

## Virale luftveisinfeksjoner

- Forkjølelse (ca 200 forskjellige virus)
- Rhinovirus
- Coronavirus
- RSV
- Parainfluenzavirus
- Adenovirus
- Influenzavirus (mild form)

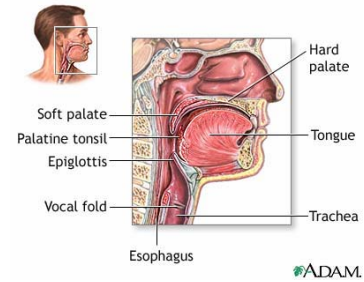
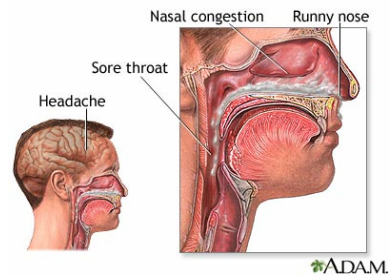
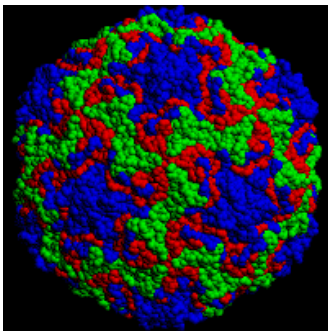


Table 2. Defense Mechanisms of the Lung	
<b>Specific pulmonary mechanisms</b>	Filtration of inhaled particles Humidification, warming of inspired air Absorption of noxious fumes/gases by the vascular upper airway
<b>Pulmonary reflexes</b>	Reflex mechanisms to expel foreign particles: reflexly shallow breathing, temporary cessation of respiration, laryngospasm, bronchospasm Closure of epiglottis (prevents aspiration of food, secretions, foreign bodies)
<b>Mucociliary system</b>	
<b>Cellular Mechanisms</b>	Phagocytosis of particles by alveolar macrophages Phagocytosis of particles by lymphocytes then transport into regional lymph nodes or bloodstream Enhancement of phagocytosis-killing process by: opsonins, small lymphocytes
<b>Humoral Mechanisms</b>	Secretory immunoglobulins (IgA, IgG, IgM) Other substances: interferon, lactoferrin, lysozymes

Symptoms of a cold:



Rhinovirus 14, color coded by protein, as solved by X-ray crystallography



Picornavirus



## Smitteveier

- Dråpesmitte (hoste)
- Kontakt med ferskt eller gammelt "snørr" på håndtak, blandedbatteri
- Håndhilsing

## Rhinovirus infeksjon

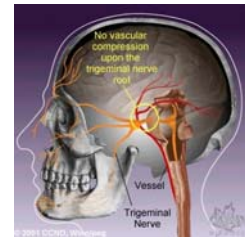
- Virus tas opp og replikerer i epiteliale celler i øvre luftveier (sjelden viremi i blodet)
- Svært få partikler er nødvendig for smitte, og nye virus dannes i ca 3 uker etter smitte
- I de fleste tilfeller dannes spesifikke antistoffer (IgM, IgG og IgA)
- Type I interferon vil også begrense infeksjonen
- Antistoffene som dannes vil reduseres med tiden etter infeksjon og det oppnås sjelden livslang immunitet

## Klinisk bilde

- Tett nese
- Sår hals
- Nysing
- Hodepine
- Rennende øyne
- Hoste
- Bihulesmerter
- Frysninger

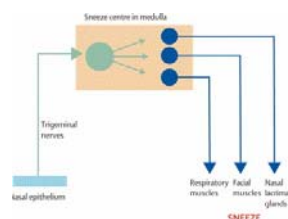
## Sår hals

- Ofte første symptom
- Skyldes dannelse av bradykinin og prostaglandiner som respons på infeksjon
- Stimulerer nerveender i svelget



## Nysing

- Tidlig symptom
- Refleks via trigeminalnerve fra nasalt epitel
- Medieres via histaminreseptorer



## Rennende nese

- Initielt sekreter fra kjertelceller (klart)
- Skyldes stimulering av trigeminalnerven
- Kan hemmes av antikolinergika (ipratropium)
- Skifter etterhvert farge til gul grønn pga rekruttering av leukocytter (grønt pigment)
- Farge ingen markør for bakterier!

## Tett nese

- Skyldes dilatasjon av store vener i nese-epitelet pga bradykininfrigjøring
- Går i bølger under infeksjonen

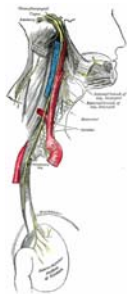
## Bihulesmerter

- Bihuler er hulrom i kraniet som er en del av luftveiene
- Trykkforandringer i sinushulen ved tilstopning av smale kanaler stimulerer nervebaner



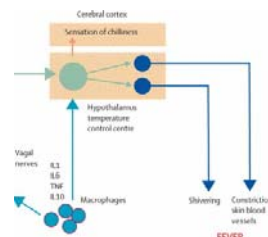
## Hoste

- Viktigste enkeltårsak til legebesøk
- Vagus refleks for ejsjon av partikler i luftveiene
- Uproduktiv hoste pga inflammatorisk respons i luftveiene
- Ofte assosiert med influensa enn forkjølelse (dypere infeksjon)



## Andre symptomer

- Hodepine, feber, muskelsmerter, tap av appetitt skyldes frigjøring av cytokiner fra leukocytter i de infiserte slimhinner



## Diagnose

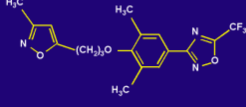
- Vanlig forkjølelse er diagnostisert basert på klinisk bilde
- Sjelden indisert typebestemmelse eller annen spesifikk diagnose
- Kan være viktig å skille forkjølelse og influensa (<4 år eller gamle)
- Forverring av symptomer (øye og halsbetennelser, feber, muskelsmerter) tyder på at det er influensa

## Behandling av forkjølelse

- Ingen generelt akseptert spesifikk terapi
- En rekke OTC preparater lindrer symptomene: slimhinneavsvellende midler
- Oxymetazolin – Iliadin, Rhinox
- Xylometazolin – Otrivin, Xolin, Zymelin
- Fenylpropanolamin - Rhinexin
- Gir karkonstriksjon og nedsatt ødem i neseslimhinnen – fare for rebound effekt ved vedvarende bruk

### Pleconaril 3

First antiviral drug with activity against picornaviruses, the predominant cause of the common cold



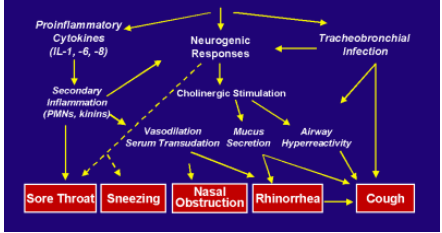
The chemical structure of Pleconaril is a complex heterocyclic molecule. It features a central benzene ring substituted with a methyl group (H<sub>3</sub>C), a propyl ether group ((CH<sub>2</sub>)<sub>3</sub>O), and a 2-methyl-5-(trifluoromethyl)-1,3,4-oxadiazol-5-yl group. The oxadiazole ring is further substituted with a methyl group (H<sub>3</sub>C) and a trifluoromethyl group (CF<sub>3</sub>).

### Current Management of Viral Respiratory Illness 6

- Influenza virus
  - 4 marketed antiviral drugs
  - Vaccines
- Respiratory syncytial virus
  - Prophylactic antibody products
  - Aerosolized ribavirin
- Picornavirus
  - No marketed antiviral drugs
  - No prospect for vaccine
  - Current treatments inadequate

### Picornavirus Colds Pathogenesis 10

*Virus Infection of Nasal Epithelium*



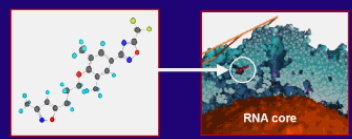
The flowchart illustrates the pathogenesis of a cold. It starts with 'Virus Infection of Nasal Epithelium', which leads to three parallel pathways: 'Proinflammatory Cytokines (IL-1, -6, -8)', 'Neurogenic Responses', and 'Tracheobronchial Infection'. 'Proinflammatory Cytokines' leads to 'Secondary Inflammation (PMNs, kinins)'. 'Neurogenic Responses' leads to 'Cholinergic Stimulation', which then causes 'Vasodilation', 'Serum Transudation', and 'Mucus Secretion'. 'Tracheobronchial Infection' leads to 'Airway Hyperactivity'. All these pathways culminate in symptoms: 'Sore Throat' (from secondary inflammation), 'Sneezing' (from cholinergic stimulation), 'Nasal Obstruction' (from vasodilation and mucus secretion), 'Rhinorrhea' (from serum transudation and mucus secretion), and 'Cough' (from airway hyperactivity and mucus secretion).

### Current Management of Colds 12

- Leading reason for physician visits
  - ~15% of colds result in an office visit
- Antibiotics
  - 30-50% of visits result in antibiotic prescription
  - No reduction in symptoms or complications
- No treatment for the underlying viral cause

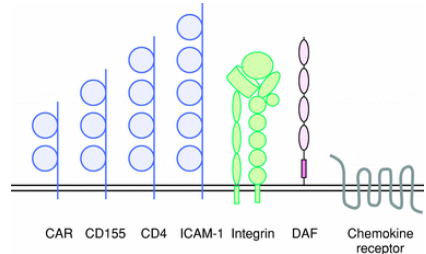
McIsaac, et al. *J Fam Prac.* 1998;47:356  
 Gonzales, et al. *JAMA.* 1997;278:901  
 Gonzales, et al. *Ann Intern Med.* 2001;134:478  
 Rosenstein, et al. *Pediatrics.* 1993;91:1131

### Pleconaril Mechanism of Action 15



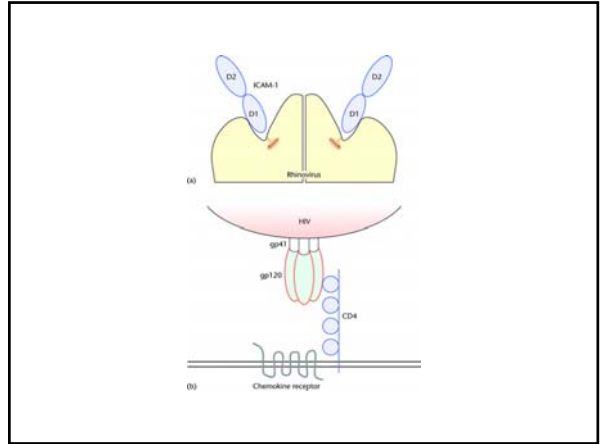
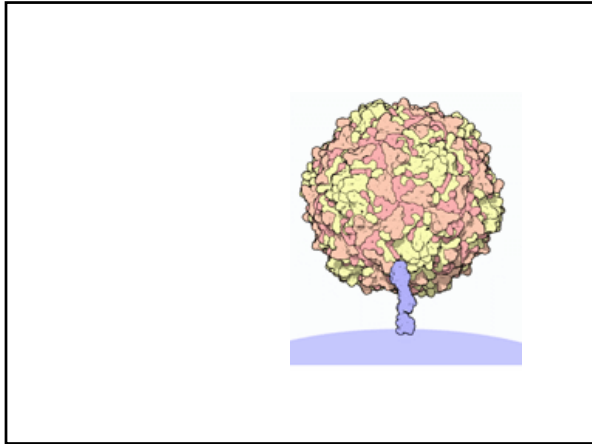
The diagram shows a virus particle with a red 'RNA core' and a blue capsid. Pleconaril molecules (represented as small blue spheres) are shown binding to the capsid, specifically blocking the uncoating and attachment processes.

Blocks uncoating and attachment by binding into a hydrophobic pocket within the capsid



The schematic shows six receptors on a cell membrane: CAR (Coxsackievirus and Adenovirus Receptor), CD155, CD4, ICAM-1, Integrin, DAF (Decay Accelerating Factor), and Chemokine receptor. Each receptor is represented by a different structure of blue and green spheres and lines.

Schematic structures of viral host cell receptors. CAR is a receptor for coxsackie B viruses and adenoviruses, CD155 is a poliovirus receptor, CD4 is recognized by human immunodeficiency virus (HIV), whereas intercellular adhesion molecule (ICAM) 1 acts as a receptor for most rhinoviruses. These four molecules are members of the immunoglobulin (Ig) superfamily containing typical Ig-like domain structures



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### Demographics: ITT-I

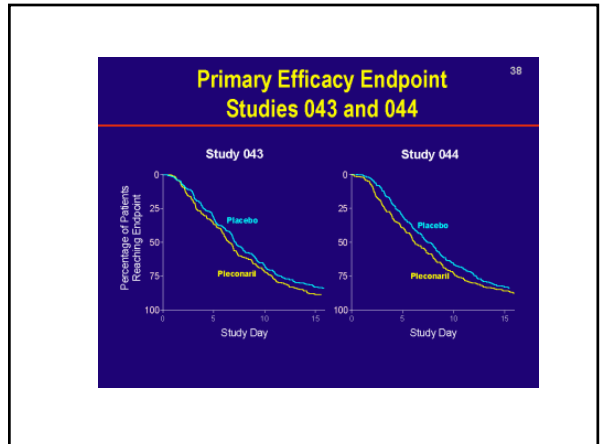
	Study 043		Study 044	
	Placebo N=326	Pleconaril N=337	Placebo N=356	Pleconaril N=344
Median Age (yrs)	35	33	35	33
Female	65%	68%	71%	67%
Race (White)	83%	80%	90%	90%
Smoker	27%	32%	27%	28%

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- ### Primary Efficacy Endpoint
- Time from initiation of study drug to
    - Absence of rhinorrhea
    - Five other cold symptoms absent or mild
    - Sustained for four consecutive reporting periods (~48 hrs)
    - Without use of concomitant cold symptom relief medications
  - Endpoint occurs at the beginning of the 48-hour interval

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### Primary Efficacy Endpoint: ITT-I

Days	Study 043			Study 044		
	Placebo N=326	Pleconaril N=337	p-value	Placebo N=356	Pleconaril N=344	p-value
25 <sup>th</sup> Percentile	4.1	3.3		4.3	3.3	
Median	7.2	6.6	0.037	7.7	6.2	0.001
75 <sup>th</sup> Percentile	11.7	10.8		12.3	10.4	



## Komplikasjoner ved forkjølelse

- Ørebetennelse
- Halsbetennelse
- Bihulebetennelse
- Bronkitt
- Lungebetennelse
- Astma? KOLS?

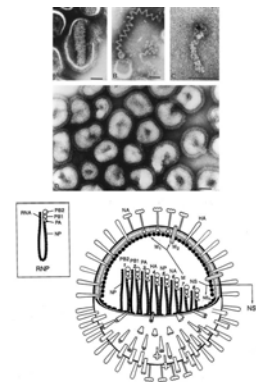
## Virusinfeksjoner i nedre luftveier

- Akutt bronkitt
- Skyldes oftest rhino-, corona-, adeno- eller influensavirus
- Hoste, sår hals, pipende pustelyder
- Ingen spesifikk terapi
- Lindrer symptomer med hostedempende midler (folkodin, noskapin ect)

## Akutt bronkiolitt

- Vanlig hos spedbarn. Skyldes RSV eller parainfluenzavirus
- Tungpustet, hvesende lyd
- Behandles med oksygen inhalasjon, adrenalin, b2r agonister (antiastmatika), Palivizumab (RSV nøytraliserende antistoff)

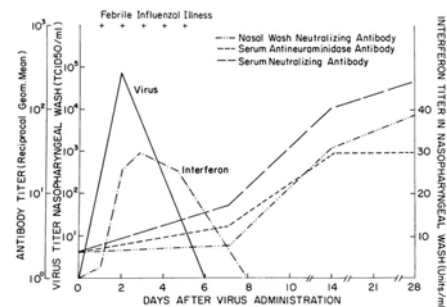
Influenza virus



## Influenza

- Deles i type A,B og C basert på overflateproteiner
- Spres ved dråpe- og kontaktsmitte
- Infiserer epitelceller i øvre luftveier og spres videre gjennom mucus eller blod
- Symptomer- sår hals, feber, frysninger, hodepine, muskel- og leddsmerte, rennende nese, hoste
- Komplikasjoner – respirasjonsbesvær, viral lungebetennelse, sekundær bakteriell pneumoni
- Diagnose – dyrking i cellekultur, serologi, diagnostisk bilde

Influenza patogenese



## Influenza patofysiologi

- Mucosal inflammasjon og ødem
- Vakuolisering av epitel og tap av cilier
- Infiltrasjon av monocytter og nøytrofiler
- Tap av epitelceller
- Blødninger

Tamiflu, Relenza – en enzymhemmere med effekt på influensa neuraminidase

