

Antivirals for Respiratory Viral Infections (other than flu)

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MAJOR
 COMMON
 FAIRLY COMMON
 OCCASIONAL
 RARE

	COLDS	PHARYNGITIS	TRACHEO-BRONCHITIS	CROUP	BRONCHIOLITIS
RNA VIRUSES					
INFLUENZA A	□	□	■	□	□
INFLUENZA B	□	□	□	□	□
PIV-1	□	□	□	■	□
PIV-2	□	□	□	□	□
PIV-3	□	□	□	■	□
MEASLES	□	□	□	□	□
RHINOVIRUS	■	□	□	□	□
ENTEROVIRUSES	□	□	□	□	□
CORONAVIRUS	□	□	□	□	□
RSV	□	□	□	□	■
DNA VIRUSES					
ADENOVIRUS	□	□	□	□	□
HERPES SIMPLEX	□	□	□	□	□
VARICELLA	□	□	□	□	□
EBV	□	□	□	□	□
CMV	□	□	□	□	□

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PNEUMONIA

ADULTS

CHILDREN

IMMUNO-
COMPROMISED

RNA VIRUSES

INFLUENZA A



INFLUENZA B



PIV-1



PIV-2



PIV-3



MEASLES



RHINOVIRUS



ENTEROVIRUSES



CORONAVIRUS



RSV



DNA VIRUSES

ADENOVIRUS



HERPES SIMPLEX



VARICELLA



EBV



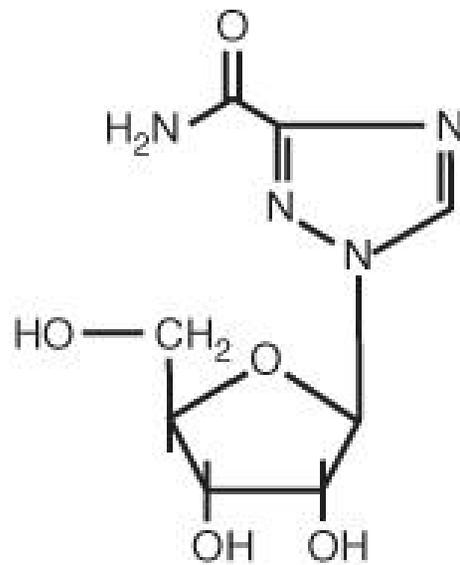
CMV



Antiviral agents for respiratory viruses

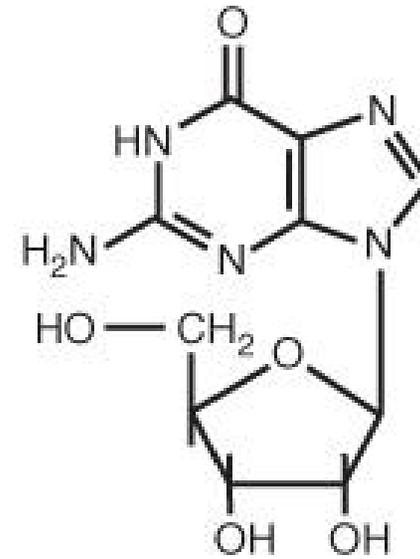
- Influenza-specific (M₂I and NI)
- Ribavirin
- Other things that don't work
- Anti-herpes virus agents
 - Acyclovir
 - Gancyclovir
 - Foscarnet
 - Cidofivir

Structure of ribavirin



Ribavirin

A



Guanosine

B

Viruses with susceptibility to Ribavirin

RNA viruses

Arenavirus
Bunyavirus
Hepatitis C virus
HIV
Orthomyxovirus
Paramyxovirus
Picornavirus
Reovirus
Togavirus

DNA viruses

Adenoviridae
Hepatitis B virus
Herpesviruses
Poxviruses

Mechanisms of action of ribavirin

- Effects on host immunity
 - Increased expression of Th1 cytokines
 - Enhanced cytokine production by macrophages
- Effects on IMP dehydrogenase (cellular guanosine triphosphate depletion)
- Effects on viral polymerase
 - Transcription and translation
 - Mutagenesis “error catastrophe hypothesis”

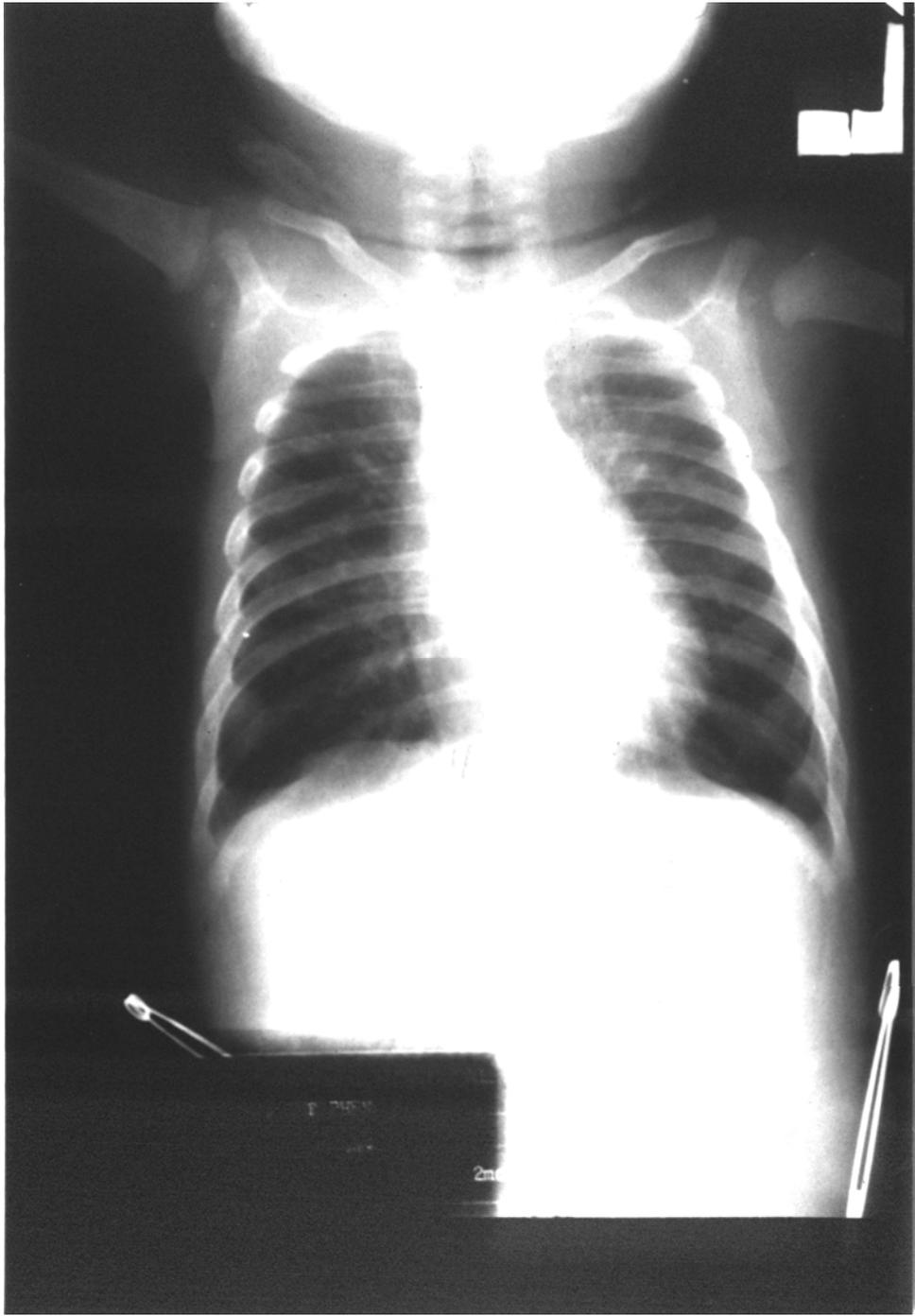
Ribavirin dosing and adverse effects

- Oral, intravenous, and small particle aerosol (SPAG-2, used for RSV, other respiratory infections)
 - Significant systemic absorption
 - Minimize exposure of pregnant women
- Accumulates in RBCs, major toxicity is hemolytic anemia
- Oral/IV contraindicated in CrCl <50

Bronchiolitis

Clinical features

- Initial rhinitis and congestion (exposure)
- Onset of dyspnea in 2-3 days
- Hallmark is wheezing
- Fever at beginning, but may be gone by presentation (1/3 of hospitalized are afebrile)
- Fever and cyanosis are not good indicators of disease severity
- CXR findings are non-specific
- Risk groups: congenital heart or lung disease, immunodeficiency, prematurity, family smoking



Bronchiolitis

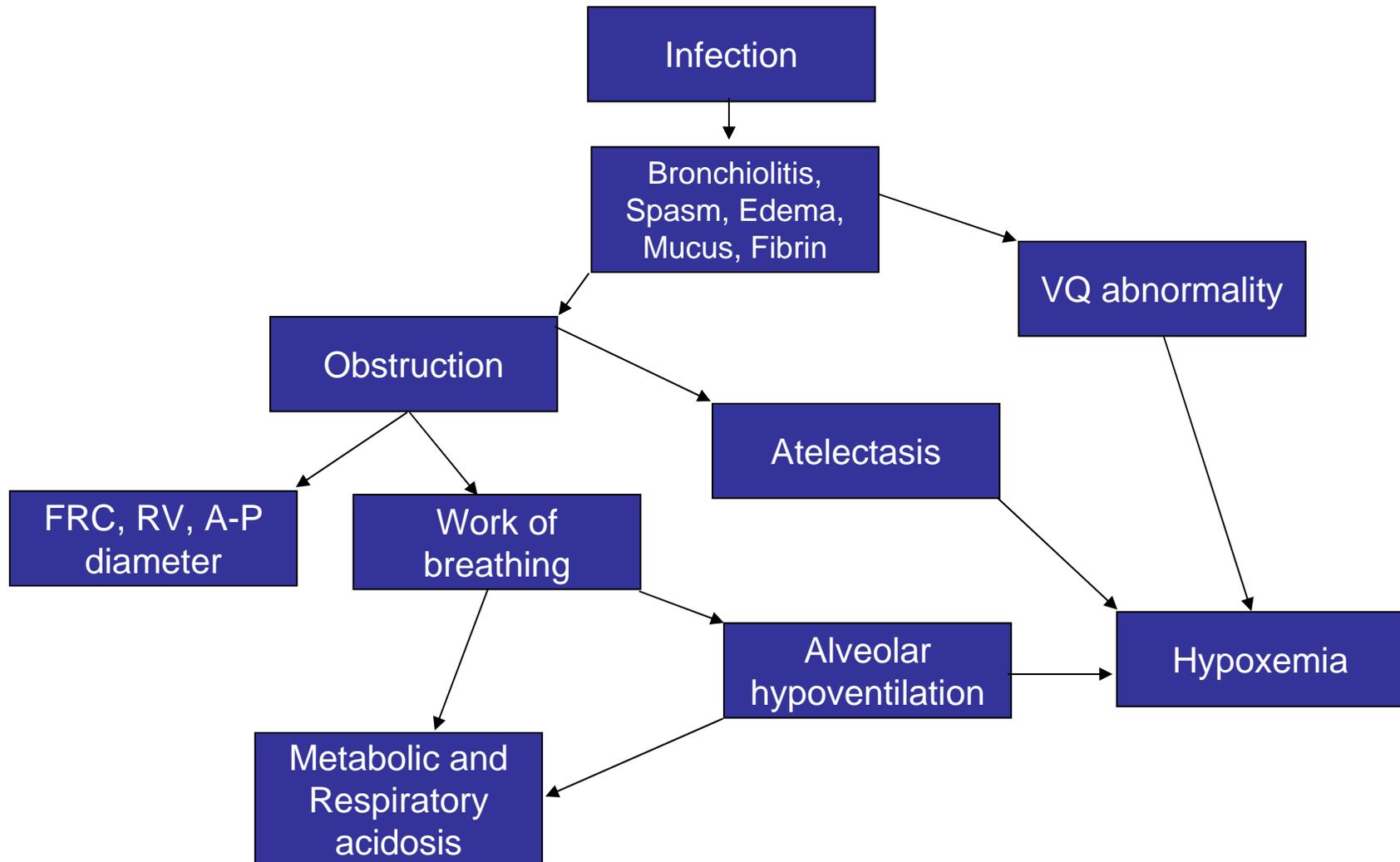
Etiology and ddx

- RSV associated with >75%
- Others: PIV, influenza, mumps, rhino, adenoviruses
- Ddx:
 - Asthma
 - Pertussis
 - Foreign bodies

Bronchiolitis: Pathophysiology

- Viral infection spreads from upper to lower respiratory tract
- Infection of epithelial cells, loss of ciliated epithelium, bronchiolar plugging, bronchospasm
- Multiple immune mechanisms are probably involved
- Increased risk of asthma after recovery

Pathophysiology of bronchiolitis

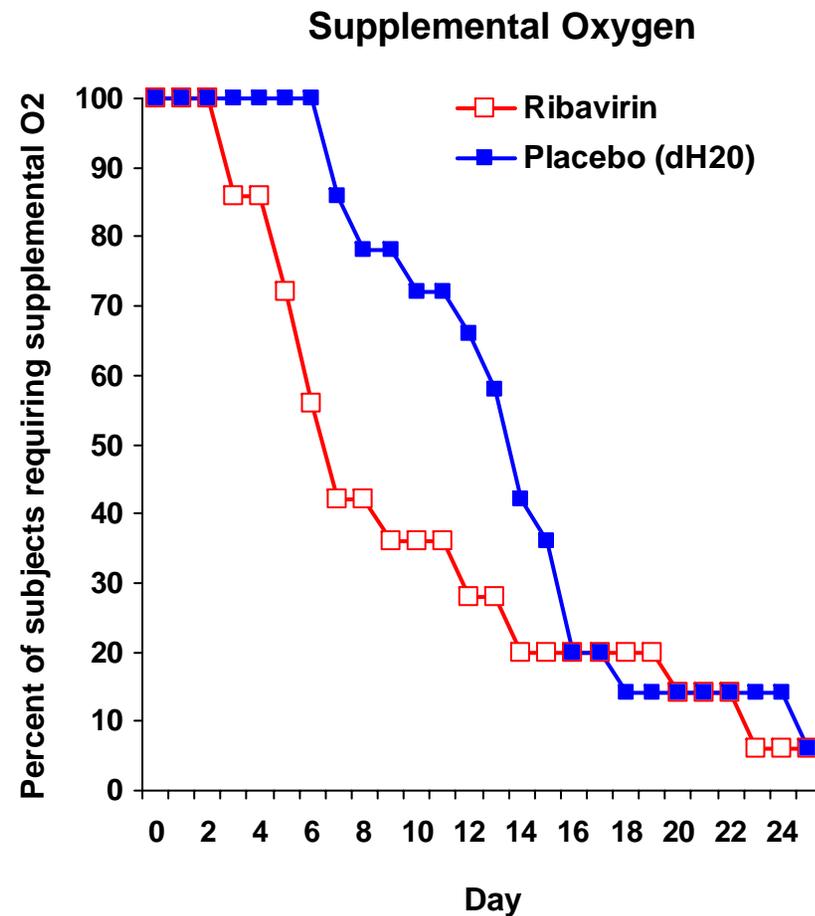
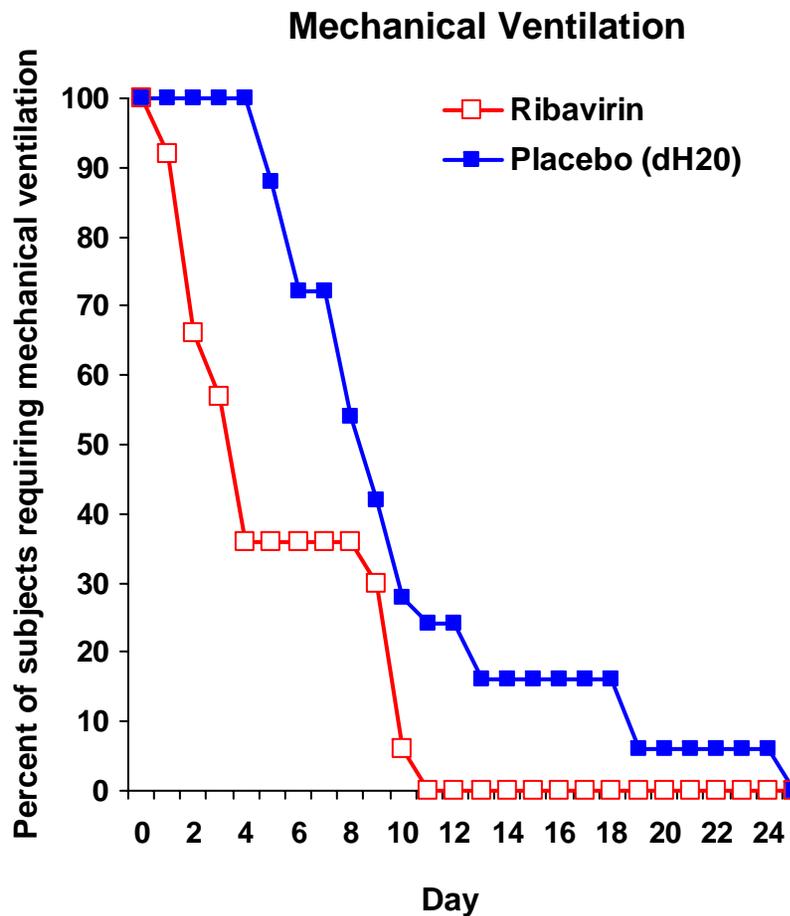


Bronchiolitis:

Treatment and prevention

- Treatment
 - Oxygen, supportive care
 - Bronchodilators and steroids have little efficacy
- Prevention
 - No effective vaccine available for RSV
 - Monoclonal antibody (anti F) palivizumab

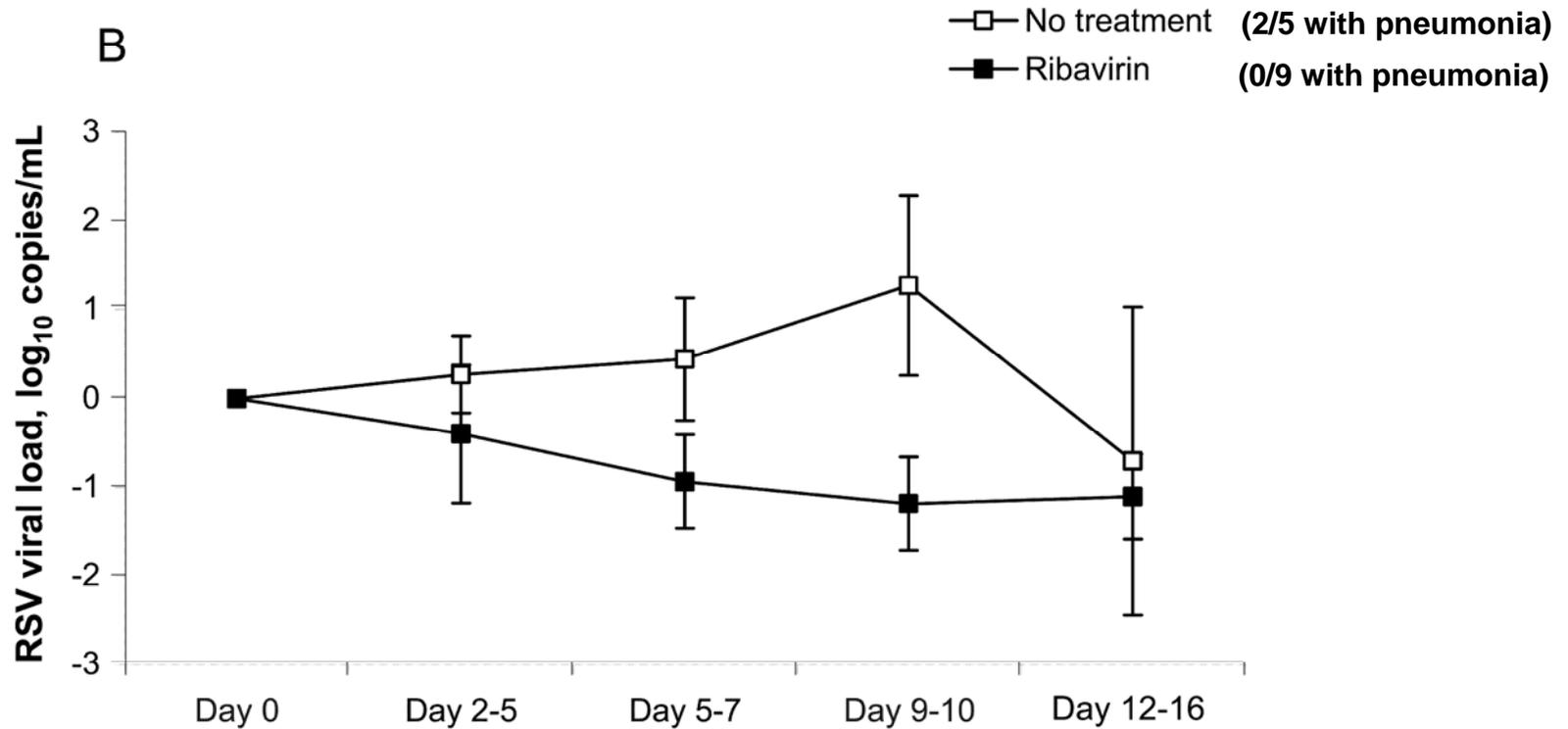
Effects of ribavirin on need for mechanical ventilation and O2 requirement in infants with severe RSV



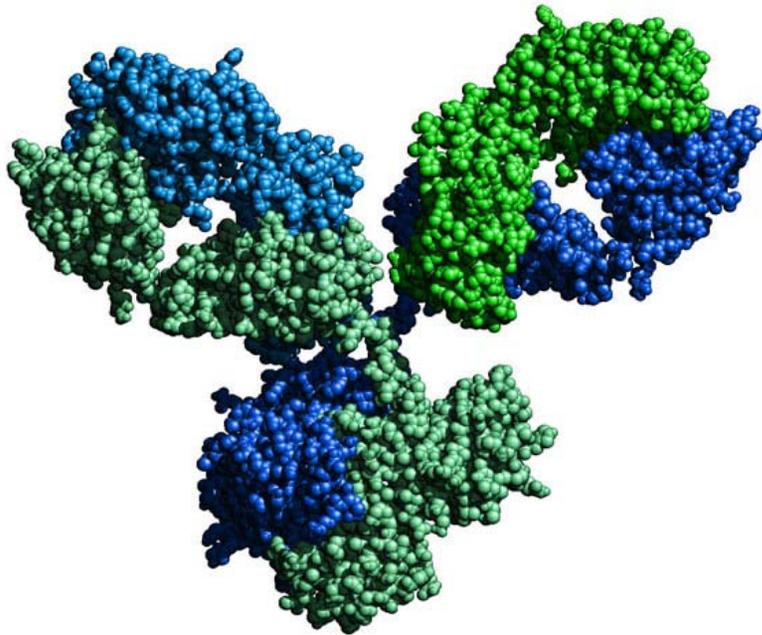
Ribavirin was not effective when compared to saline in treatment of severe RSV

Outcome (hours)	Study Group		P
	Ribavirin (n=20)	Saline (n=27)	
Length of aerosol therapy	59.97 ± 29.15	70.57 ± 37.12	0.31
Length of ventilation	102.16 ± 65.26	126.29 ± 79.12	0.29
Length of ICU stay	140.20 ± 90.87	161.45 ± 96.06	0.42
Length of oxygen therapy	195.24 ± 102.94	209.20 ± 97.99	0.44
Length of hospitalization	255.95 ± 124.93	294.95 ± 124.40	0.32

Aerosolized ribavirin for prevention of progression of RSV in hematologic cell transplants



Palivizumab: humanized monoclonal to the F glycoprotein of RSV

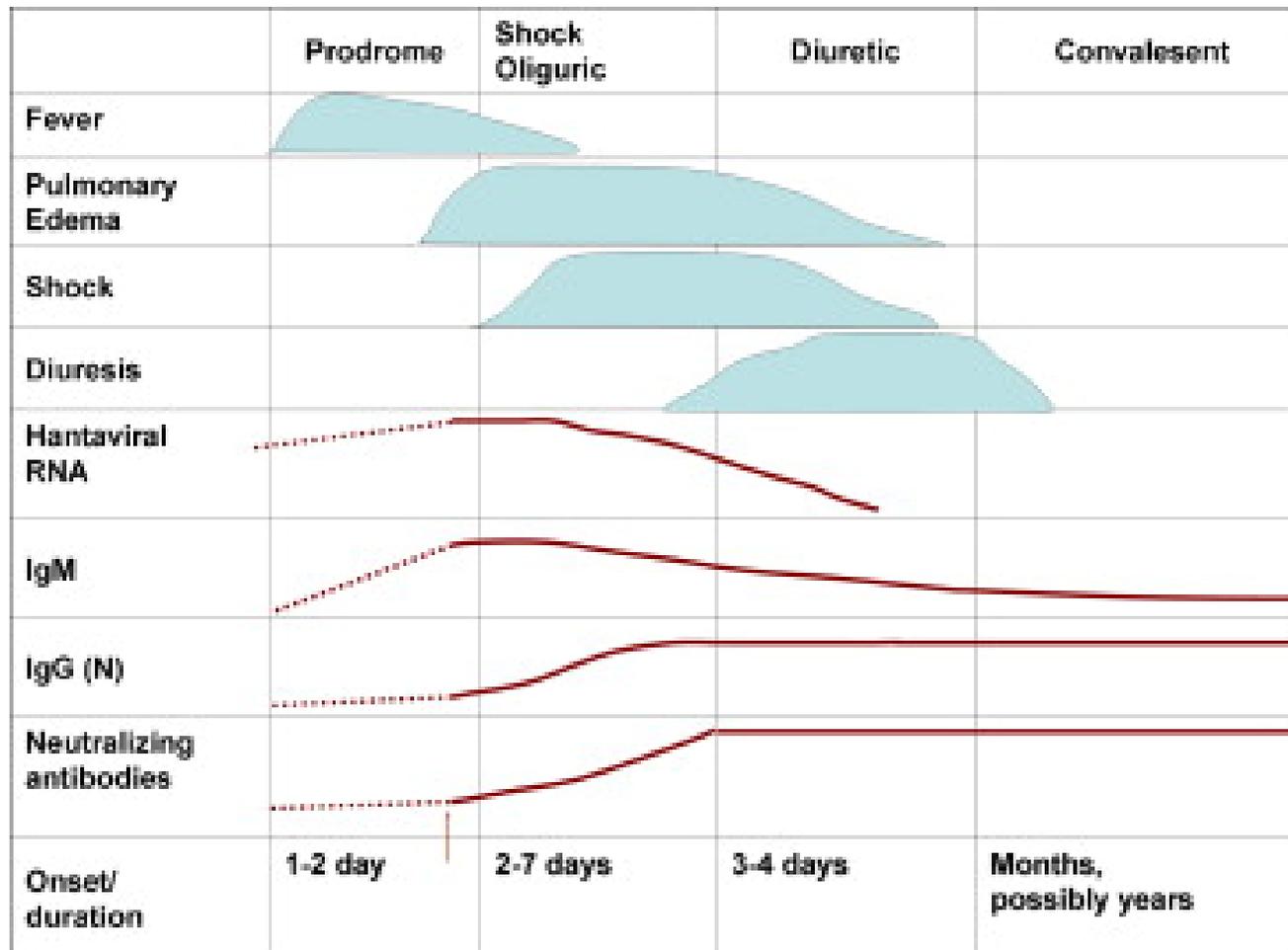


- Neutralizes RSV infectivity in cell culture
- Highly effective for prevention of RSV in high risk infants
- Safe when administered in conjunction with Ribavirin
- Efficacy in treatment of established RSV infection is unclear

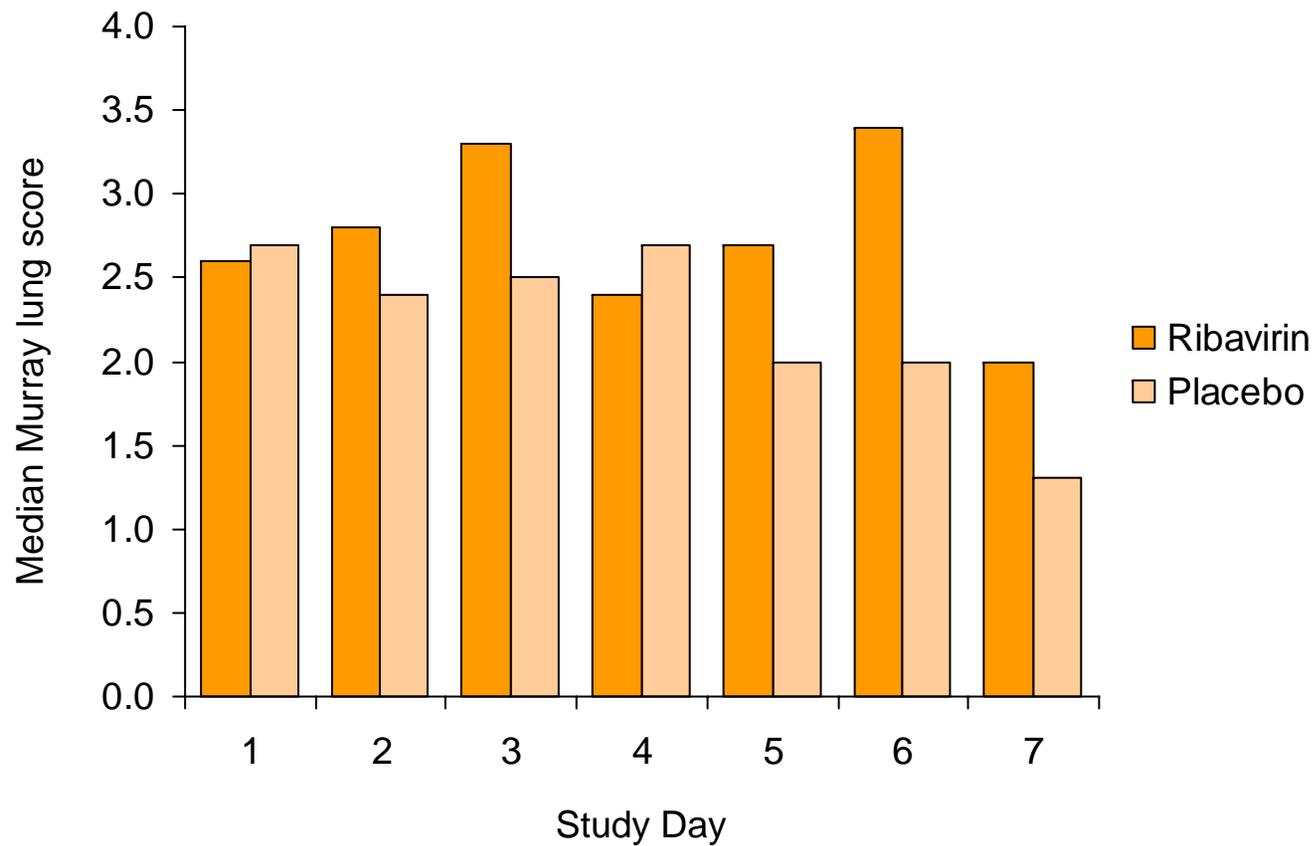
Hantavirus pulmonary syndrome



Clinical course of hantavirus pulmonary syndrome

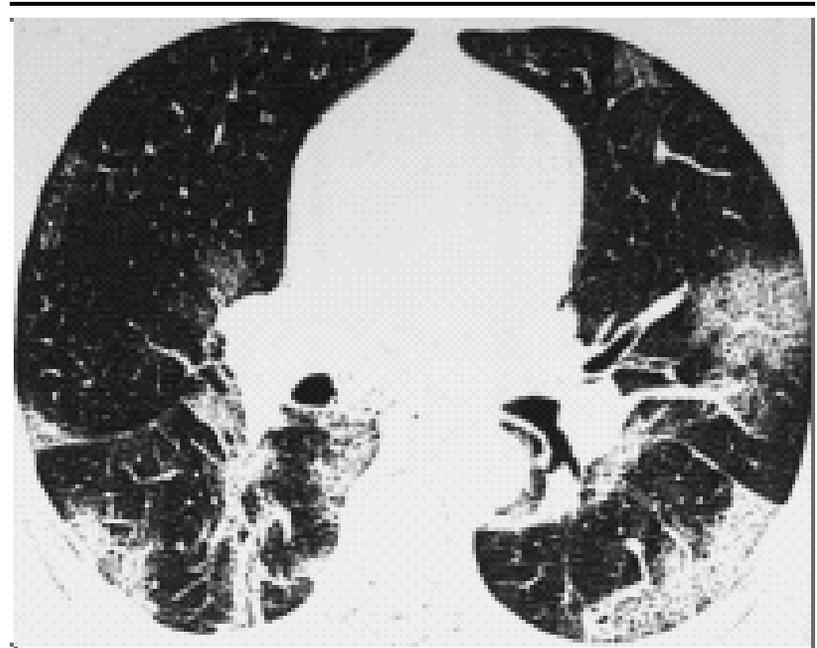
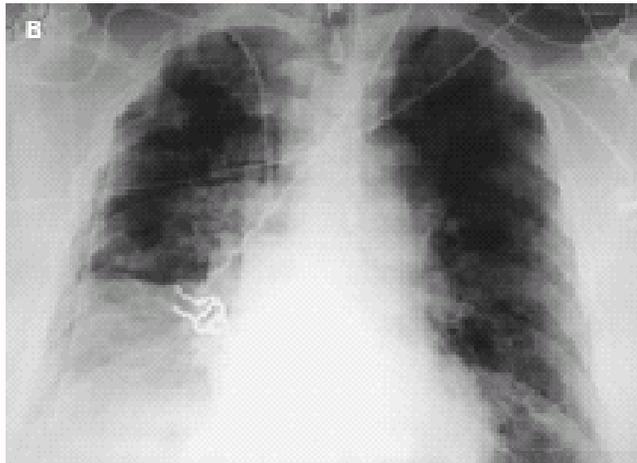
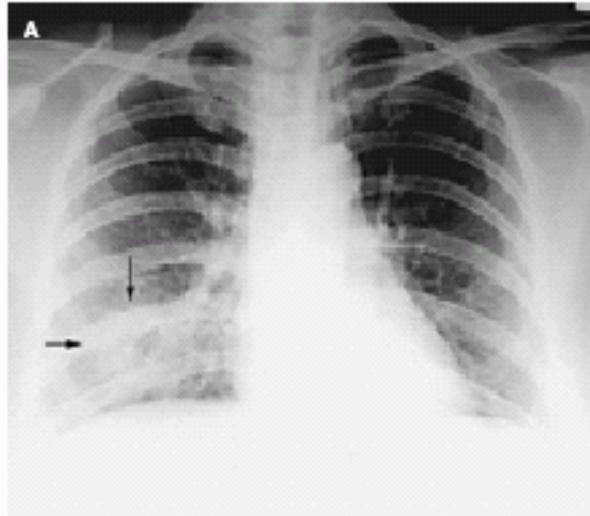


Effect of intravenous ribavirin on lung injury in HPS

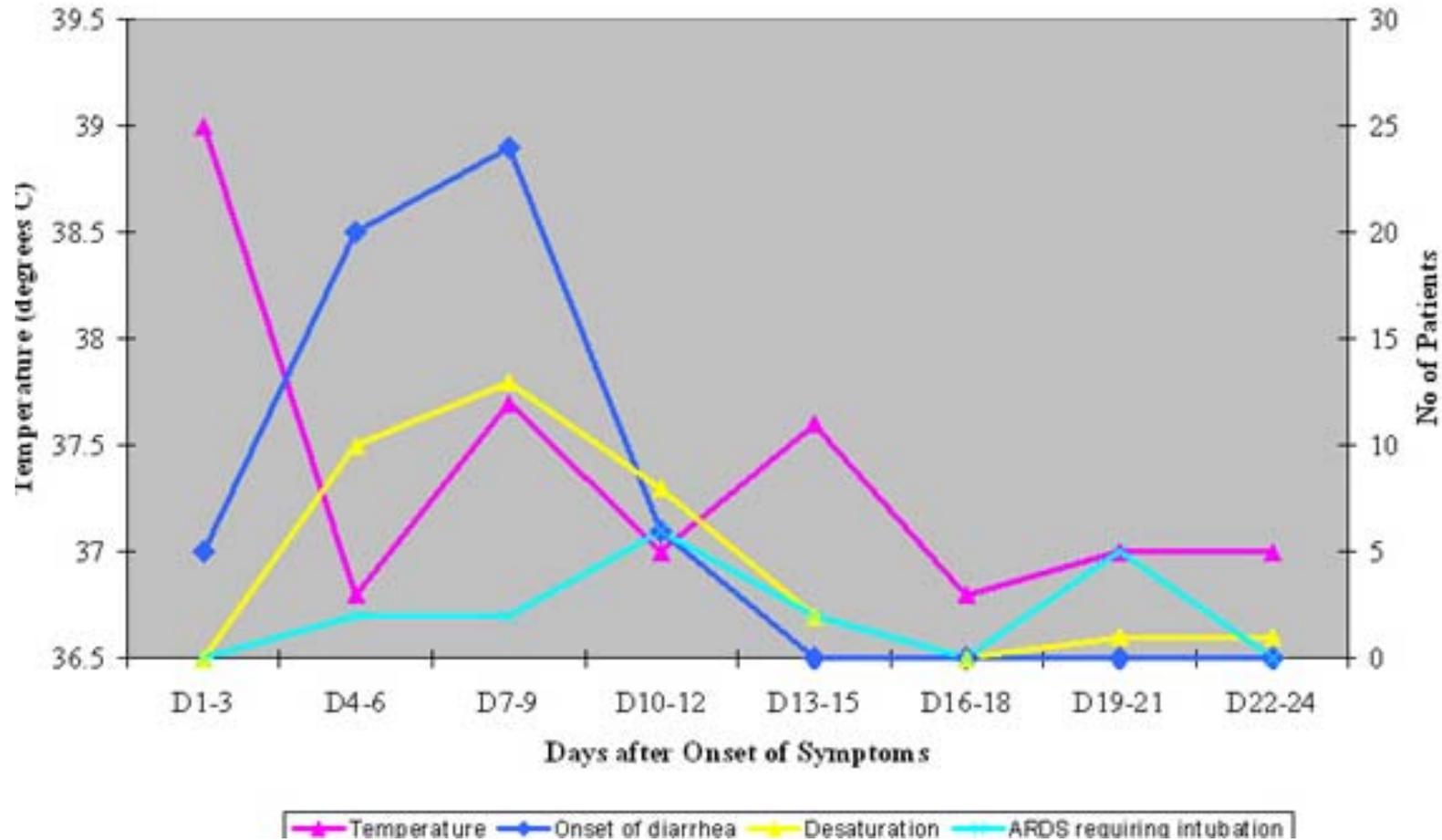


SARS

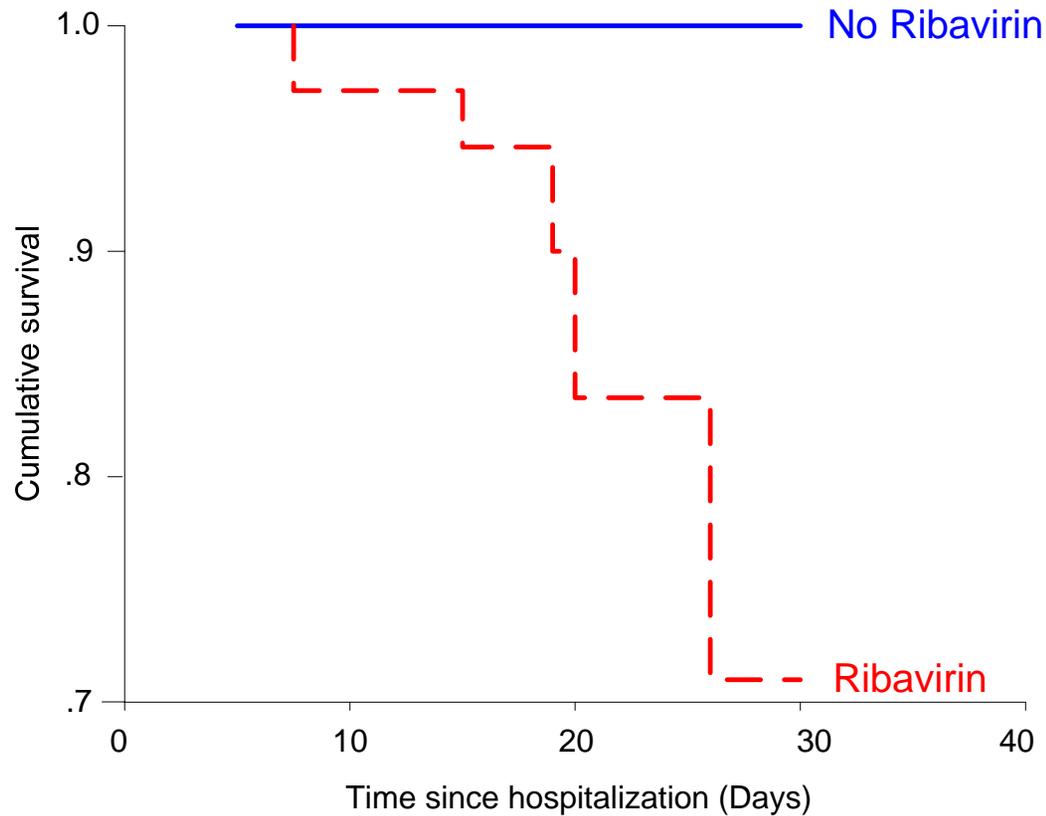
Clinical features



Clinical Features of SARS



Effects of ribavirin on SARS (coronavirus)



Ribavirin - summary

- Broad spectrum antiviral drug with multiple mechanisms of action
 - Resistance is uncommon
- Active against many respiratory viruses
- Few studies directly demonstrate efficacy in any of these conditions
- Expense and toxicity limit usefulness

Rhinovirus

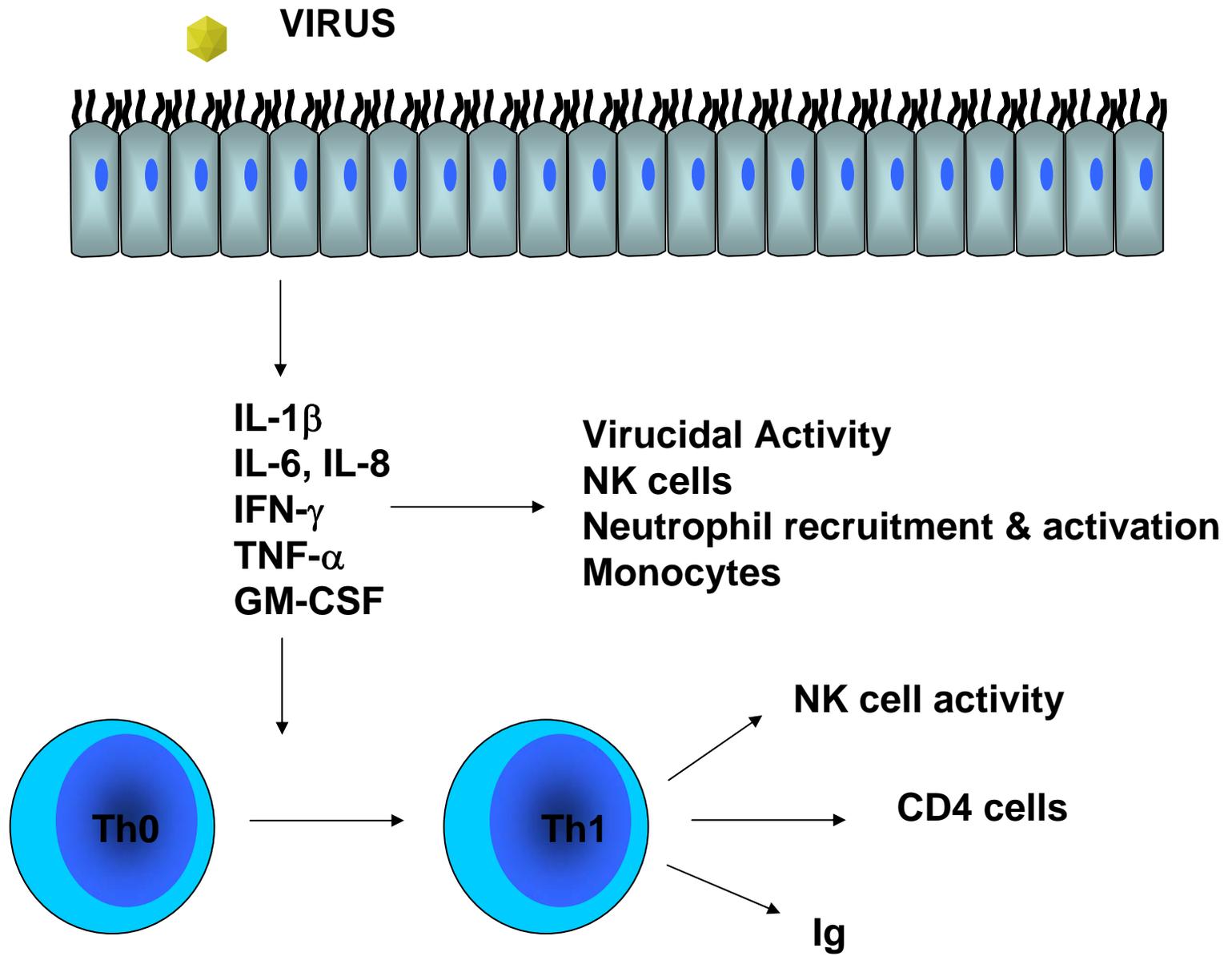
- PicoRNAvirus – small, single-stranded RNA genome
- Most frequent cause of common cold syndrome, one of the most common disease experiences in US
- Associated with exacerbations of asthma, LRT disease in immunocompromised hosts
- Over 100 serotypes, short-term immunity, vaccine development has major obstacles

Common cold: Etiology & ddx

- Pico Rna Viruses (picornaviruses)
 - Rhinoviruses
 - Enteroviruses } ~ 70% of cases
- Coronavirus, RSV, PIV
- Ddx
 - Allergic rhinitis
 - Differentiation from influenza

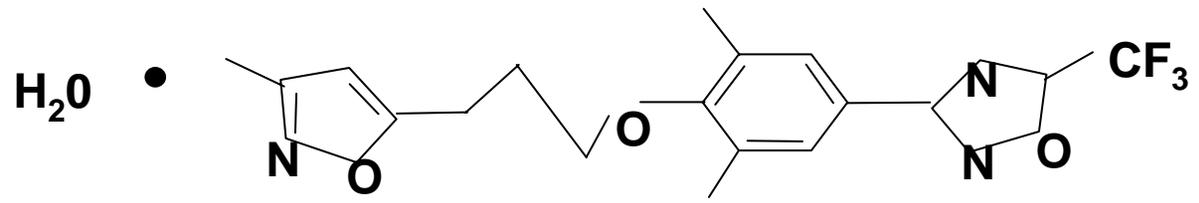
Common cold Pathogenesis

- Transmission by contact with secretions
- Limited replication in upper respiratory tract
- Inflammatory mediators play important role
 - Kinins and IL-8
 - Not histamine
- Psychological stress, smoking

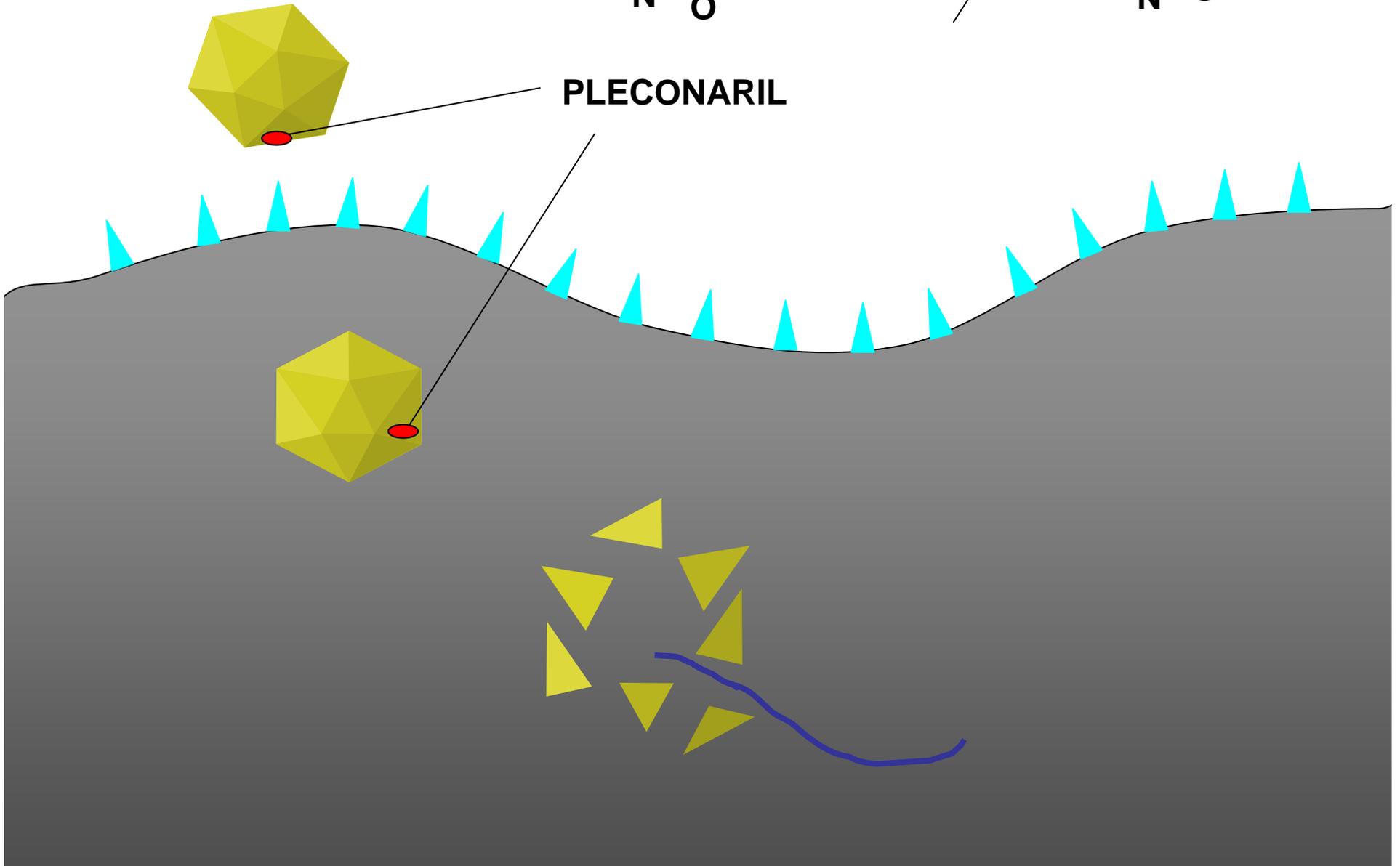


Common cold: Treatment and prevention

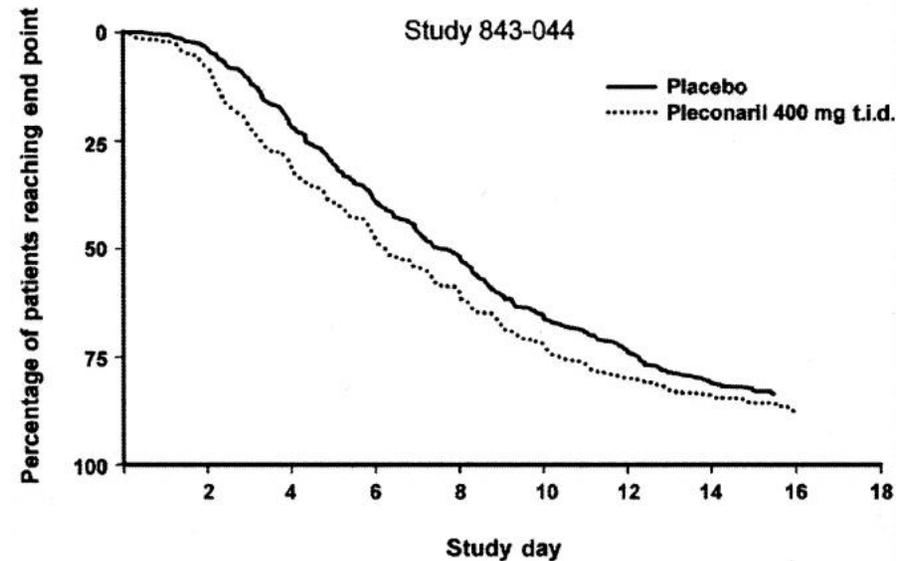
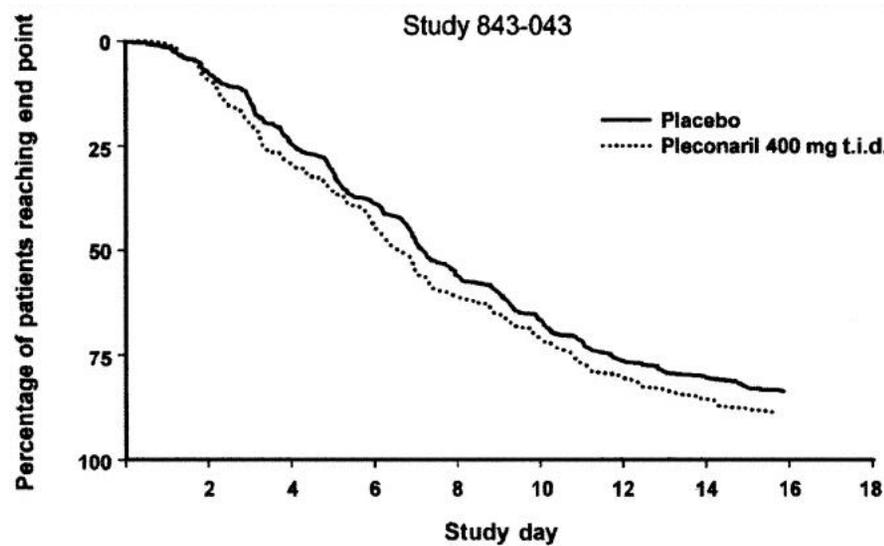
- Vaccine? - Over 100 serotypes of rhinovirus
- Symptomatic therapy
 - Non-selective antihistamines (anticholinergic)
 - Topical vasoconstrictors (rebound)
 - NSAID for sore throat
 - Pseudoephedrine (not phenylpropanolamine)
- Antivirals
 - Pleconaril – capsid binding agent
 - Ruprintovir - 3C protease inhibitor



PLECONARIL



Efficacy of pleconaril in naturally occurring picornavirus colds



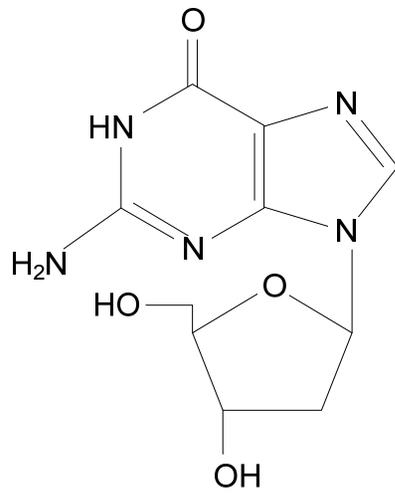
Pleconaril

- Statistically significant reductions in severity and duration of common cold
- Effective for prevention of colds in seasonal prophylaxis
- Induction of CYP4 enzymes resulted in failure of OCP in prophylaxis studies
- Effective treatment of aseptic meningitis
 - Ongoing clinical trial in treatment of chronic aseptic meningitis in SCID, other immunodeficiencies

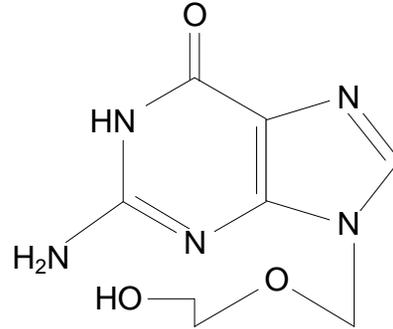
Classification of human interferons

	α	β	γ
Other designations	Type 1, leucocyte	Type 1, fibroblast	Type II, immune
No. species	>12	1	1
MW (kDA)	165-172	166	143
Disulphide bonds	16-27.6	20-23	15.5-25
Glycosylation	2	1	0
Acid stability	Variable	Yes	Yes
Commercial formulations	Stable rIFN-a-2b (Intron A) IFN-a-2a (Roferon A) PEG-IFN-a-2a (Pegasys) PEG-IRN-a-2b (Peg-Intron)	Stable rIFN-b-1b (Betaseron) rIFN-b-1a (Avonex)	Labile rIFN-g-1b (Actimmune) rIFN-g (Immuneron)

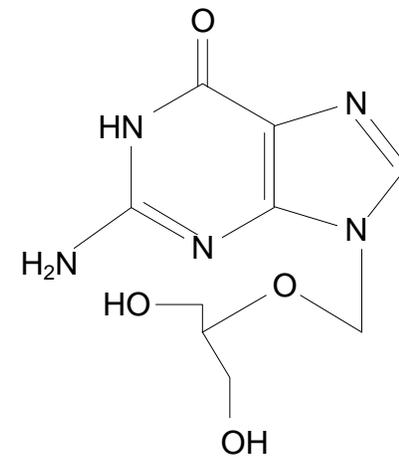
Acyclic nucleoside analogs



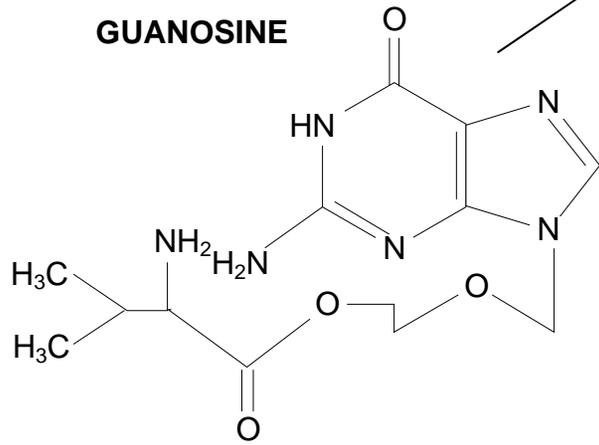
GUANOSINE



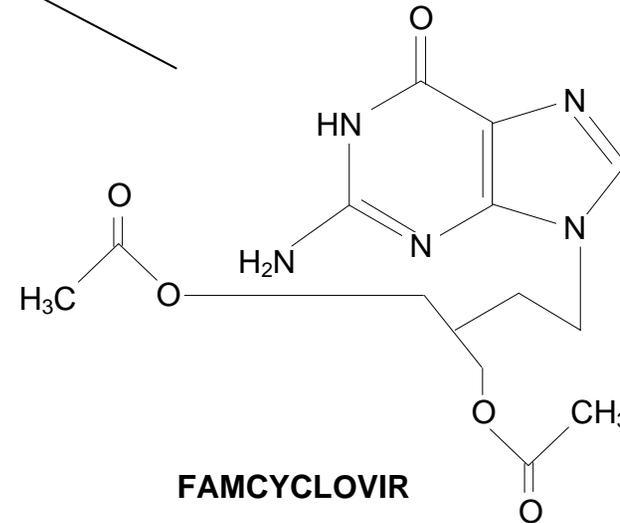
ACYCLOVIR



GANCICLOVIR

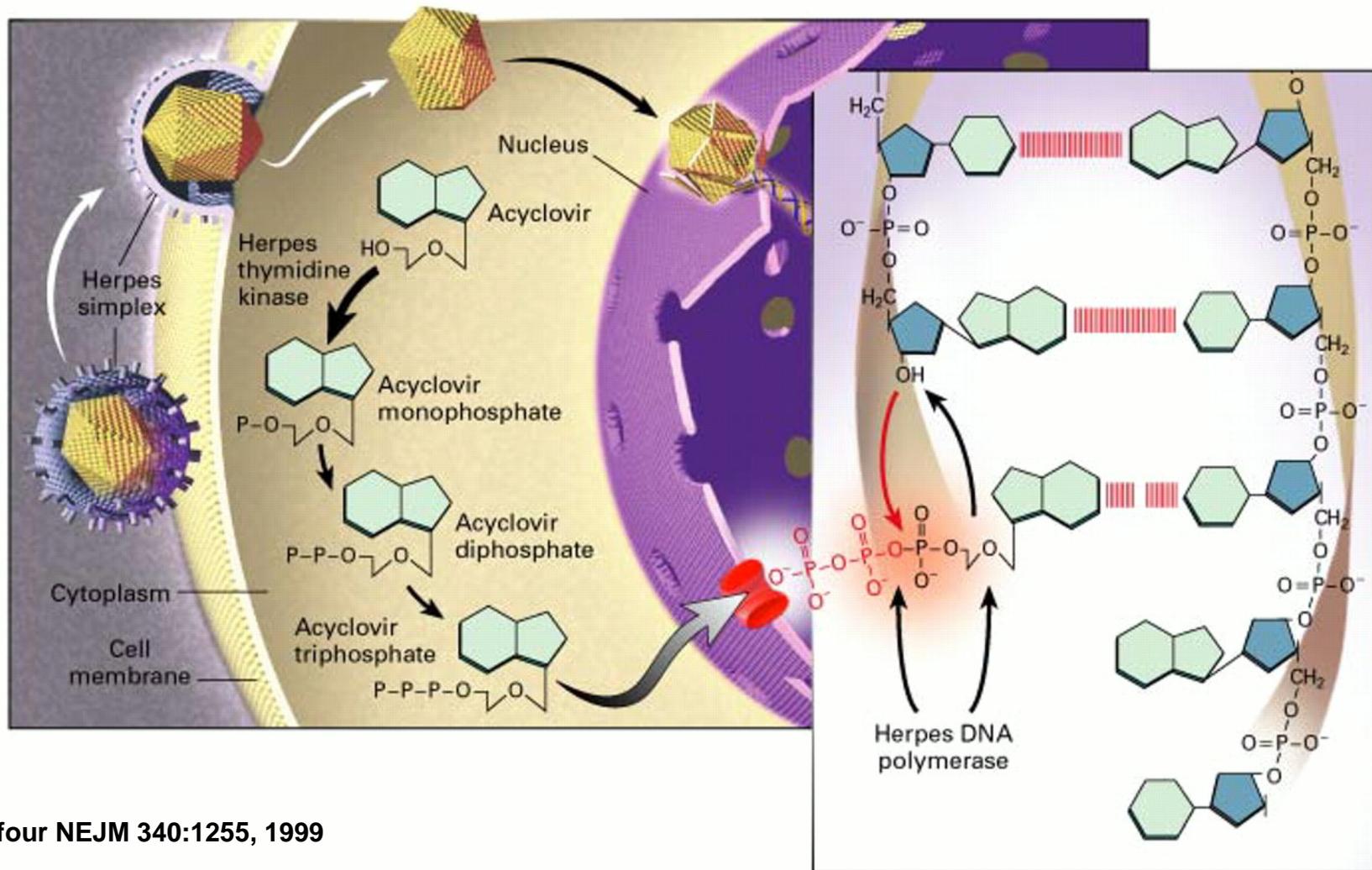


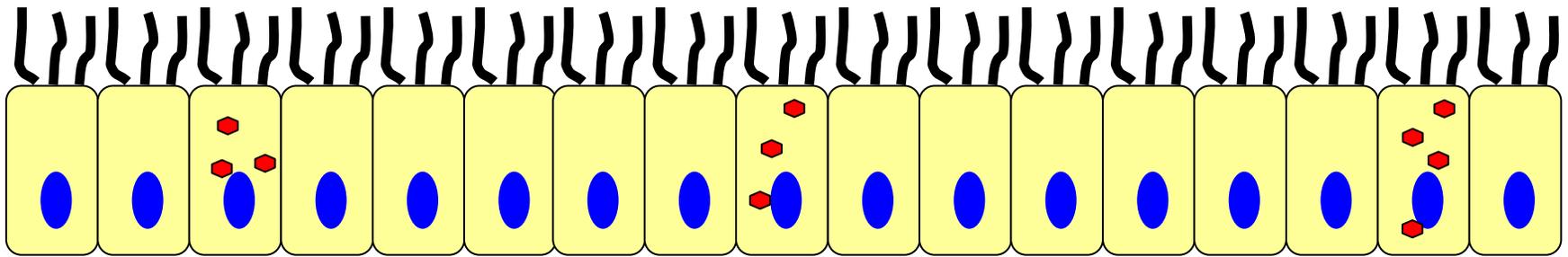
VALACYCLOVIR

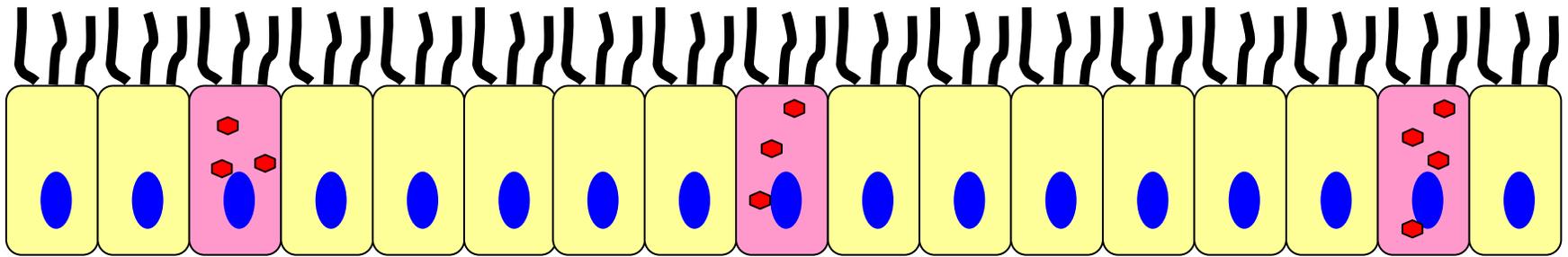


FAMCYCLOVIR

Mechanism of action of Acyclovir







Human herpesviruses

Virus	Thymidine Kinase?
Herpes simplex type 1 (HSV1)	YES
Herpes simplex type 2 (HSV2)	YES
Varicella-zoster virus (VZV)	YES
Cytomegalovirus (CMV)	NO
Epstein Barr Virus (EBV)	NO

Representative in vitro inhibitory concentrations against clinical isolates of human herpesviruses in human cells

Inhibitory Concentration ($\mu\text{g/mL}$)

Virus	Acyclovir	Pencyclovir	Gancyclovir	Cidofovir
HSV 1	0.02-1.9	0.2-1.8	0.05-0.6	0.4-3
HSV 2	0.3-2.9	0.3-2.4	0.05-0.6	0.4-3
VZV	0.8-5.2	0.9-5.1	0.2-2.8	0.25
CMV	2-57	52	0.2-2.8	0.2-0.9
EBV	1.6	--	1.5	<0.03

Acyclovir

- Oral bioavailability 10-20%
- Protein binding 9%-33%
- CSF penetration 13%-52% of plasma
- Renal elimination
 - Half life depends on renal function
 - Removed by hemodialysis
- Common adverse effects
 - Renal – crystal nephropathy
 - Local – thrombophlebitis
 - Neurologic – at high doses

Ganciclovir

- Putative enzyme capable of phosphorylating GCV in UL97 region of CMV genome
- Poor oral bioavailability, IV administration
 - Valganciclovir oral prodrug
- Widely distributed including CSF, little or no metabolism, renal excretion
- Adverse effects
 - Phlebitis
 - Anorexia
 - Marrow suppression: anemia, neutropenia, thrombocytopenia
 - Nephrotoxicity

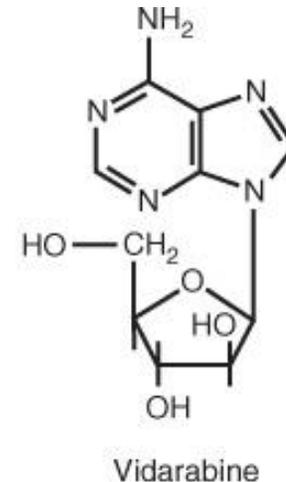
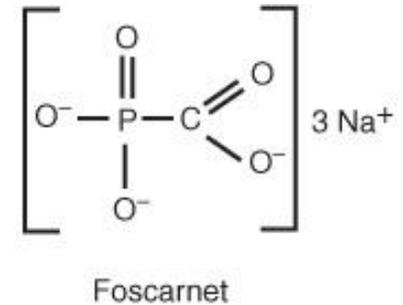
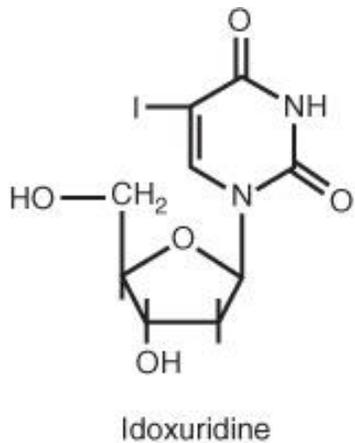
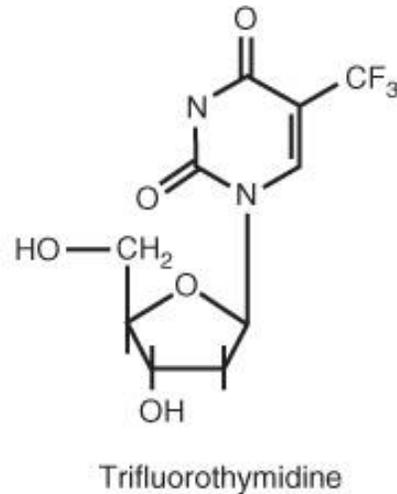
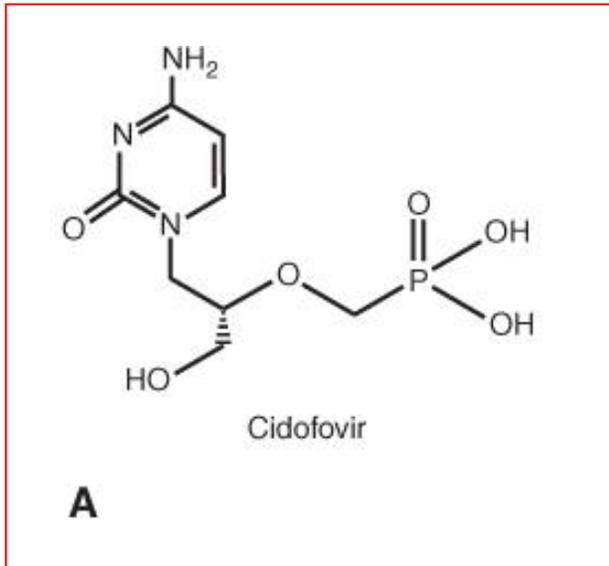
CMV pneumonia

- Pathogenesis and treatment depend on the host.
- Marrow Transplant
 - High mortality
 - GCV alone is not effective, must combine with IVIG
- Solid Organ Transplant
 - Lower mortality
 - GCV alone, need for IVIG not well documented
- HIV
 - Uncommon in era of HAART
 - Often seen in conjunction with other opportunistic infections

Antiviral resistance in herpes viruses

- Antiviral agents metabolized by a unique viral enzyme
- Relative affinity for viral DNA polymerase compared to cellular
- Activity depends on presence of TK
- Antiviral resistance d/t TK⁻ mutation
 - Virus with decreased fitness
 - Generally seen in IC host

Other agents with activity against herpesviruses



Cidofovir

- Broad activity against herpesviruses
- In vitro activity against adenoviruses, multiple case reports of treatment of disseminated adeno in IC host with cidofovir
- Active against vaccinia virus, use in treatment of disseminated vaccinia following smallpox vaccination

Principals of antiviral therapy

- Targeted to virus-specific enzymes or proteins
 - Rapid screening
- Selectivity depends on differentiation from the host
 - Toxic/therapeutic ratio
- Generally very specific (unlike antibacterial agents)

Principles of antiviral therapy

- Target a unique step in viral replication (i.e., the “silver bullet” approach)
- Match pharmacokinetics to site of drug action – the drug must be at the right place, at the right time
- Consider the host and disease process
- Anticipate resistance

Resistance to antivirals

- May result from mutations in the target or from second-site mutations
- Often a clue to the mechanism of action
- May result in complete or partial abolition of activity
- Can be associated with decreased fitness
- Combination therapy reduces risk

Clinical use of antivirals

- Effectiveness is tied to the host immune response:
 - Rapid response, need to use early
 - Slow or ineffective response, later rx
 - No response, less likely to work, more frequent resistance