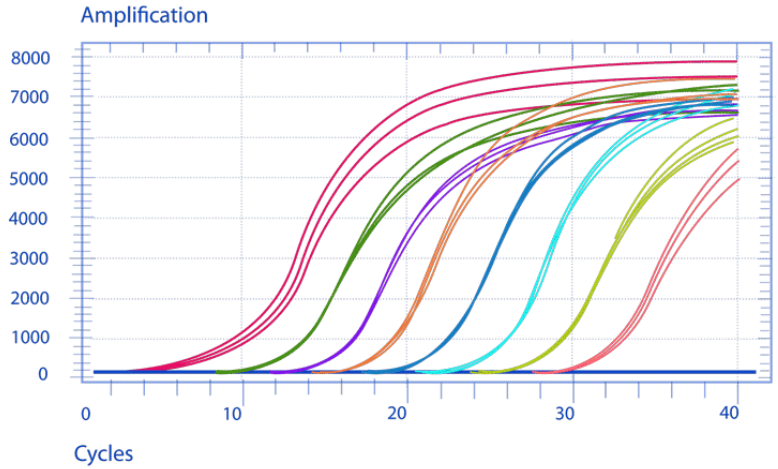
ADENOVIRUS

- Primary and reactivated adenovirus infections can result in **disseminated disease** in immunocompromised hosts, in particular paediatric and adult bone marrow transplant recipients, with **high mortality rate**

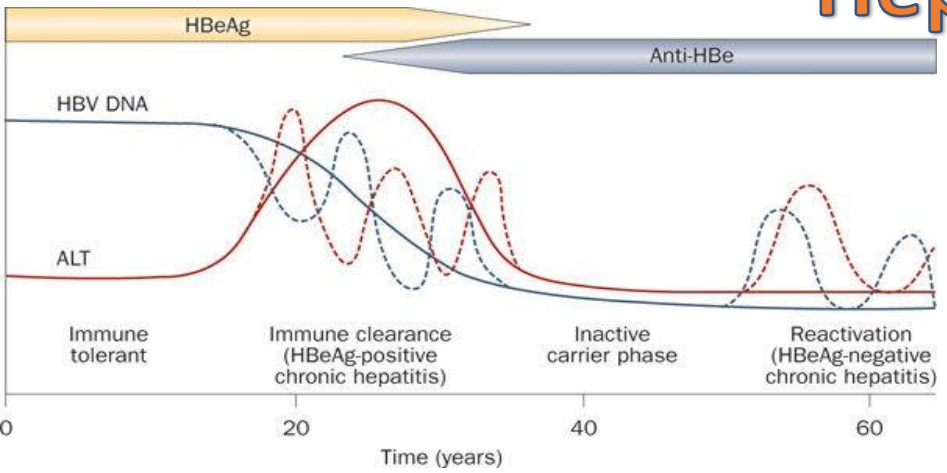
- **Hepatitis and pneumonia** are most frequently reported

In line with the epidemiology of HAdV infections, young age was shown to confer an elevated risk of HAdV infection

Adenovirus surveillance is often carried out in centres by collecting blood samples post- transplantation, which are tested for **adenovirus DNA** in order to detect early viraemia



Hepatitis B virus (HBV)



Bone marrow transplant recipients with evidence of previous hepatitis B infection are likely to suffer a **HEPATITIS B REACTIVATION** post-transplantation

Phase 1: immunosuppression, no cytotoxic T-cell response
→ **ASYMPTOMATIC INFECTION**
Phase 2: engraftment
→ **SYMPTOMATIC INFECTION** (jaundice, high morbidity and mortality)

DIAGNOSIS
1. HBV serology screening→ Risk assessment
2. HBsAg and HBV DNA monitoring

THERAPY
→ **Past** HBV infection: antiviral prophylaxis (lamivudine, tenofovir or entecavir)
→ **Current** HBV infection: pre- and post-transplant therapy

PHASE	FEATURE	DIAGNOSTIC MARKERS	COMMENTS
1	Increase in HBV Replication Period	HBV DNA HBeAg HBsAg	Rise of > 1 $\log_{10}$ IU/mL In HBeAg negative Reverse seroconversion
2	Liver Disease Activity Period	ALT Jaundice Symptoms	Rise of > 3 times baseline Injury Indicates more serious
3	Recovery Period	HBV DNA ALT HBsAg	Drops to the baseline level Drops to the baseline level May be negative late

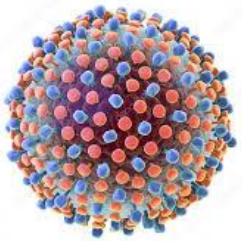
Guo L et al, 2018

Tree phases of HBV Reactivation

Hepatitis C virus (HCV)

HCV infection is associated with veno-occlusive disease in **bone marrow transplant recipients**.

- Venous congestion occurs in the liver owing to a non-specific vasculitis and results in liver necrosis.
- Multiorgan failure can be precipitated because of increased capillary permeability throughout the body.

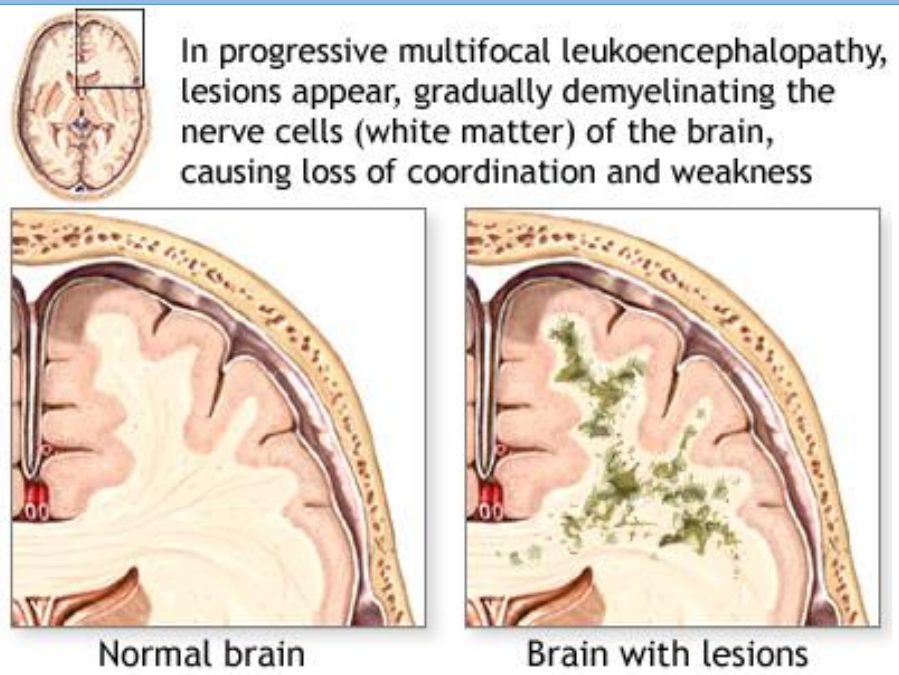


Polyomaviruses

BK or JC viruses are acquired via the respiratory tract and lie latent in the kidney

JCV

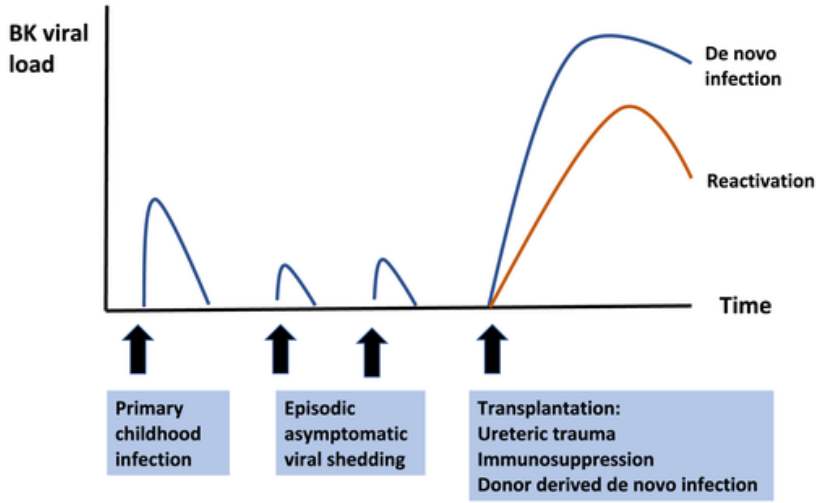
JC virus can reactivate and disseminate to cause central nervous system infections such as progressive multifocal leukoencephalopathy (PML) in individuals with AIDS, hematological malignancies, autoimmune disorders



→ Real Time PCR in urine and CSF

BKV

Clinically significant disease occurs almost exclusively in **renal and haemopoeitic stem cell transplants**.
Incidence of BKV nephropathy is as high as 10% in renal transplant recipients.
The clinical features of infection range from asymptomatic viruria or viraemia to **interstitial nephritis, ureteric strictures, and haemorrhagic cystitis**

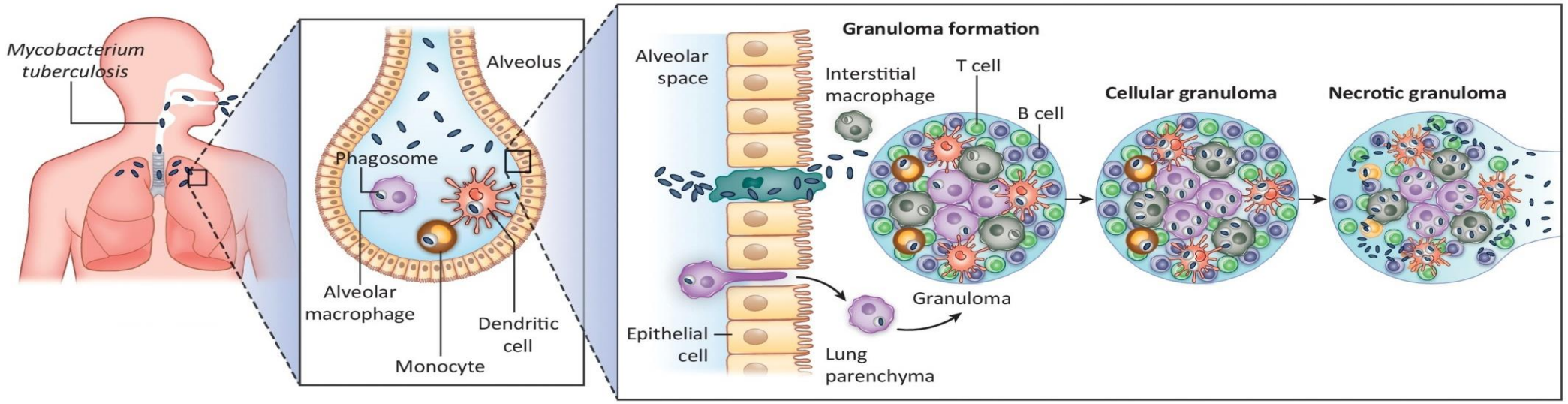


→ Real Time PCR in urine

Chong S et al, 2019

Mycobacterium spp.

Disseminated infection with ***Mycobacterium tuberculosis*** and ***M. avium*** **complex MAC** is a severe complication and often a terminal event of advanced HIV/AIDS disease



- **Primary infection**

usually mild and asymptomatic and in 90% of cases does not proceed further

- **Secondary tuberculosis**

reactivation of dormant mycobacteria, usually in immunocompromised

- **Miliary tuberculosis**

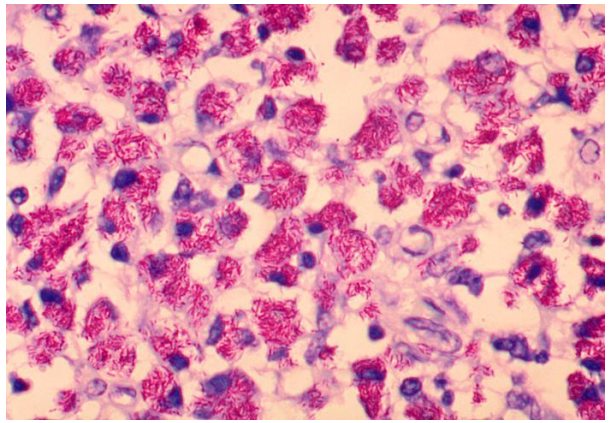
disseminated disease (lymphnodes, kidney, bones, genital tract, brain, meninges)

Koch and Mizrahi, 2018

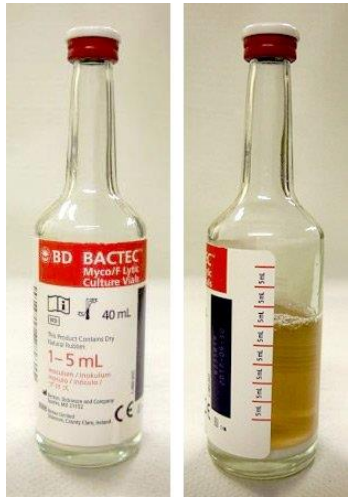
Mycobacterium spp.

Disseminated infection with ***Mycobacterium tuberculosis*** and ***M. avium* complex MAC** is a severe complication and often a terminal event of advanced HIV/AIDS disease

- *M. avium-intracellulare* belongs to the so-called '**atypical' mycobacteria or mycobacteria other than tuberculosis (MOTT)**. It resembles *M. tuberculosis* in that it is slow growing, but it is resistant to the conventional antituberculosis drugs.
- These organisms can be isolated from **BLOOD CULTURES** from patients with AIDS



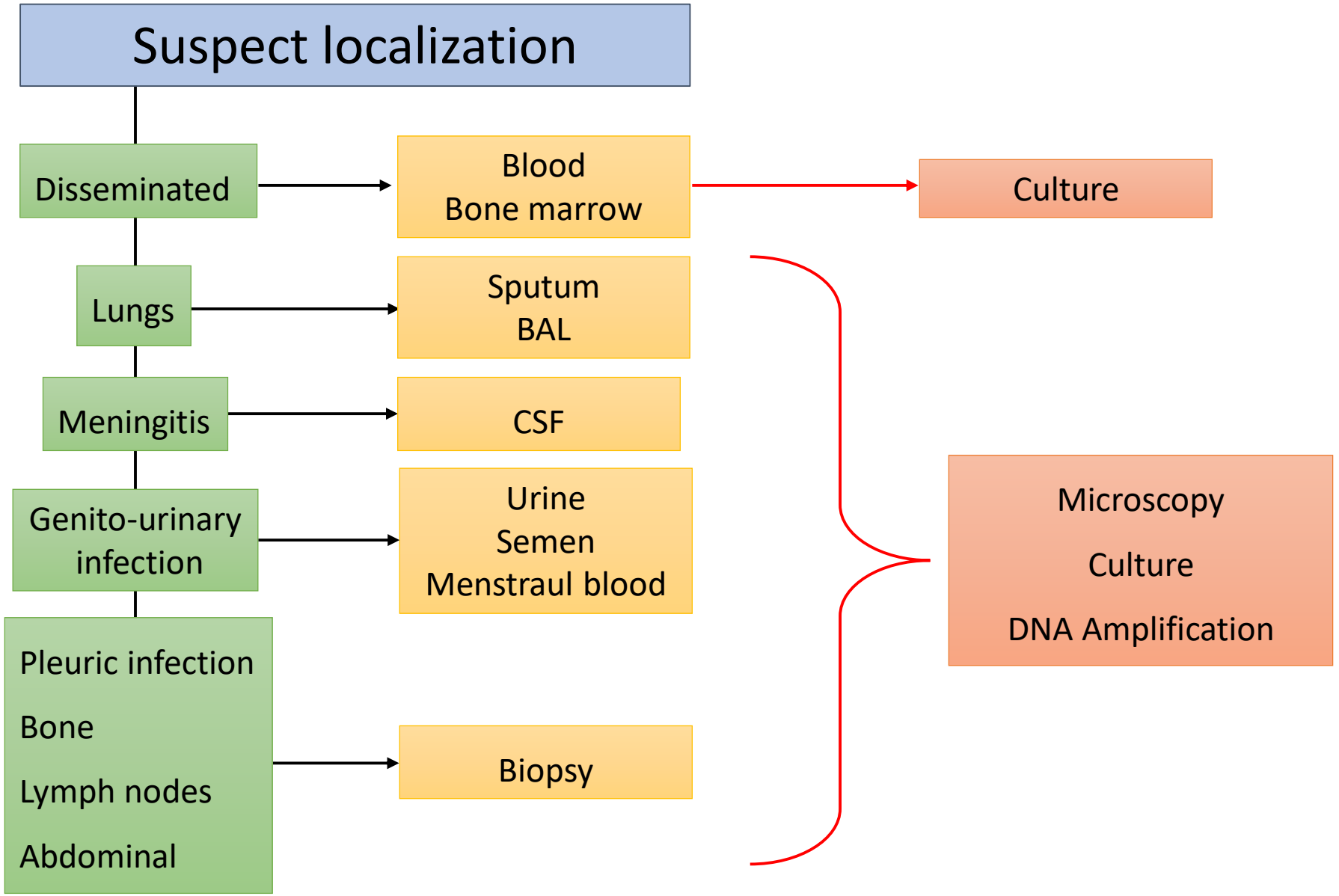
Mycobacterium avium-intracellulare infection of lymph node in patient with AIDS. Ziehl-Neelsen stain.



Species	Clinical disease
Slow growers[a]	
M. tuberculosis	Tuberculosis
M. bovis	Bovine tuberculosis
M. leprae	Leprosy
M. avium[b] *M. intracellulare*[b]	Disseminated infection in AIDS patients M. avium complex (MAC)
M. kansasii	Lung infections
M. marinum	Skin infections and deeper infections (e.g. arthritis, osteomyelitis) associated with aquatic activity
M. scrofulaceum	Cervical adenitis in children
M. simiae	Lung, bone and kidney infections
M. szulgai	Lung, skin and bone infections
M. ulcerans	Skin infections
M. xenopi	Lung infections
M. paratuberculosis	? Association with Crohn's disease
Rapid growers[a]	
M. fortuitum *M. chelonae*	Opportunist infections with introduction of organisms into deep subcutaneous tissues; usually associated with trauma or invasive procedures

SAMPLE COLLECTION

Mycobacterium spp.

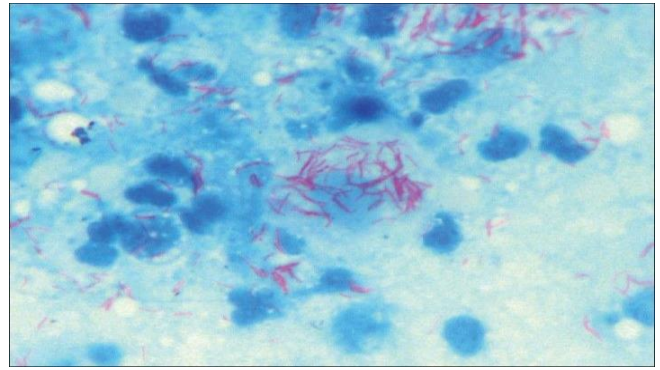


Mycobacterium spp.

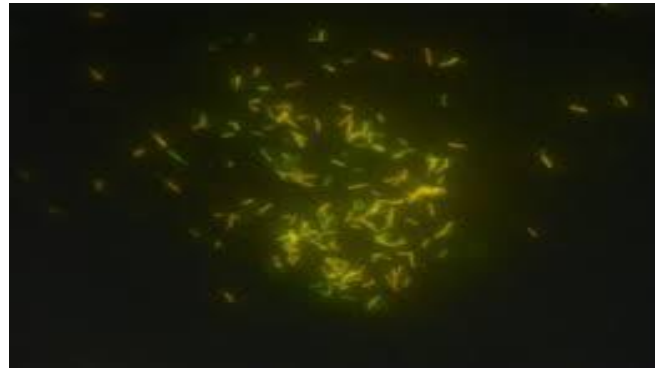
LABORATORY DIAGNOSIS

MICROSCOPIC EXAMINATION

Ziehl–Neelsen's staining
Microscopic demonstration of **ACID-FAST RODS**



Auramine–rhodamine stain
Microscopic demonstration of **FLUORESCENT RODS**



Important because of the time required for culture results

Mycobacterium spp.

LABORATORY DIAGNOSIS

Culture

Complex media are required
Liquid broths: Middlebrook 7H9 or 7H12
Egg-based solid media Lowenstein-Jensen
Solid agar-based media: Middlebrook 7H11 or 7H10

Slow growth rate:
up to 6 weeks to grow in culture

AUTOMATED SYSTEMS

- Continually monitor the media for detection of mycobacteria for 6 weeks
- Most widely used FDA-cleared automated systems for rapid detection of mycobacteria using liquid media:
  - Biomerieux BacT/ALERT® 3D
  - Becton Dickinson BACTEC MGIT™
  - Thermo Scientific VersaTREK™

Mycobacterium spp.

LABORATORY DIAGNOSIS

RAPID METHODS

- ✓ PCR
- ✓ Xpert MTB-RIF molecular test:
  detects TB and rifampicin resistance

Nocardia asteroides

- Uncommon opportunist
- Worldwide distribution
- Family Actinomycetes, relatives of the mycobacteria but resembling fungi in that they form branching filaments
- Infections have been reported in immunocompromised patients, especially in renal transplant
- Primarily a **pulmonary infection**, but secondary spread to form **abscesses in brain or kidney** is common

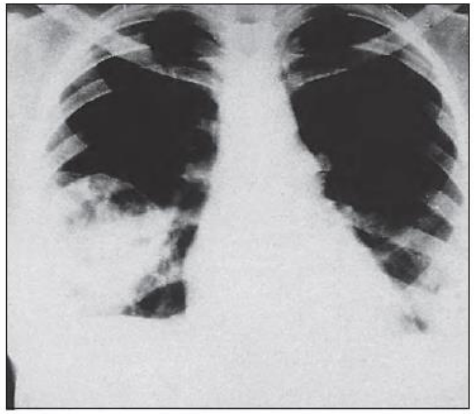


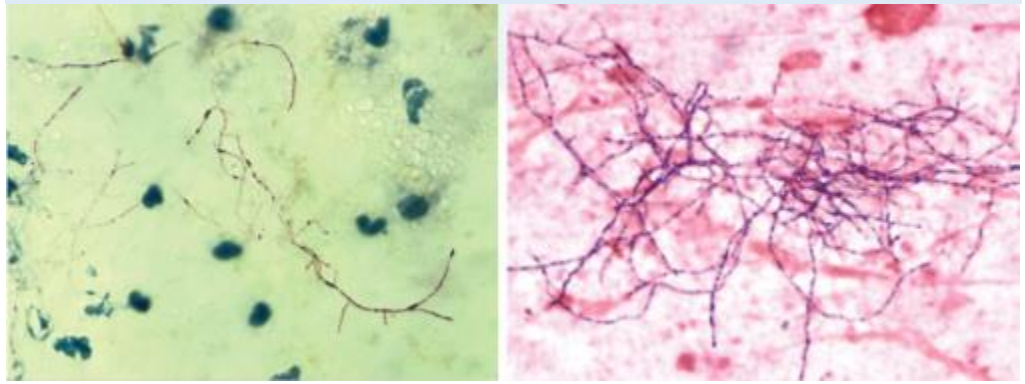
Figure 31.14 Pulmonary nocardiosis. Chest radiograph showing a large rounded lesion in the right lower zone with multiple cavities. (Courtesy of T.F. Sellers, Jr.)

DIAGNOSIS

Nocardia can be isolated on routine laboratory media, but is often slow to grow and is consequently easily overgrown by commensal flora. Therefore the laboratory staff should be informed if nocardiosis is suspected clinically, so that appropriate media are inoculated.

- Grow as 'breadcrumb' colonies on blood agar within 2–10 days' incubation
- Catalase positive

The organism is a Gram-negative branching rod and weakly acid fast



Acid-fast stain Gram's stain

Nocardia asteroides in sputum

OPPORTUNIST PATHOGENS - FUNGI

Fungal infections are much more common in patients who are **neutropenic** for more than 21 days.
Infections caused by fungi are increasing, partly because more patients are surviving the early neutropenic period with the aid of modern antibacterial agents and granulocyte transfusions

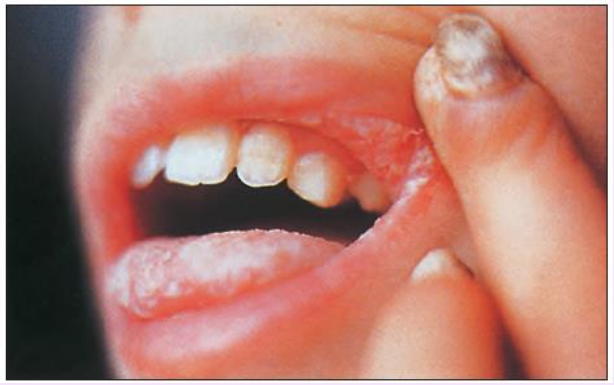
Neutropenia following cytotoxic therapy and in advanced HIV infection (AIDS) predisposes to fungal infections (e.g.*Candida*, *Aspergillus* and *Cryptococcus*) especially when the patient has received previous antibacterial therapy

Candida spp.

Candida is the most common fungal pathogen in a variety of compromised patients and in various body sites. It is the cause of:

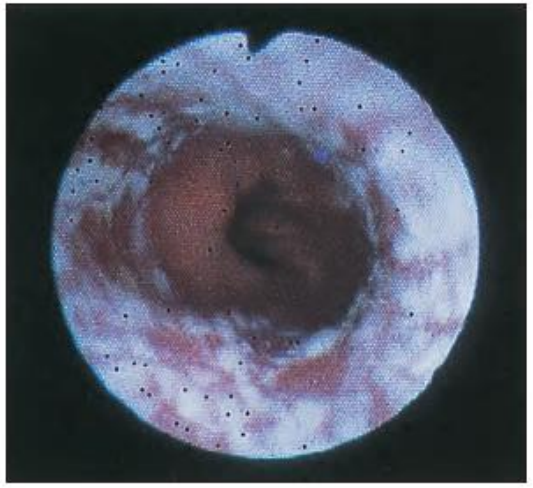
- vaginal and oral thrush
- skin infections
- endocarditis, particularly in injecting drug users

Different manifestations depending on the nature of the underlying compromise:



Chronic mucocutaneous candidiasis

Persistent but non-invasive infection of mucous membranes, hair, skin and nails in patients, often children, with a specific T-cell defect rendering them anergic to *Candida*



Oropharyngeal and oesophageal candidiasis

Gastrointestinal candidiasis in patients who have undergone major gastric or abdominal surgery and with neoplastic disease

Disseminated candidiasis

- Invasion via the gastrointestinal tract
- Does not often originate from skin infection unless there is disruption to the skin barrier (e.g. Presence of a central venous catheter)
- Neutropenia is necessary for the invasion of deeper subcutaneous tissue
- Patients with lymphoma and leukaemia are most at risk
- Blood-borne spread to almost any organ can occur

Candida spp.

DIAGNOSIS

SAMPLES

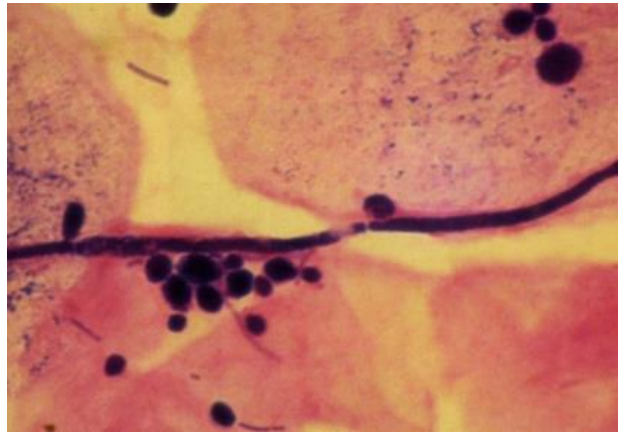
- Skin/nail scraping or swab
- Sputum, urine, biopsies, blood, CSF (**systemic forms**)

MICROSCOPIC EXAMINATION: visualization of pseudohyphae and budding yeast cells typical of many *Candida* species

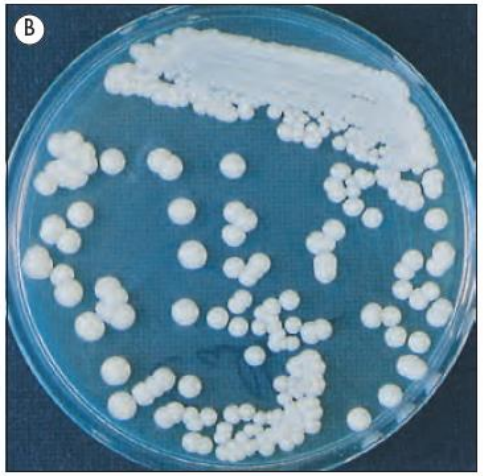
CULTURE (SDA)

IDENTIFICATION

SEROLOGICAL METHODS can be used for disseminated disease, but less helpful in neutropenic patients

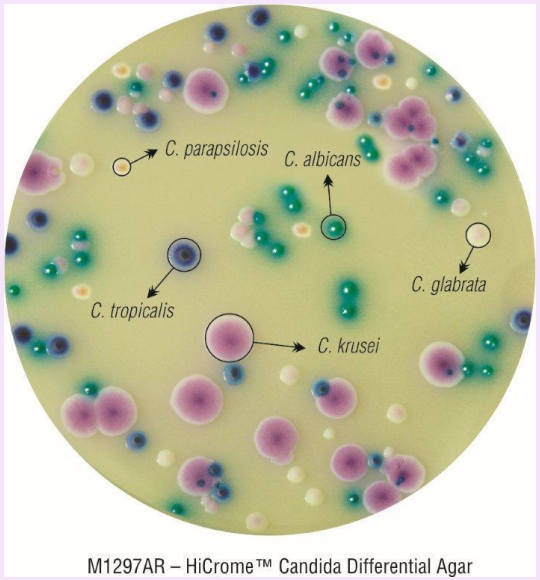


Blastoconidia and pseudohyphae (Gram stain)



Culture

Culture on chromogenic agar: allows the differentiation of the various *Candida* species based on the coloration of the colonies



Candida spp.

DIAGNOSIS

SAMPLES

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CULTURING (SDA)

IDENTIFICATION

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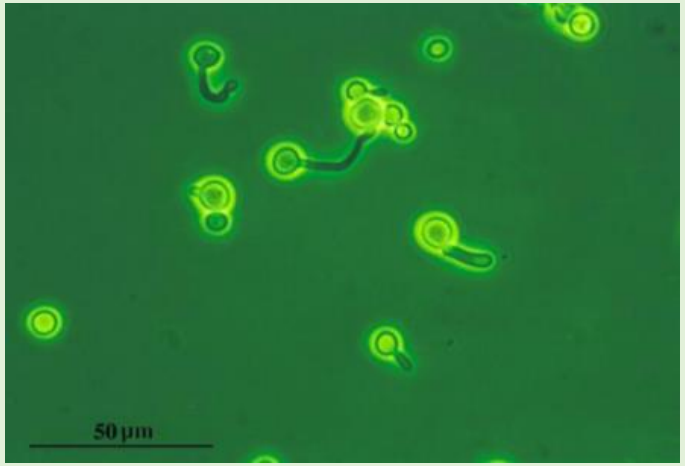
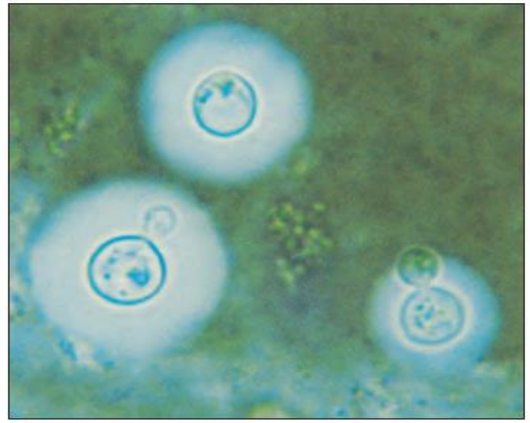


GERM TUBE TEST

When cells are incubated in serum at 37°C for 2-4 hours, *Candida albicans* produce short, slender, tube like structures called germ tubes.
Germ tube test is the confirmatory test for *Candida albicans* and a rapid method for identifying and differentiating *C. albicans* from other *Candida* spp.

Cryptococcus neoformans

- Encapsulated yeast
- Worldwide distribution
- Infection is seen more frequently in people with impaired cell-mediated immunity
- Infection usually results in **lung infection** or **meningoencephalitis**; occasionally other sites such as skin, bone and joints are involved
- In the severely immunocompromised, mortality is approximately 50%. In patients with AIDS it is almost impossible to eradicate the organism even with intensive treatment



India ink stained preparation of CSF sediment

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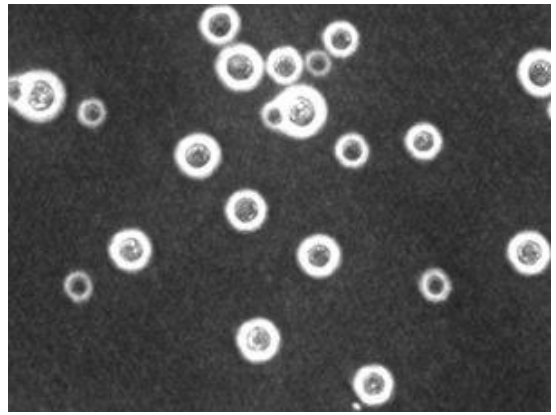


India ink stained preparation

DIAGNOSIS

SAMPLES

Sputum or CSF

MICROSCOPIC EXAMINATION: yeasts can be seen in **Indian-ink**-stained preparations and are characterized by their large polysaccharide capsule

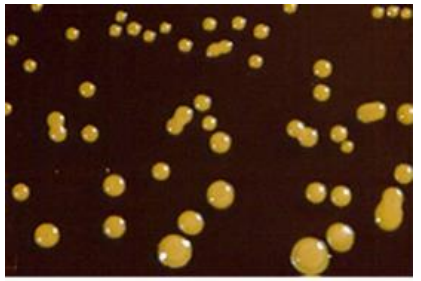
CULTURING (SDA)

RAPID ANTIGEN DETECTION: latex agglutination test using specific antibody-coated latex particles

Treatment can be **monitored** by detecting a fall in CSF antigen concentration

MOLECULAR METHODS

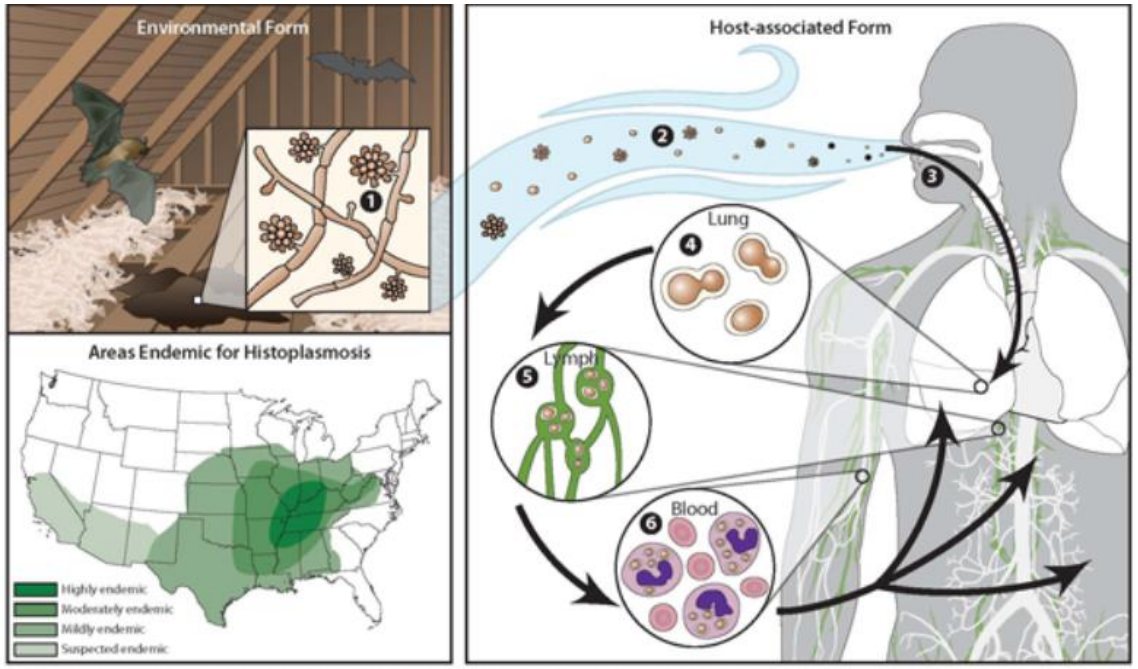
SEROLOGICAL METHODS



Culture of C. neoformans

Histoplasma capsulatum

- Acute but benign **pulmonary infection** in healthy people
- **Chronic progressive disseminated disease** in the compromised host
- Endemic only in tropical parts of the world and notably in the so-called ‘histoplasmosis belt’ of the central USA
- African histoplasmosis, caused by *Histoplasma duboisii,* is found in Equatorial Africa
- The natural habitat of the organism is the soil: **airborne transmission**
- Disseminated disease may occur many years after the initial exposure in immunocompromised patients



In the environment, *Histoplasm capsulatum* exists as a mold (1) with aerial hyphae. The hyphae produce macroconidia and microconidia (2) spores that are aerosolized and dispersed. Microconidia are inhaled into the lungs by a susceptible host (3). The warmer temperature inside the host signals a transformation to an oval, budding yeast (4). The yeast are phagocytized by immune cells and transported to regional lymph nodes (5). From there they travel in the blood to other parts of the body (6).

DIAGNOSIS

Biopsy and histological examination of bone marrow, liver or lymph nodes

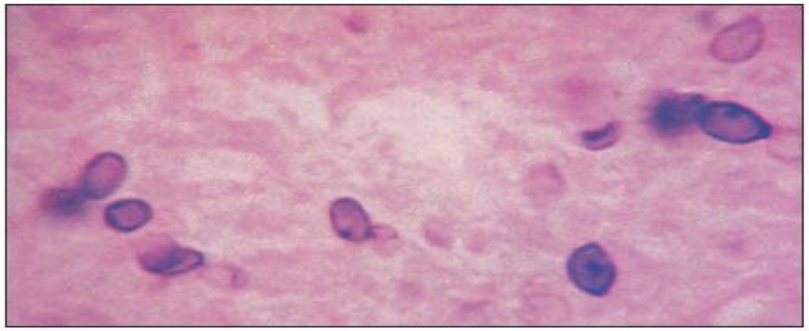
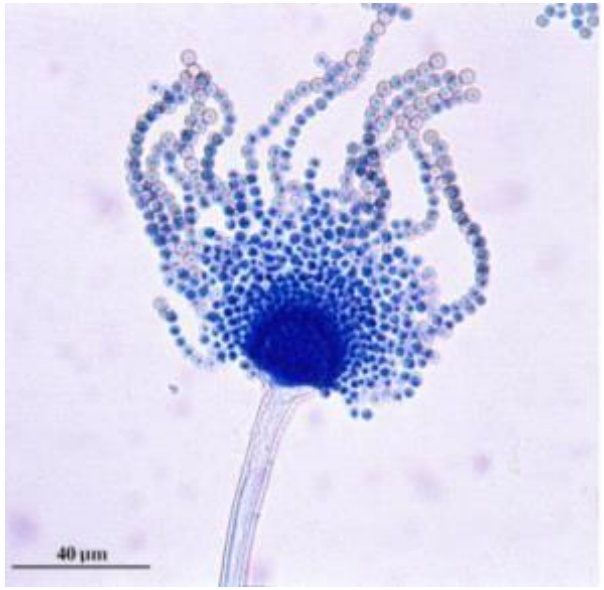


Figure 31.10 Histological section of the lung showing yeast forms of *Histoplasma capsulatum* (methenamine silver stain). (Courtesy of T.F. Sellers, Jr.)

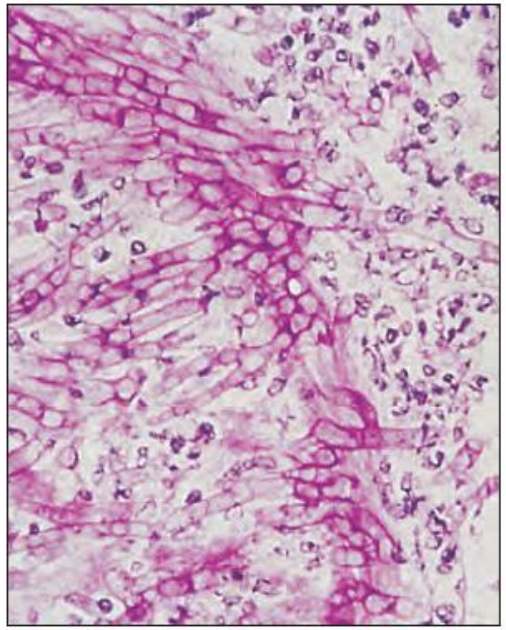
Invasive aspergillosis



- Increasingly reported as a cause of invasive disease in compromised patients, usually in profoundly neutropenic patients or those receiving high-dose corticosteroids
- Aspergilli are found in soil: **airborne transmission**
- Dissemination to other sites, particularly the central nervous and heart, occurs in about 25% of compromised individuals with lung infection
- Invasive aspergillosis has a **high fatality rate** in the compromised patient
- Outbreaks of hospital-acquired infection have been reported

Diagnosis

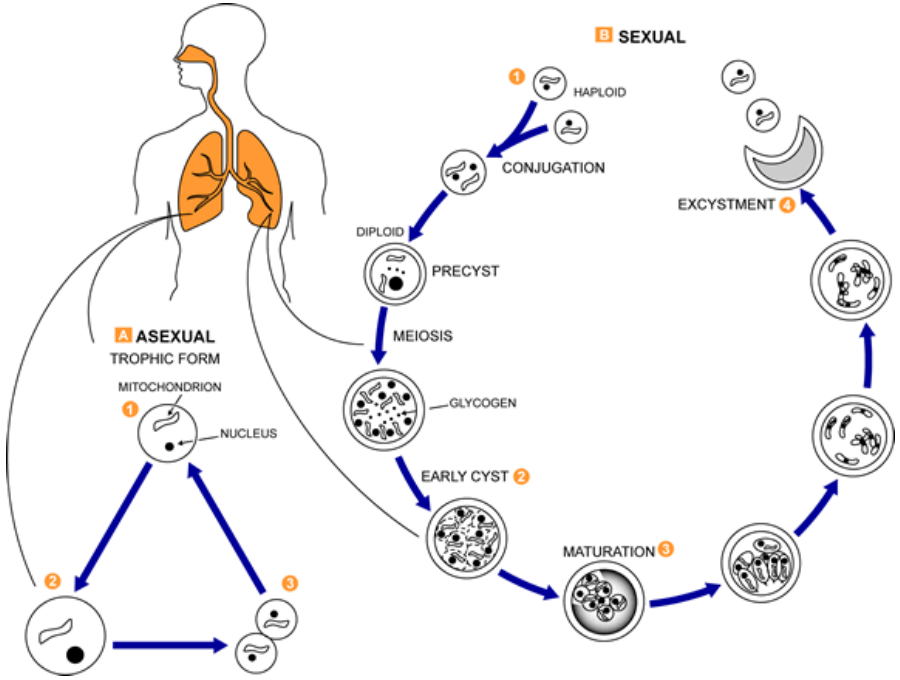
SAMPLE: bronchoalveolar lavage specimens, lung biopsy
MICROSCOPY
CULTURE
ANTIGEN DETECTION
POLYMERASE CHAIN REACTION
SEROLOGIC DIAGNOSIS: galactomannan antigen



Numerous septate hyphae invading a blood vessel wall in cerebral aspergillosis (periodic acid-Schiff stain).

Pneumocystis jirovecii

- Widespread atypical fungus
- Symptomatic disease in people whose cellular immune mechanisms are deficient
- High incidence of *P. jirovecii* **pneumonia** in patients receiving immunosuppressive therapy to prevent **transplant** rejection and in individuals with **HIV**
- The symptoms are non-specific and can mimic a variety of other infectious and non-infectious respiratory diseases



Diagnosis

- Requires a high index of suspicion
- Bronchoalveolar lavage sampling is required
- Silver or immunofluorescent stains
- DNA amplification by PCR improves the sensitivity of the diagnostic tests

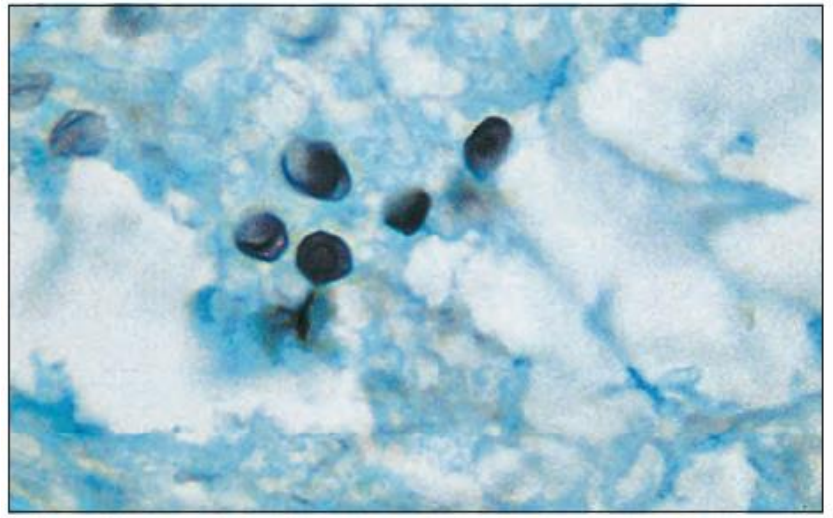
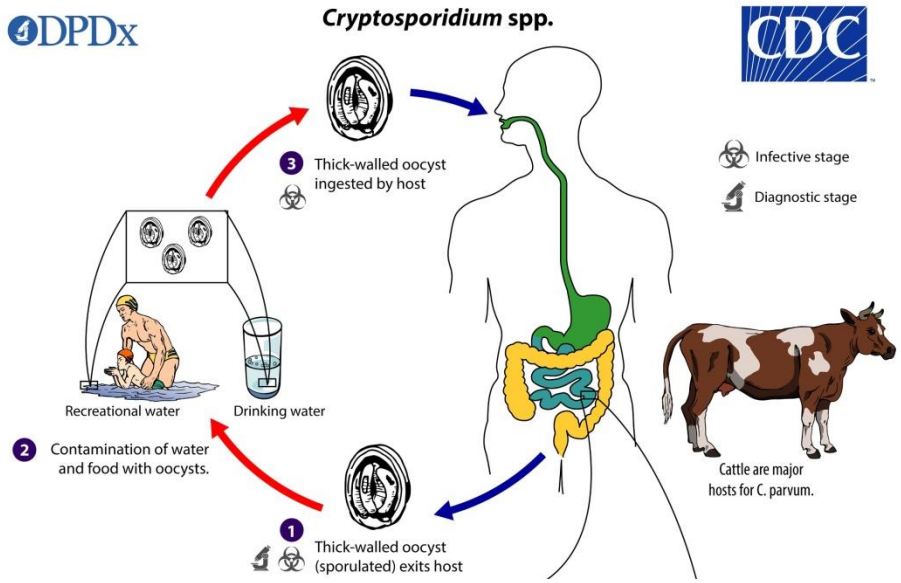


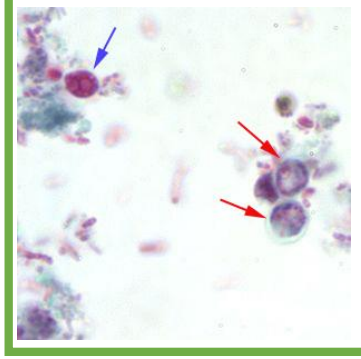
Figure 31.13 Darkly staining cysts of *Pneumocystis jirovecii* in an open lung biopsy from an AIDS patient with pneumonia (Grocott silver stain). (Courtesy of M. Turner-Warwick.)

DIARRHOEA-CAUSING PROTOZOA

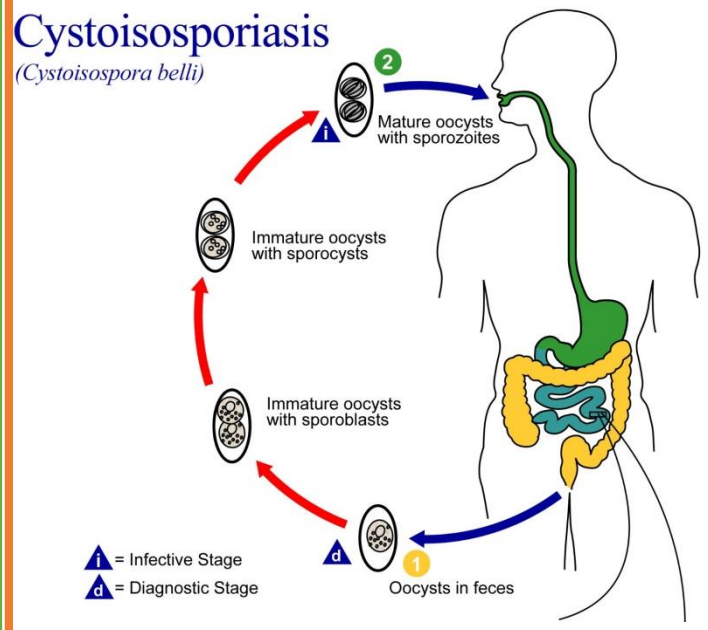
Cryptosporidium
Cystoisospora belli
Cyclospora cayetanensis

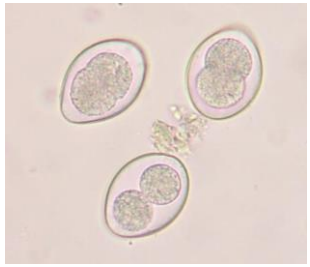
Protozoa causing significant but self-limiting diarrhoea in healthy people with an intact immune system, but **severe and chronic diarrhoea** in severely immunocompromised people, e.g. with advanced HIV-infection



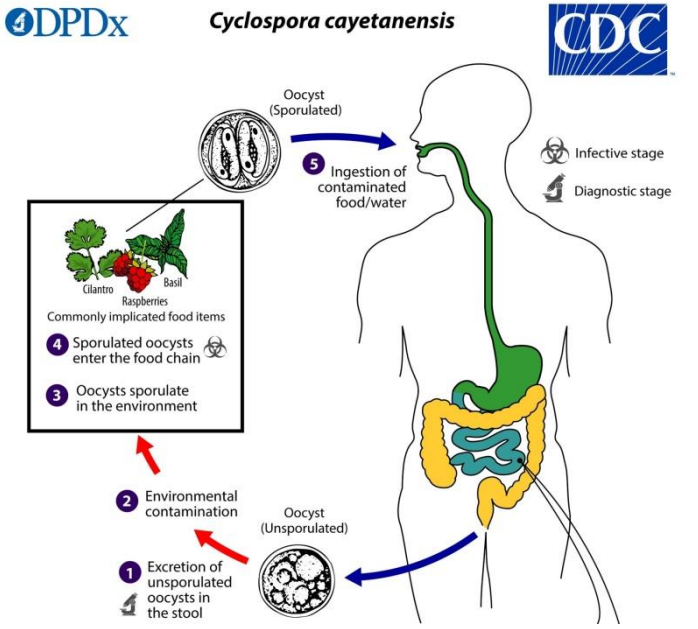


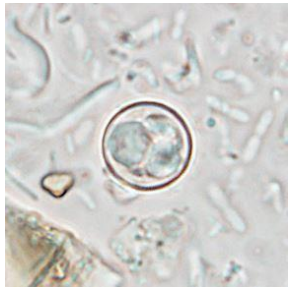
- Small (5 µm) oocysts in faeces, detected by acid-fast staining and/or immunofluorescent staining
- PCR





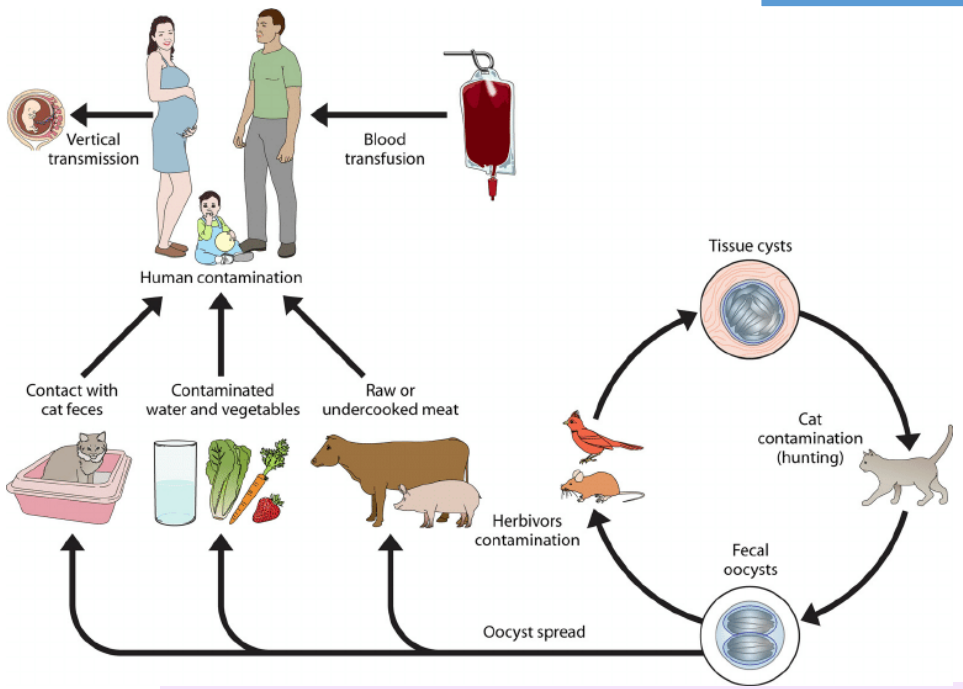
Observation of oocysts in faeces





- 8–10 µm oocysts with two sporocysts found in faeces, detected by microscopy of faecal concentrate and/or acid-fast staining
- PCR

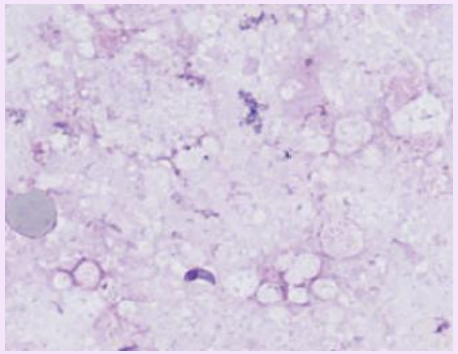
TOXOPLASMA



- Immunocompetent persons with primary toxoplasmosis are usually asymptomatic, and latent infection can persist for the life of the host
- In immunosuppressed patients, especially **patients with AIDS**, the parasite can reactivate from dormant tissue cysts and cause CNS infection, usually when the CD4 count falls below 100 cells/microL

DIAGNOSIS

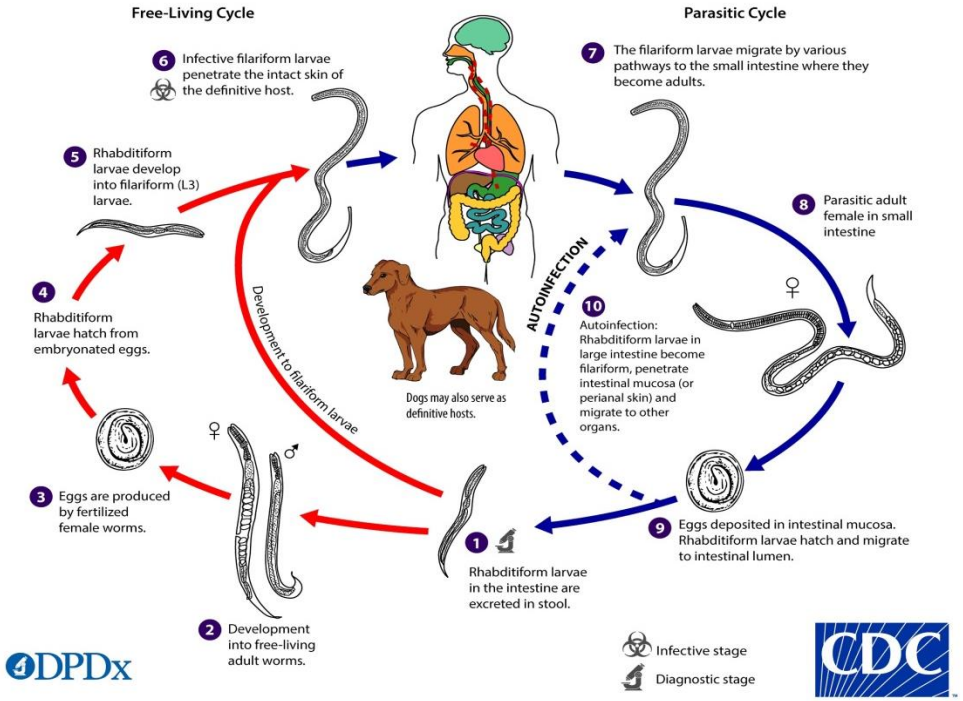
- Direct observation of the parasite in stained tissue sections, cerebrospinal fluid (CSF), or other biopsy material
- PCR



Toxoplasma tachyzoite in a brain biopsy smear

Strongyloides stercoralis

- Parasitic roundworm
- Endemic areas: tropics and southern USA
- Remains dormant for years following initial infection, but may be **reactivated by immunosuppression** to produce massive autoinfection



AUTOINFECTION: Faecal larval stages may develop directly into the infective stage whilst still in the intestine and penetrate the mucosa or perianal skin to re-infect the host. It can lead to hyperinfection or disseminated strongyloidiasis, **the larvae invading almost all organs and causing severe and sometimes fatal pathology**.

Human T-cell lymphotropic virus type 1 (HTLV-1) infection is associated with disseminated strongyloidiasis due to the modified immune response to this enteric helminth.
The lungs, liver and brain are the most common organs affected.

DIAGNOSIS

- *M*icroscopy and culture of faeces to detect larvae (often scarce in asymptomatic infections, but are very readily seen in hyperinfection)
- Faecal PCR
- Serology for IgG antibody to *Strongyloides* is helpful in migrants from endemic areas, but less sensitive in travelers. It may be negative in hyperinfestation.