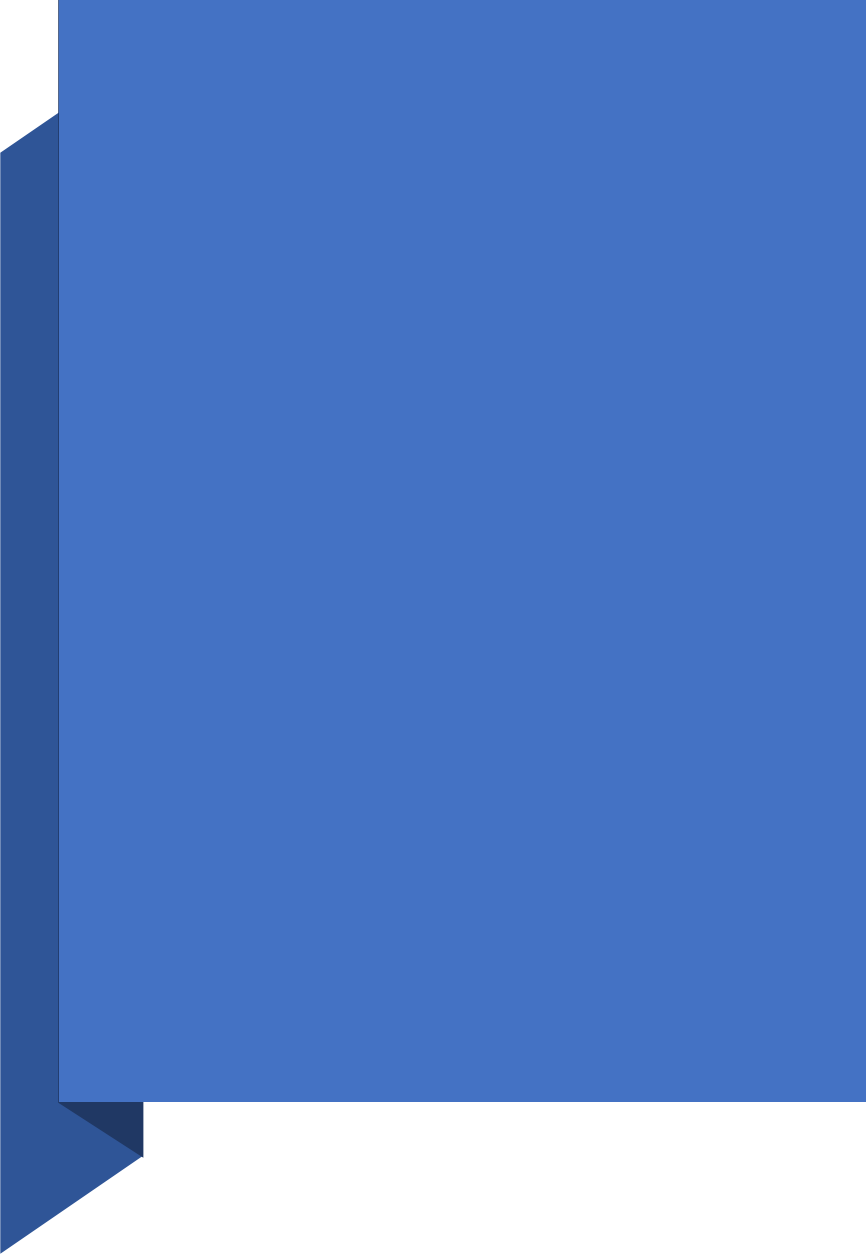


Riscul infecțios la pacienții imunodeprimati

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Constanta, 2. Clinical
Infectious Diseases Hospital

- 
- La pacientii aflatii in tratament imunosupresor, infecțiile au fost recunoscute de mult timp ca fiind:
 - periculoase
 - amenintatoare de viata și
 - dificil de tratat
 - pot periclita succesul terapeutic al unor regimuri chimioterapeutice eficiente

American Cancer Society

Bacteria	Viruses	Fungi	Protozoa
Pseudomonas aeruginosa	Varicella zoster virus	Pneumocystis jirovecii	Toxoplasma gondii (brain)
Klebsiella pneumoniae	Herpes simplex virus - pneumonia - encephalitis	Candida - Esophagus - bloodstream infection	Cryptosporidium
Escherichia coli	Cytomegalovirus - Pneumonia - Enteritis - Hepatitis - Retinitis	Aspergillus - Lung infections - Sinuses - kidneys - brain - heart valves	
Salmonella	HBV/HCV	Cryptococcus - meningitis	
Clostridium difficile	Flu	Histoplasma	
Staphylococcus aureus	Respiratory syncytial virus	Coccidioides	
Staphylococcus epidemidis	Polyomaviruses BK and JC		
Streptococcus viridans			
Pneumococcus			
Enterococcus			

Infections in Cancer and other immunocompromised children

Bacterial	75%
<i>Staphylococcus epidermidis</i>	50%
<i>Staphylococcus aureus</i>	15%
<i>Escherichia coli</i>	3%
<i>Pseudomonas aeruginosa</i>	2%
<i>Klebsiella/Enterobacter</i> sp.	1%
Others	4%
Viral	20%
Varicella-zoster virus	7%
Herpes simplex virus	5%
Cytomegalovirus	5%
Others	3%
Fungal	5%
<i>Candida albicans</i>	4%
Others	1%

Factorii de risc pentru aparitia infectiilor bacteriene

Local factors; mucosal and skin lesions

Drugs (eg, cyclophosphamide)

Procedures (intravenous administration, cutdown, bone marrow biopsy)

Surgical wounds

Urinary catheters

Intravascular devices (intravenous, intraarterial, central venous pressure, Swan-Ganz catheters, etc)

Respiratory support (ventilator, intermittent positive pressure breathing, etc)

Transfusion-transmitted disease

Splenectomy

Hospital-acquired resistant bacteria (caused by inadequate handwashing)

Absolute Neutrophil Count/mm³	Predisposition to Bacterial Infection
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>1000	Little
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500-1000	Mild
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<500	Moderate (50%)
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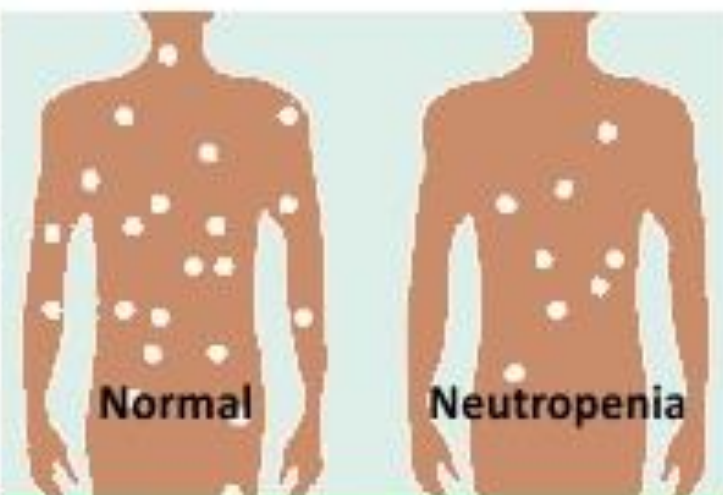
<100 anticipated >7 days	Severe (100%)
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How Chemotherapy Increases Risk for Infections



Chemotherapy

Chemotherapy drugs are used to treat cancer by killing the fastest-growing cells in the body—both good cells and cancer cells.



Neutropenia

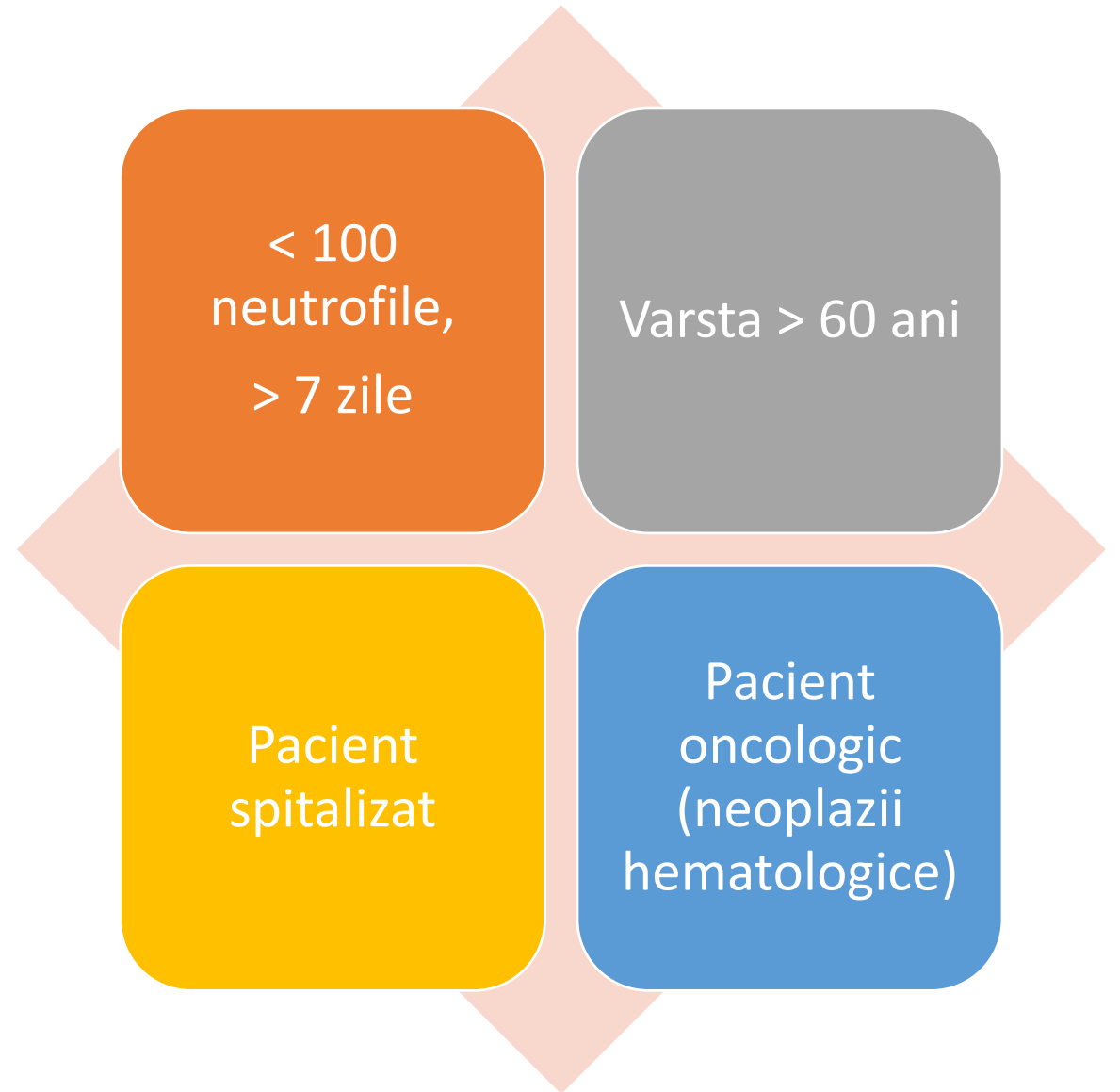
Neutropenia is a side effect of chemotherapy that means your body has fewer than normal infection-fighting white blood cells.



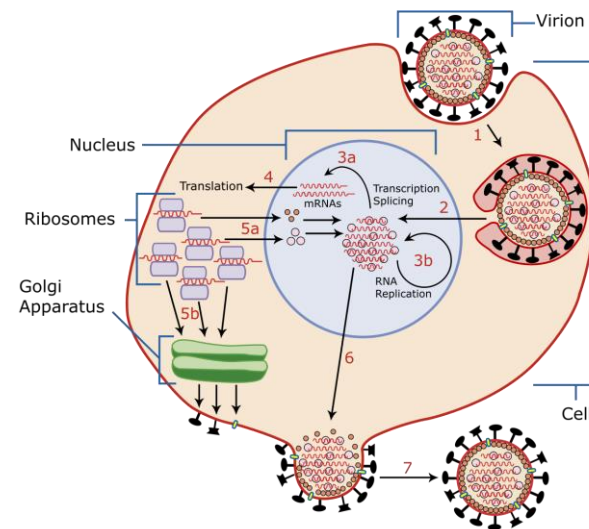
Infection

Infection is when germs enter your body and cause illness. Neutropenia can lead to infection.

MASCC risk



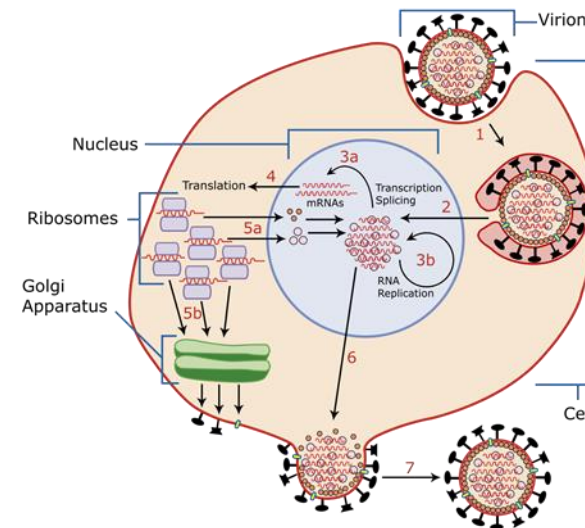
Reactivarea virusurilor latente



Introducere

- Terapiile biologice au devenit o clasă importantă de medicamente utilizată în tratamentul:

- Malignităților
- Bolilor autoimune
- Transplantului de organe



Biological (trade name)	Biological type	Molecular target	indications
Adalimumab (Humira)	Recombinant human IgG1 monoclonal antibody	TNF α	Rheumatoid arthritis Psoriatic arthritis
Etanercept (Enbrel)	Recombinant fusion protein of human TNF receptor 2 with IgG1 Fc	TNF α	Rheumatoid arthritis Juvenile chronic arthritis Psoriatic arthritis Ankylosing spondylitis
Infliximab (Remicade)	Chimaeric IgG1 monoclonal antibody	TNF α	Rheumatoid arthritis Crohn's disease Ankylosing spondylitis Psoriatic arthritis
Rituximab (MabThera)	Chimaeric IgG1 monoclonal antibody	CD20	Lymphoma
Basiliximab (Simulect)	Chimaeric IgG1 monoclonal antibody	CD25	Prophylaxis of acute organ transplant in de novo allogeneic renal transplantation
Natalizumab (Tysabri)	Recombinant humanised IgG4 monoclonal antibody	α_4 subunit of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins	Multiple sclerosis
Omalizumab (Xolair)	Recombinant humanised IgG1 monoclonal antibody	IgE	Severe persistent allergic asthma
Bevacizumab (Avastin)	Recombinant humanised IgG1 monoclonal antibody	vascular endothelial growth factor.	Colorectal carcinoma
Palivizumab (Synagis)	Recombinant humanised IgG1 monoclonal antibody	The A epitope of the RSV F protein	Prevention of serious lower respiratory tract disease requiring hospitalisation caused by RSV in children at high risk for RSV disease (respiratory syncytial virus)

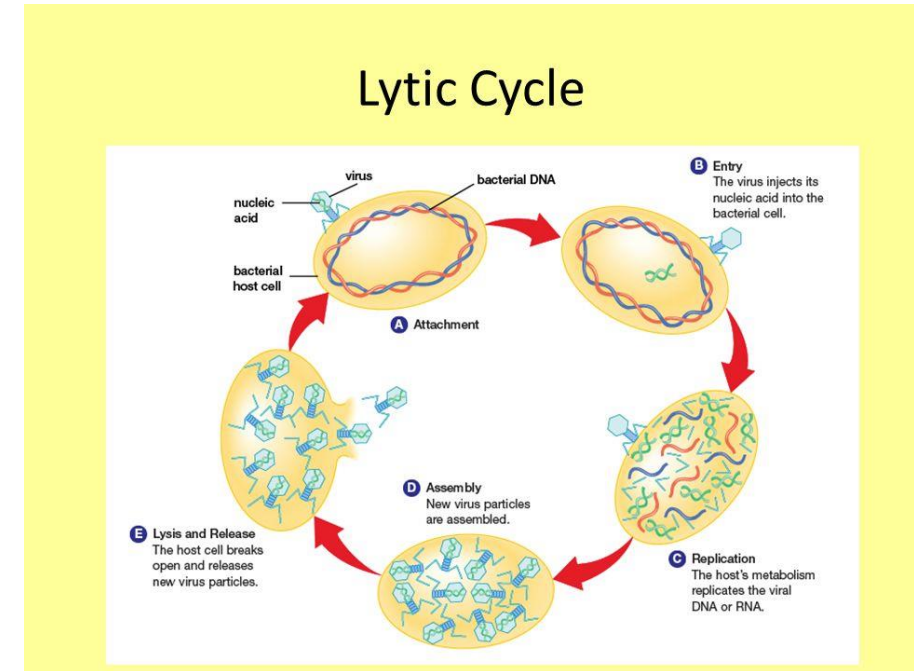
Replicarea virală

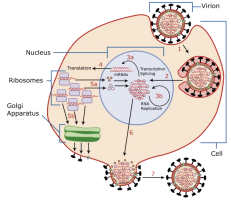
- **Faza litică**

- genomul viral replicat (ARN sau ADN), este eliberat de celula-gazdă
- înconjurat de o capsulă proteică formând astfel virionul.
- eliberarea virionului determină liza celulei-gazdă.

- **Faza latentă,**

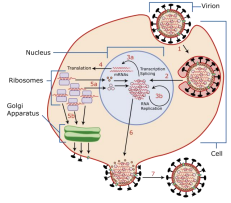
- perioada de timp în care virusul rămâne dormant



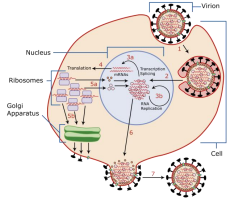


- **Reactivarea** se produce atunci când **virusul trece din faza latentă în faza litică**, timp în care genomul viral suferă procese de transcripție și translație în proteine virale.

Drug	Drug type	Target	Indications	Viruses reactivated
Infliximab ²⁴	Chimeric (human-murine)	TNF α	CD, UC, RA, AS, PA	HBV, CMV
Etanercept ²⁵	Human dimeric fusion protein	TNF α	RA, AS, PA, JIA	VZV
Adalimumab ²⁶	Human antibody	TNF α	CD, RA, AS, PA, JIA	CMV, VZV
Certolizumab ¹	Humanized antibody	TNF α	CD	Unspecified
Rituximab ²⁶	Chimeric (human-murine)	CD20	NHL, RA	HBV, VZV, HSV, CMV, PML
Alemtuzumab ⁷	Humanized antibody	CD52	MS, CLL, NHL	VMV, HZH, VZV
Anakinra ⁷	Nonglycosated IL-1R	IL-1 receptor	RA	Unspecified
Abatacept ⁷	Fusion protein	T-cell costimulation inhibitor	RA, JIA	HSV, VZV



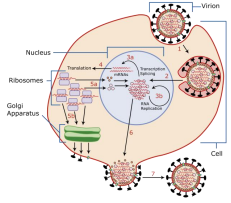
- Mai mult de 90% din populația adultă a fost expusă la virusuri din familia Herpesviridae reprezentată de:
 - Cytomegalovirus (CMV),
 - Epstein–Barr virus (EBV),
 - Virusul varicelo-zosterian(VZV),
 - Herpes simplex virus (HSV).
- După infecția primară, aceste virusuri pot persista în celula-gazdă (în fază latentă a replicării) .
 - VZV și HSV rămân dormante, de obicei, în ganglionii senzitivi
 - CMV și EBV persistă în celulele hematopoietice



- Virusuri care intră într-o fază latentă a replicării latente
 - Polyomaviruses (John Cunningham [JC] și BK viruses)
 - Adenovirusurile

- Reactivarile se produc atunci când virusul nu este eliminat în totalitate după infecția primară, acesta continuând să se replice la o rată mică fără a produce modificări sesizabile celulei-gazdă
 - HVB

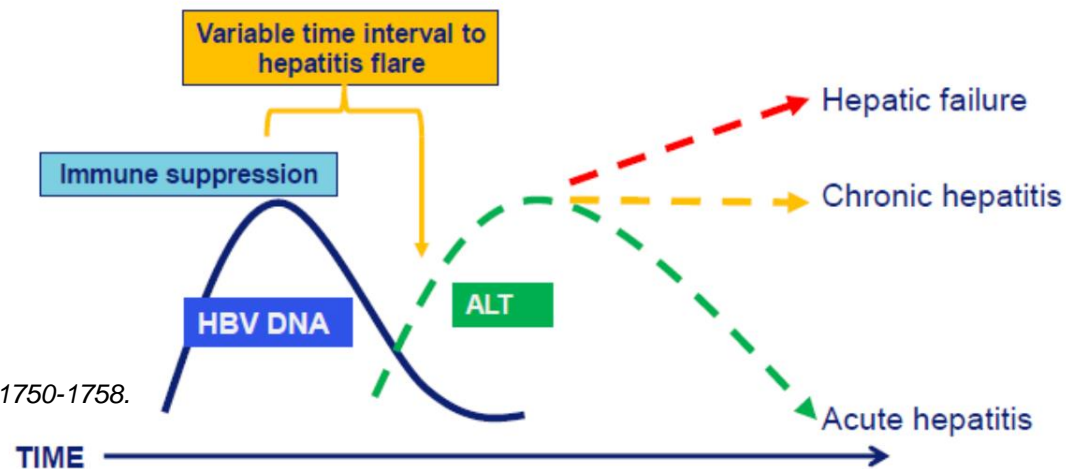
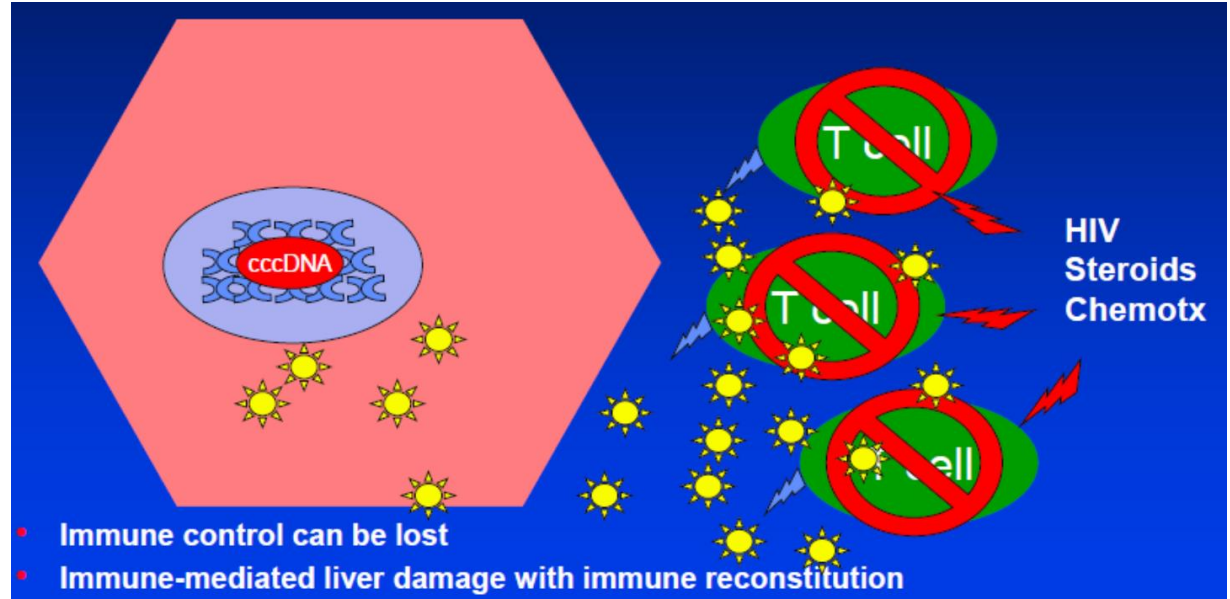
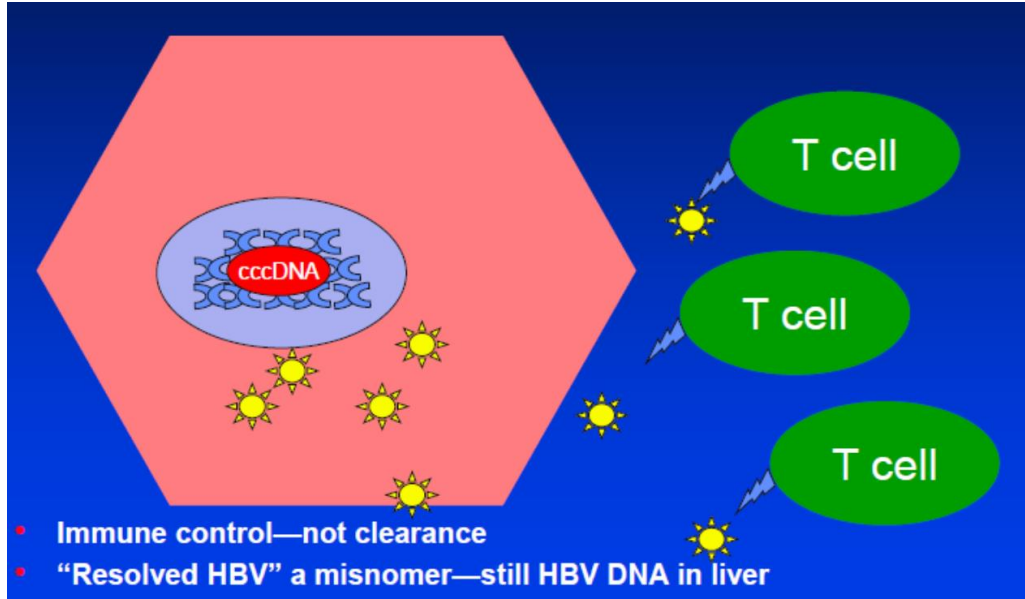
Virusul hepatitic B



Reactivare VHB

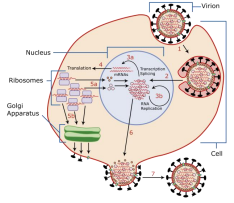
Definitie	<ul style="list-style-type: none">- creșterea bruscă , importanta a replicării VHB (ADN-VHB) frecvent însoțită de- creșterea TGP/TGO
Seroconversie inversă	Reaparitia AgHBs la o persoană AgHBs-, AcHBc+
Tratament imunosupresor	Poate să apară până la 12 luni după un tratament cu agenți imunosupresori
Tablou clinic	Variază de la asimptomatic la insuficiență hepatică
PREVENIBILA PRIN PROFILAXIA ANTIVIRALA	

Virusul hepatitic B



Werle-Lapostolle B, et al. *Gastroenterology*. 2004;126:1750-1758.

Factori de risc pentru reactivarea VHB



PACIENT

- SEX MASCULIN
- STATUS DE IMUNODEPRESIE

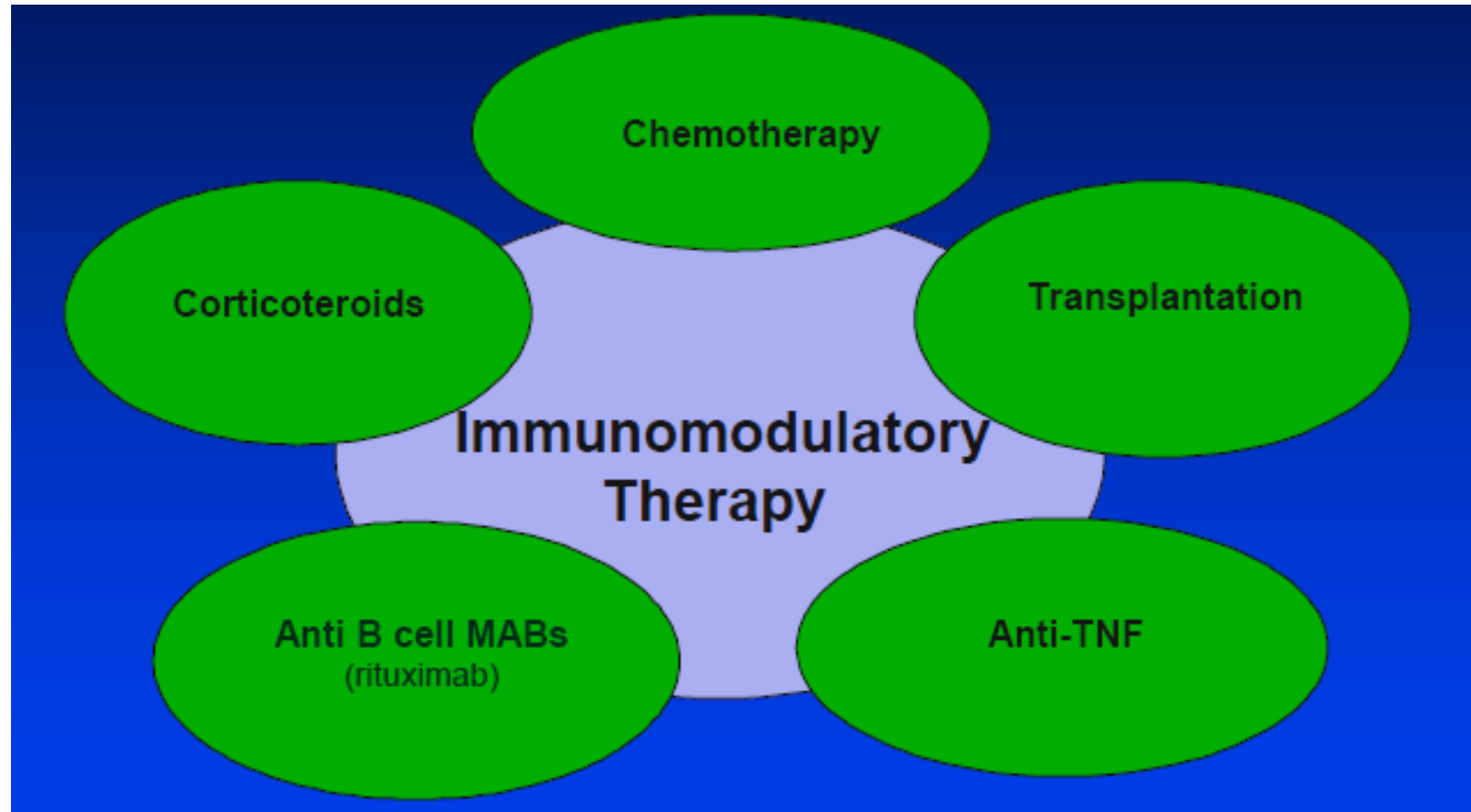
VIRUS

- AgHBs pozitiv
- AgHBe pozitiv
- ADN-VHB >2000ui/ml si AgHBe+ sau ADN-VHB>20000UI/ml si AgHBe -
- Mutatia pre-core

TRATAMENT

- DOZE MARI DE CORTICOSTEROIZI
- INTENSITATEA IMUNOSUPRESIEI
- TIMMINGUL TRATAMENTULUI ANTIVIRAL LA PACIENTII CU RISC

TERAPII IMUNOSUPRESOARE IMPLICATE IN REACTIVAREA VHB



Riscul de reactivare VHB in functie de statusul serologic si potentia imunosupresoare a medicamentului

Nivelul de risc	Status Serologic de risc	Agent Imunosupresor status de risc
Inalt	AgHBs+, inalt HBV- DNA, sau AgHBe+	<ul style="list-style-type: none"> ● B-cell–depleting agents ● Chimioterapie sistemica ● Doze/moderate/mari de corticosteroizi *
Intermediar	AgHBs-, Ac-HBc+, Ac-HBs-	<ul style="list-style-type: none"> ● inhibitori TNF ● Inhibitori de Tyrosin- kinase ● alte citokine si inhibitori de integrina ● Chemoembolizare transarteriala ● Doze /moderate/mari de corticosteroizi†
Redus	AgHBs-, Ac-HBc+, Ac-HBs+	<ul style="list-style-type: none"> ● Methotrexate ● Azathioprine ● 6-mercaptopurine ● Doze reduce corticosteroids‡

*≥ 10 mg for ≥ 4 sapt pt HBsAg+/anti-HBc+.

†< 10 mg for ≥ 4 sapt pt HBsAg+/anti-HBc+; ≥ 10 mg pt ≥ 4 sapt pt HBsAg-/anti-HBc+.

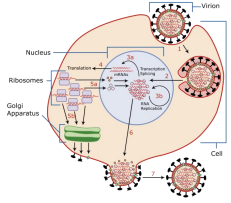
‡< 1 sapt pt HBsAg±/anti-HBc+; < 10 mg pt ≥ 4 sapt pt HBsAg-/anti-HBc+.

Perrillo RP, et al. Gastroenterology. 2015;148:221-244.

Bessone F, et al. World J Hepatol. 2016;8:385-394, Slide : clinicaloptions.com

TERAPII CU RISC INALT

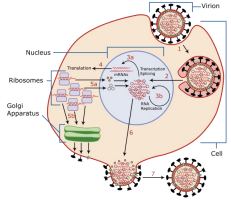
RISC DE REACTIVARE >10%



- **Agenti supresori ai celulelor B (B-cell–depleting agents):** ex. **Rituximab**, Ofatumumab
 - **30-60% AgHBs+, AcHBc +**
 - >10% AgHBs-, AcHBc+
- **Chimioterapie sistematica : Antracyclin (ex.doxorubicin, Epirubicin)**
 - **15-30% AgHBs+, AcHBc +**
- **Tratament corticoterapic > 4sapt doze mari (echivalent prednisolon PDN>20mg/zi)**
 - **>10% AgHBs+, AcHBc +**

PDN= prednisolon

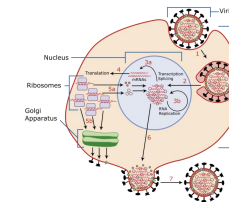
TERAPII CU RISC INTERMEDIAR



RISC DE REACTIVARE 1-10%

- **Inhibitori TNF-alfa:** ex; Infliximab, Etanercept, Adalimumab
 - 1-10% AgHBs+, AcHBc +
 - 1% AgHBs-, AcHBc+
- **Alte citokine si inhibitori de integrina:** ex: Abatacept, Ustekinumab,
 - 15-30% AgHBs+, AcHBc +
- **Inhibitori de tirozinkinaza :** ex. Imatinib, Nilotinib
 - 1-10% AgHBs+, AcHBc +
 - 1% AgHBs-, AcHBc+
- **Antracicline:** ex: Doxorubicina, Epirubicina
 - 1-10% AgHBs- , AcHBc +
- **Tratament corticoterapic ≥ 4 sapt doze mici** (echivalent prednisolon PDN<10mg/zi)
 - 1-10% AgHBs+, AcHBc +
- **Tratament corticoterapic ≥ 4 sapt doze intermediare/mari** (echivalent prednisolon PDN<10-20mg/zi / >20mg/zi)
 - 1-10% AgHBs-, AcHBc+

TERAPII CU RISC SCAZUT



RISC DE REACTIVARE <1%

- **Medicatie umunosupresoare traditionala:**
 - <1% AgHBs+, AcHBc +
 - <<1% AgHBs-, AcHBc+
- **Tratament corticoterapic ≤ 1 sapt 1-10% AgHBs+, AcHBc +**
 - <1% AgHBs+, AcHBc +
 - <<1% AgHBs-, AcHBc+
- **Tratament corticoterapic ≥ 4 sapt doze mici (echivalent prednisolon PDN<10/zi)**
 - <1% AgHBs+, AcHBc+
- Mecanisme posibile de crestere a replicarii virale datorita corticosteroizilor:
 - Scaderea functiei limfocitelor T citotoxice
 - Stimularea directa a secventierii genomice a VHB
- Riscul de reactivare este determinat de durata si dozele de tratament corticosteroid
- Se produce o crestere marcata a replicarii virale si a AST la terapii cortizonice cu doze initiale de 30-60mg care se scad progresiv in 4-12 sapt
- Cresteri ale ADN VHB insotita de cresteri bruste ALT apar la 30-70% din Pacientii AgHBe ce primesc terapii cortizonice descrescande
 - Doze mici (<10mg) corticoterapie pentru o perioada mai mare de o luna la pacientii AgHBs+ a fost asociat cu risc intermediar de reactivare VHB

COVID – 19

- corticoterapie
- imunosupresoare (tocilizumab, anakinra)

Infectii fungice

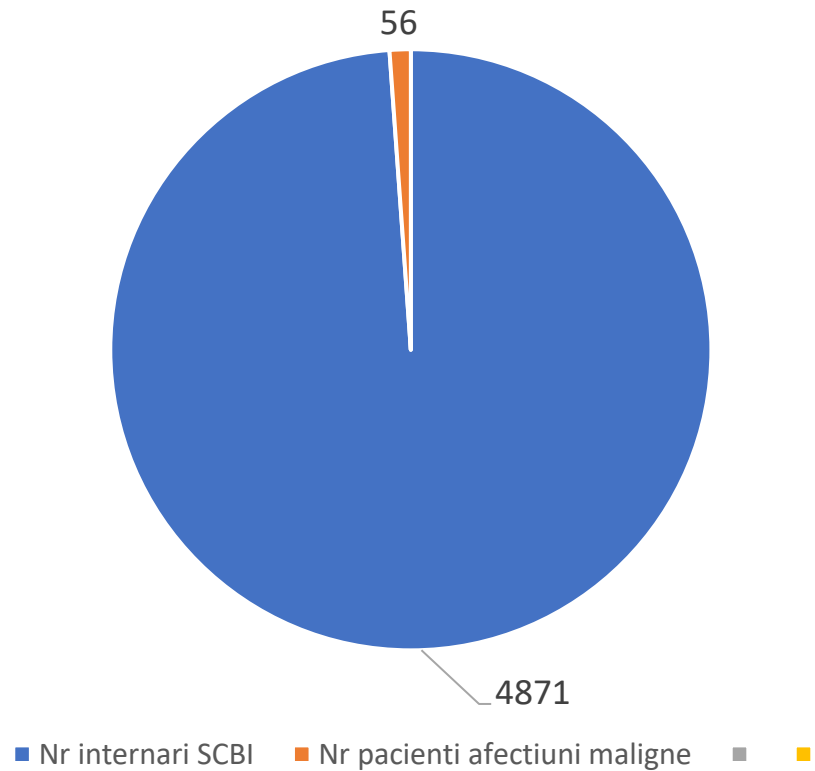
- *Candida spp* (albicans, glabrata, auris)
- *Aspergillus spp* (flavus, fumigatus)
 - *Pacientii cu forme severe de pneumonie au un risc crescut de aspergiloza invaziva*
- *Mucor*
 - *Mucormycosis, life-threatening fungal infection, is adding to India's COVID-19-related death.*
 - *immunocompromised due to COVID or by the use of steroids, tocilizumab and/or concomitant diabetes.*
 - *galactomannan index of 1 or greater on BAL or 0.5 or greater on serum*

Spitalul de Boli Infectioase Constanta

- **56 de pacienți adulți (39 F, 17 B)** internati in SCBI Constanta :
 - cunoscuți cu afecțiuni maligne (tumori solide sau afecțiuni hematologice)
 - aflatii in tratament chimioterapic,
 - diferite boli infecțioase (virale, bacteriene, fungice)
 - 6 pacienți infectați cu HIV

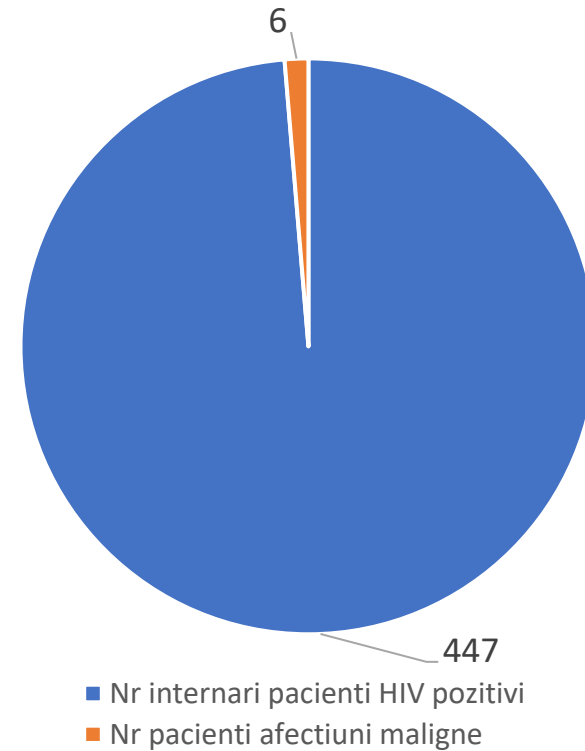
Rezultate

Total internari



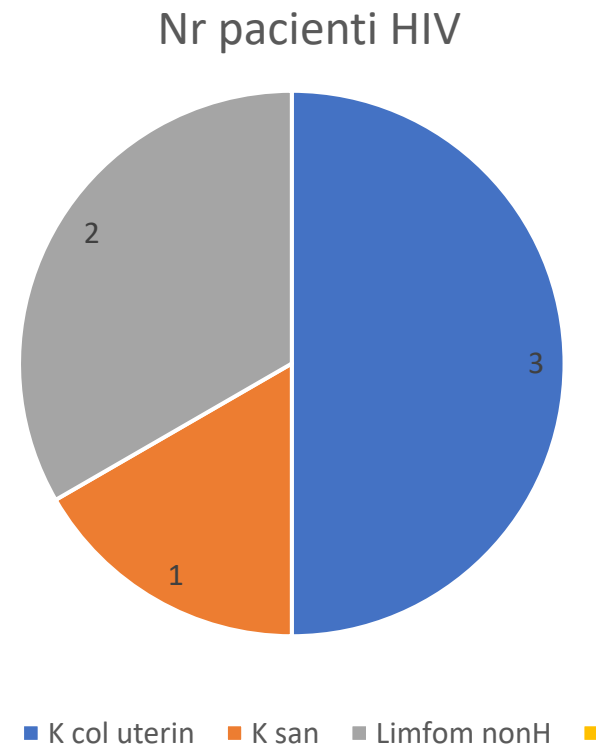
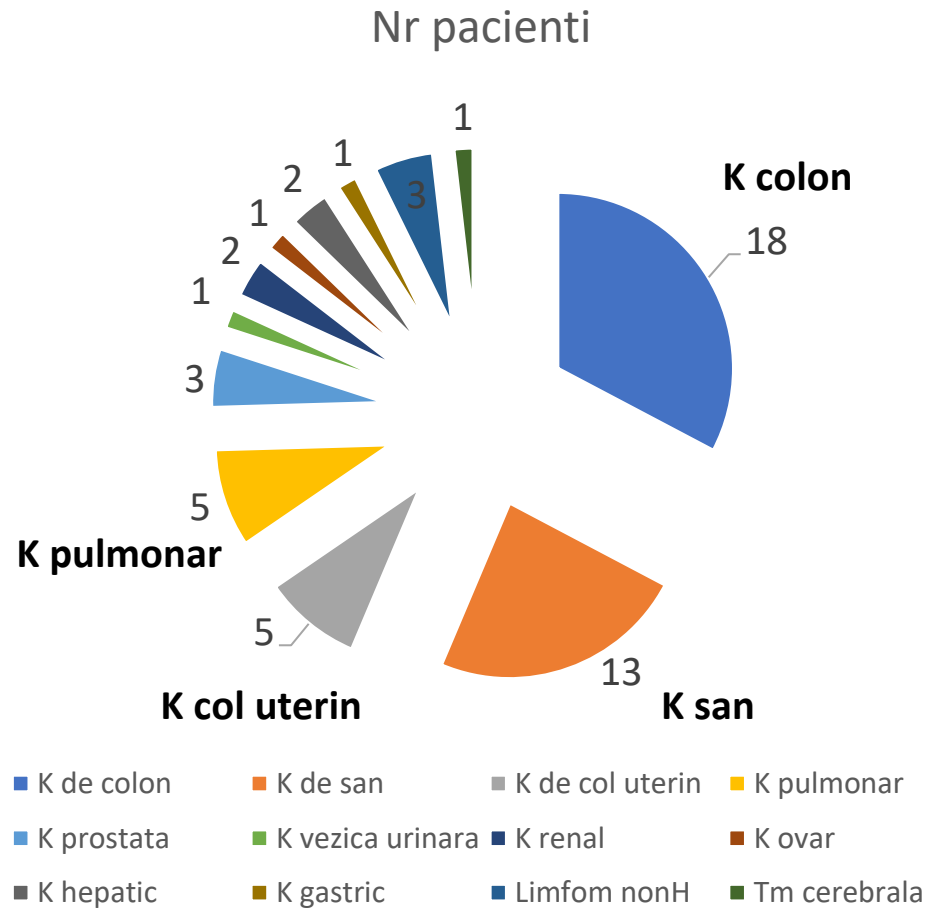
1.14% din totalul internarilor

Total internari pacienti infectati HIV



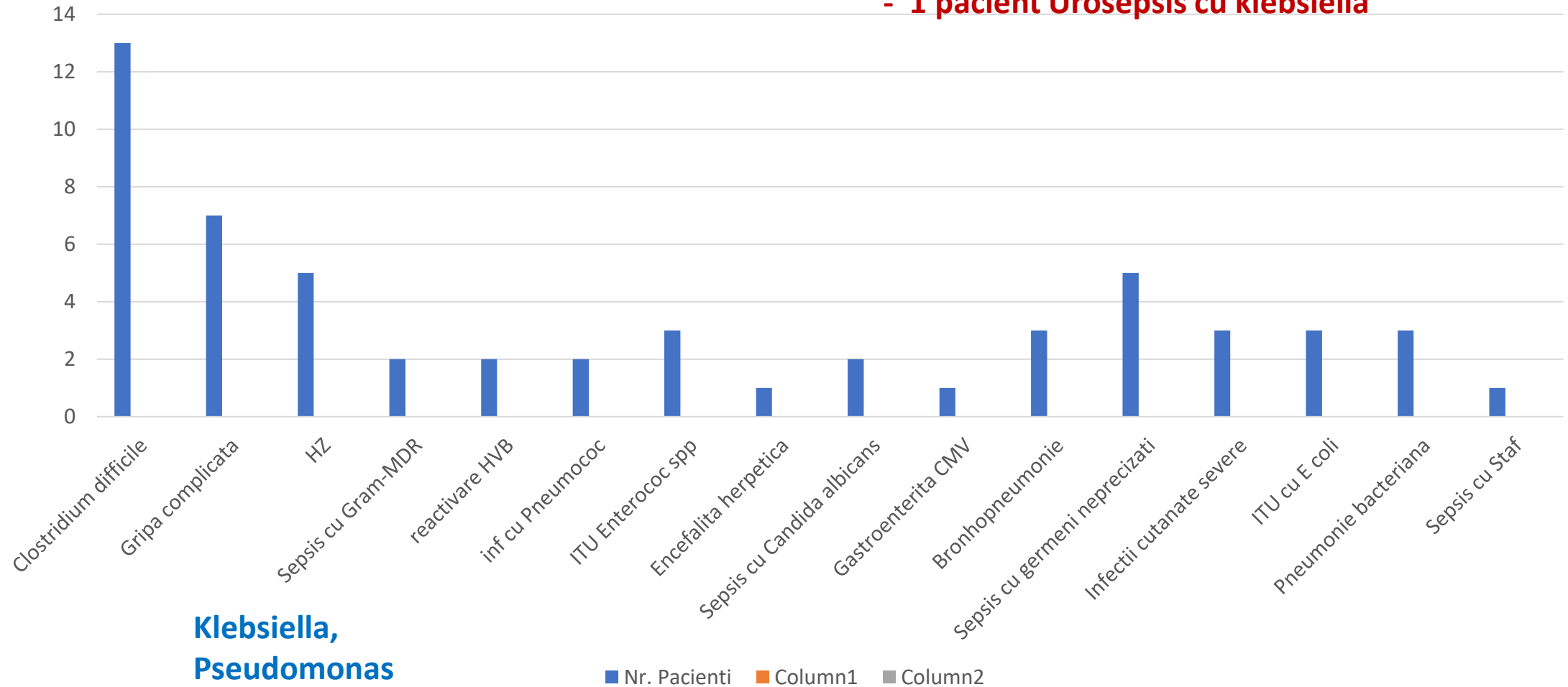
1.34% din totalul internarilor cu HIV

Tipurile de cancer



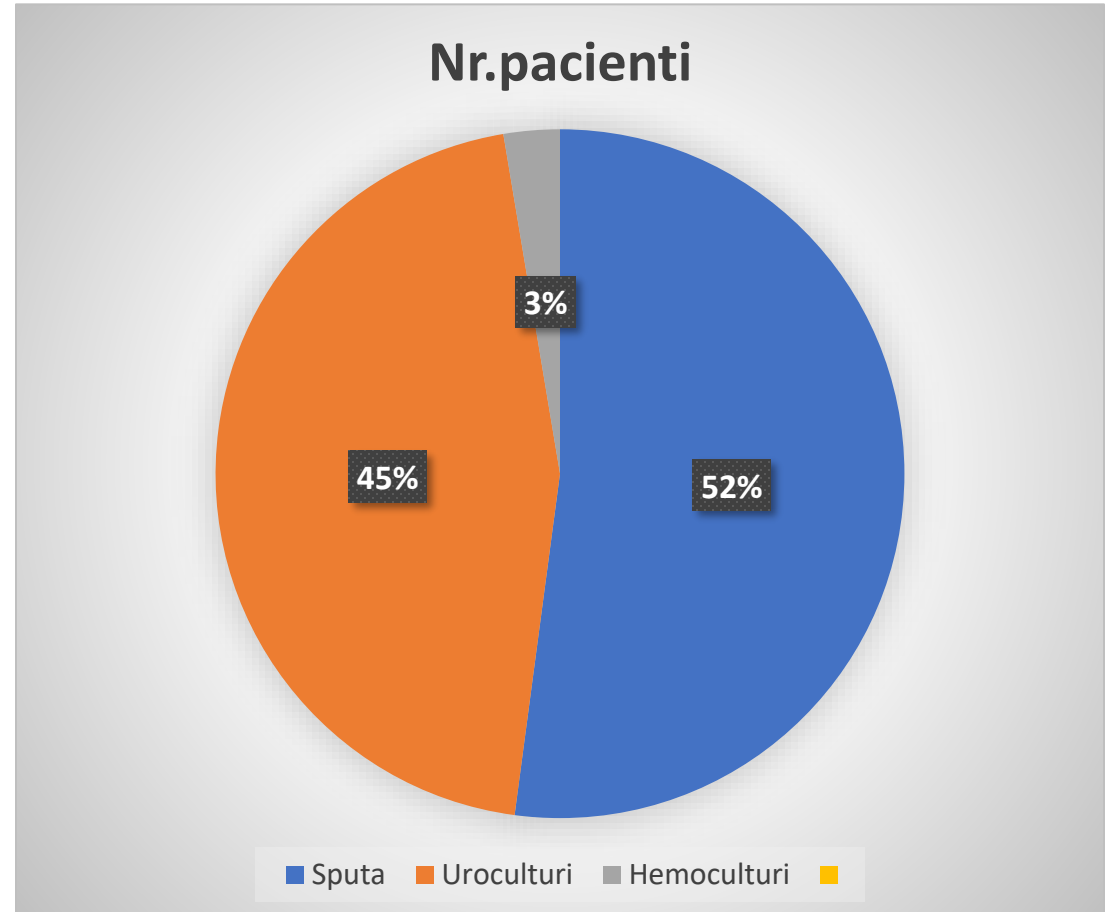
Manifestari clinice

Decese – 1 pacient cu Gripa complicate
- 1 pacient EA cu Clostridium diff
- 1 pacient Urosepsis cu klebsiella

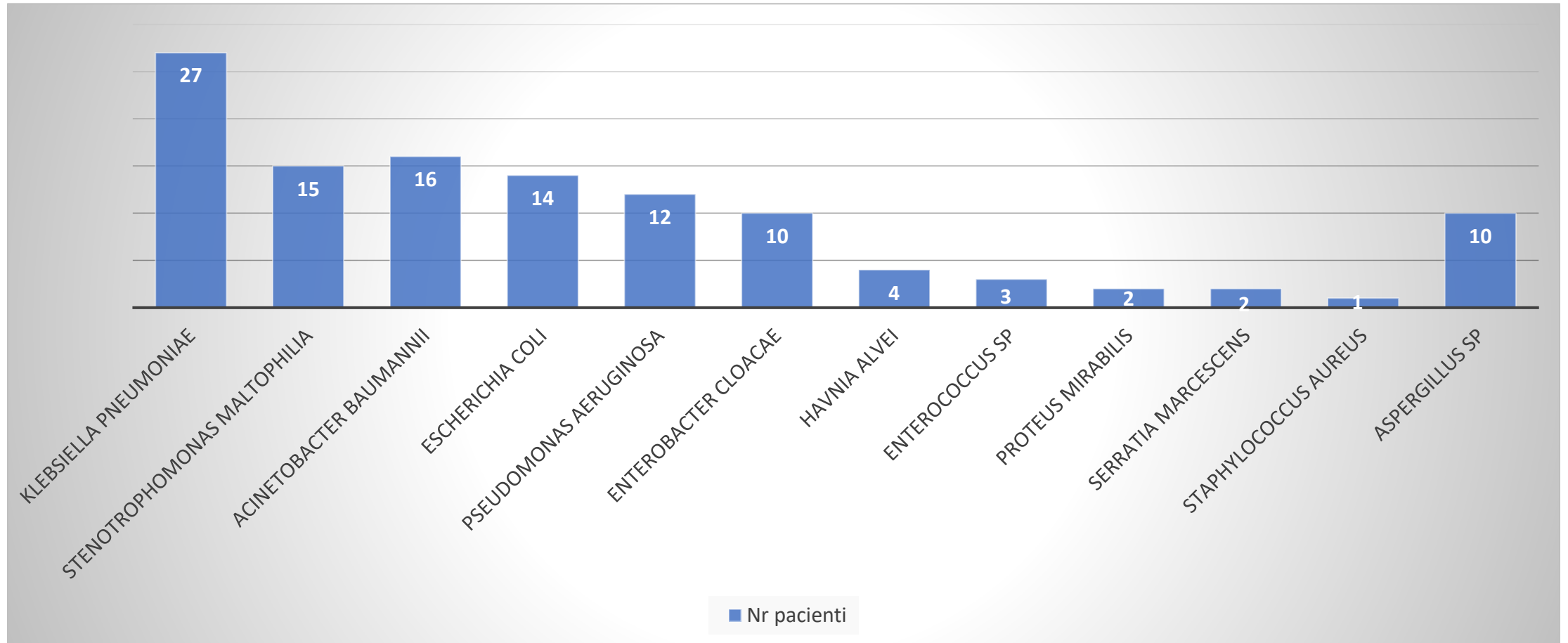


Spitalul de Boli Infectioase Constanta martie – octombrie 2020

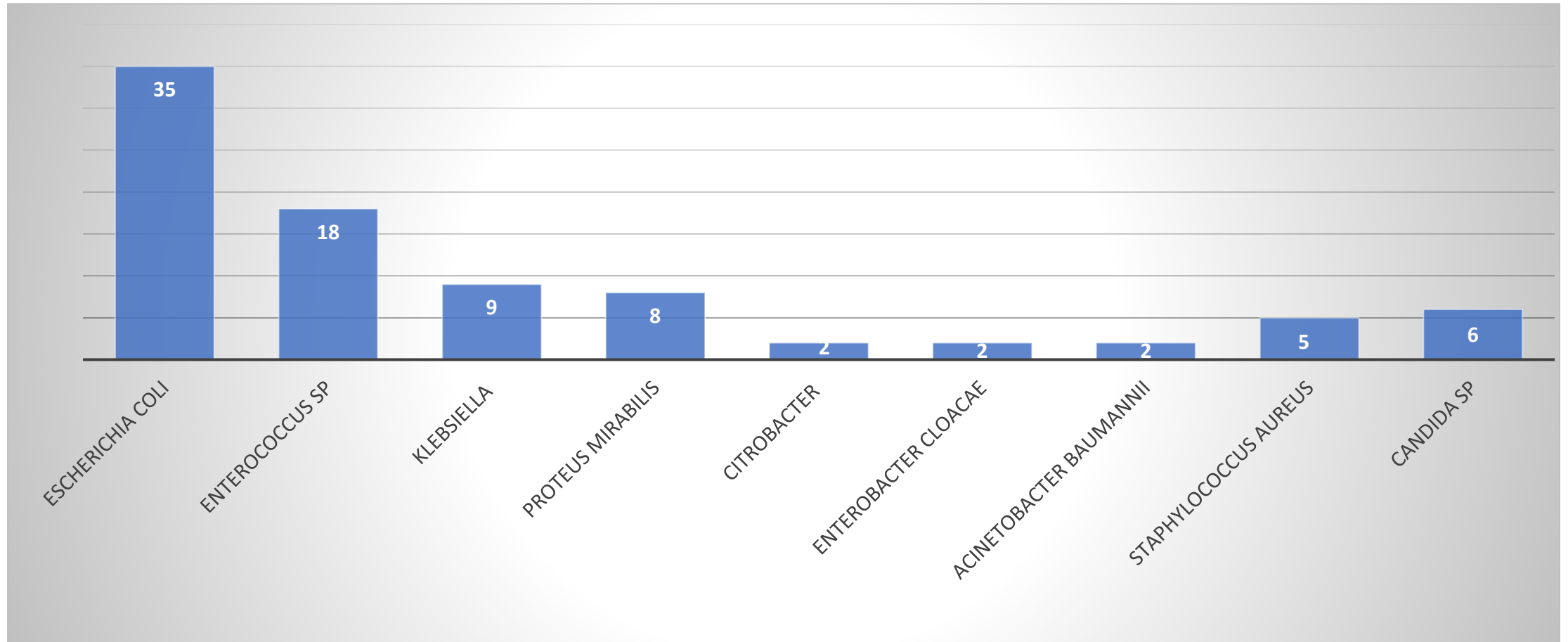
- 1573 pacienti spitalizati
- 190 pacienti cu infectii bacteriene/fungice (12%)
 - 99 ex sputa
 - 86 uroculturi
 - 5 hemoculturi



Etiologie – ex sputa



Etiologie – Uroculturi



Candida albicans – 1 pt, Candida krusei -2 pts Candida glabrata – 3 pts

Etiologie - Hemoculturi

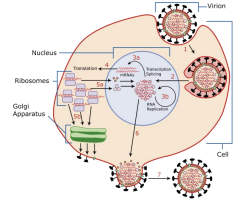
Klebsiella pneumoniae – 2 cazuri

- ESBL – pozitiv
- Carbapenemaza-pozitiv
- S – Gentamicina,
- S - Sulfometoxazol-Trimetoprim

Acinetobacter baumannii – 3 cazuri

- S – Colistin – 2 pacienti
- R – Colistin -1 pacient

Concluzii



- Reactivarea virusurilor latente este un proces complex și o problema tot mai frecvent întâlnită în cadrul utilizării terapiei biologice
- La inițierea unei noi terapii biologice, clinicianul trebuie să stratifice riscul pacientului prin screening viral.
- Factorii ce trebuie luați în considerare pentru screening-ul viral preterapeutic includ
 - factorii de risc cunoscuți,
 - zona de proveniență dar și
 - riscurile infecțioase ale terapiei biologice ce urmează a fi implementată.

Concluzii

- Management judicios al pacientului oncologic in tratament chimioterapic
- Vaccinarea înainte de chimioterapie ar putea preveni infecțiile severe cu virusul gripal, virusul varicelo-zosterian și infecțiile pneumococice severe.
- Screening-ul pentru hepatita B este necesar înainte de chimioterapie.
- Profilaxia infectiilor fungice