Herpes virus reactivation in the ICU

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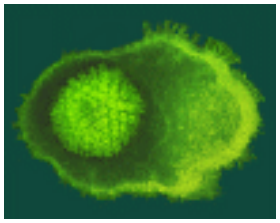
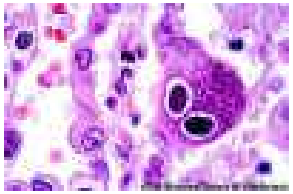
Introduction: Viruses identified in critically ill ICU patients

- Viral diseases have recently been the subject of numerous investigations in critically ill patients in ICU
- Which viruses for ICU non-immunocompromised patients??

Virus	Endogenous	Exogenous*
Community	HSV, CMV 	Influenza, parainfluenza, adenovirus,rhinoviruses, RSV, coronaviruses, metapneumovirus
Nosocomial	HSV, CMV 	Mimivirus (??), CMV (transfusion), H1N1 pandemic influenza

- **Herpesviruses: the threat from the inside!!!**
- * Limited in non-immunocompromised patients

Chiche L et al., Curr Opin Infect Dis 2011; 24: 152-156

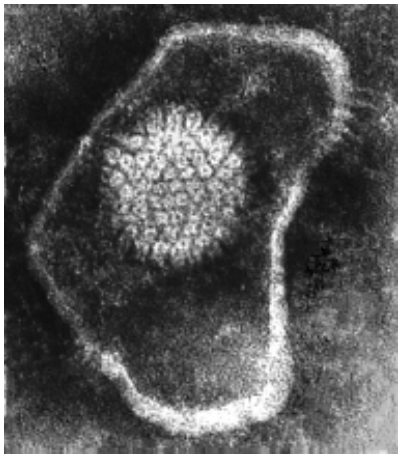
Clinical studies of HSV respiratory infections in critically-ill patients

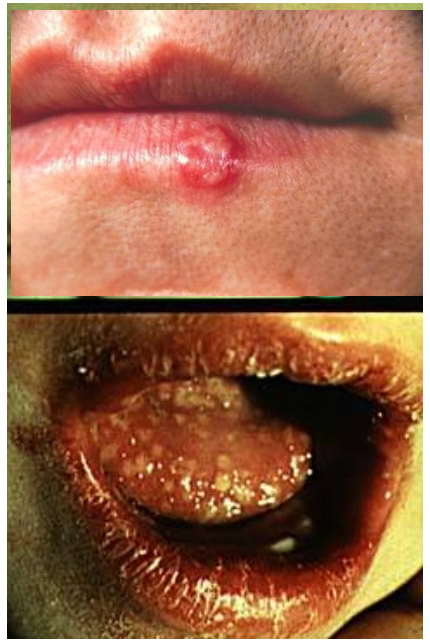
- Review of 12 studies between 1982 and 2003
- Design of studies: mostly retrospective
- Incidence of HSV in the LRT:
  - 2%- 30% of patients studied
- Clinical manifestations
  - Tracheobronchitis
  - Pneumonia or pulmonary infiltrate
  - Mortality: 0% to > 50%
- Risk factors if studied:
  - Immunosuppression
  - Intubation
  - Age
  - APACHE II score

Simmons-Smit AM et al., Clin Microbiol Infect 2006

HSV in the lower respiratory tract

- Incidence of HSV in the LRT:
  - Large post-mortem series: 0.002 – 0.05 %
  - ARDS patients: 30 – 78 %
- Radiographic & bronchoscopic findings:
  - inconclusive
- Origin of the virus in the LRT?
  - Endogenous reactivation
  - In the LRT
    - Reactivation in the throat and aspiration?
    - Reactivation in LRT?
    - Hematogenous spread?
- Innocent bystander or cause of infection?



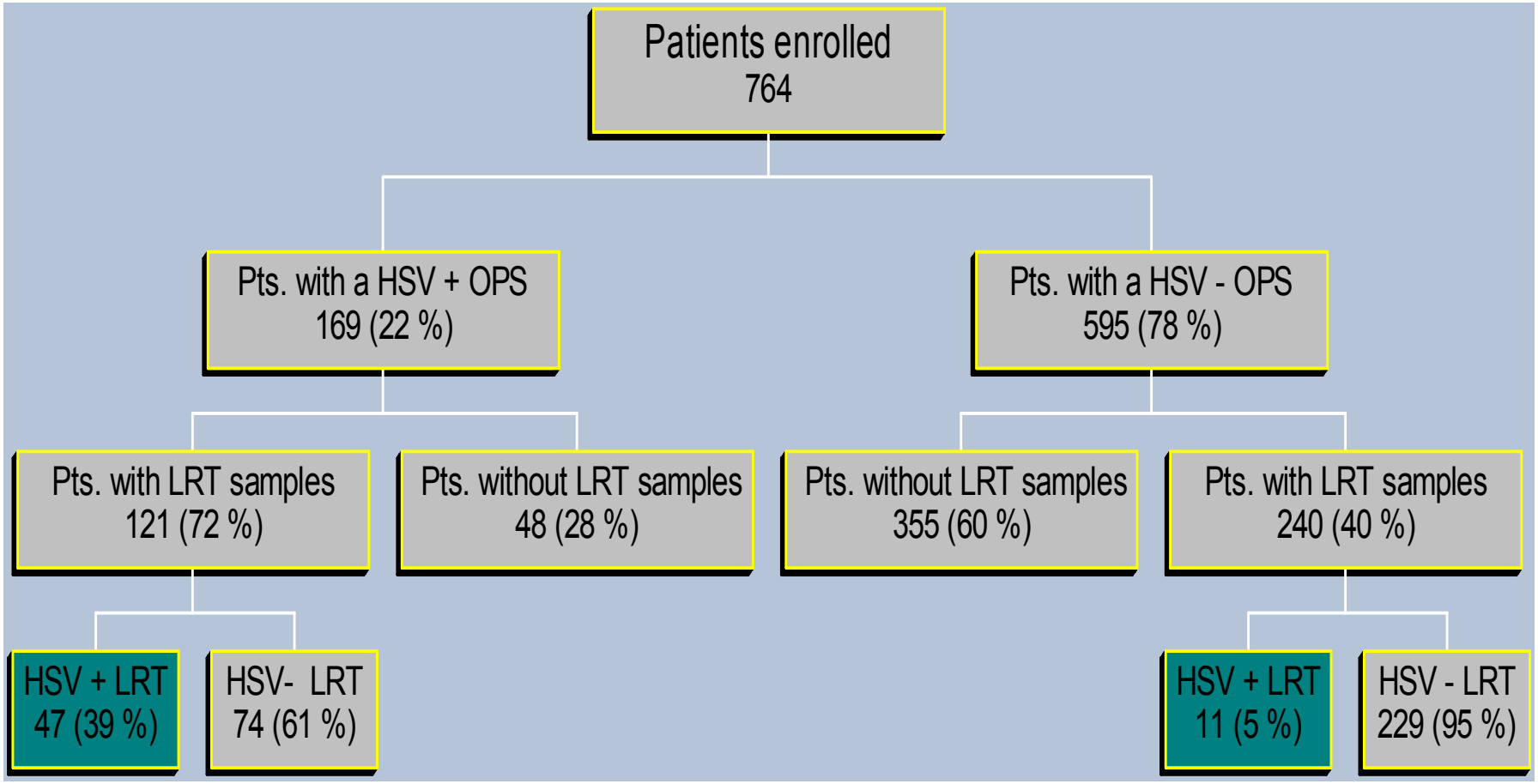


HSV in the respiratory tract of critical care patients: a prospective study

- Objectives: to study:
  - the incidence of respiratory HSV in ICU patients
  - the clinical significance of the virus
  - risk factors for the development of LRTI with HSV
    - Immunosuppression? Surgery?
    - Role of intubation and mechanical ventilation?
    - Role of other pathogens?
  - the origin of the virus, nosocomial transmission?
- Design:
  - During a 20-month period, all adults in ICU for ≥ 3d
  - Screened in OPS for HSV
  - BAL of intubated patients cultured for HSV and respiratory pathogens
  - Clinical data and outcome evaluated in HSV+ and HSV - patients

Bruynseels P et al. *Lancet* 2003, 362: 1536-41

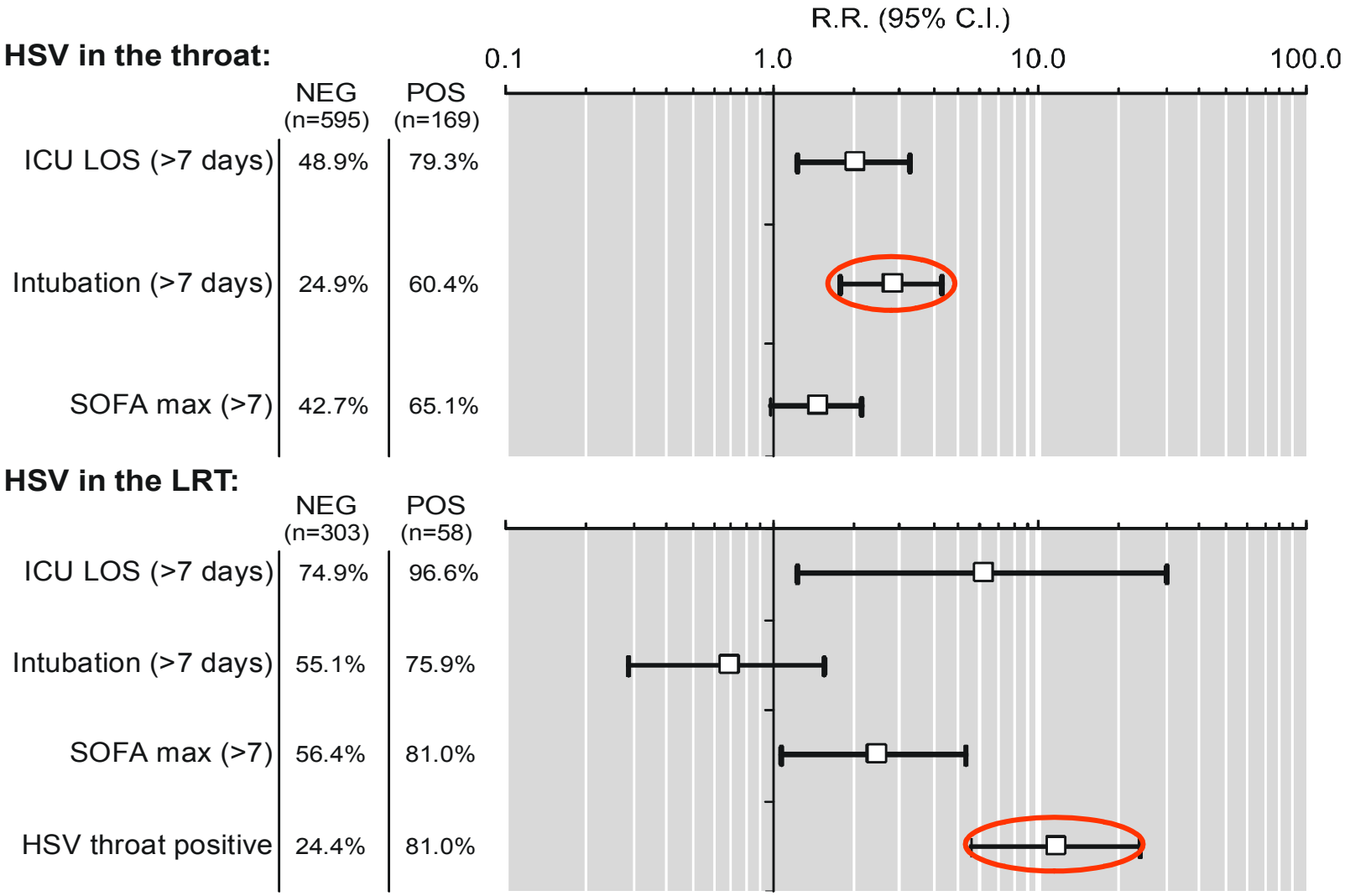
HSV in the respiratory tract of critical care patients: profile of the study group



HSV detected in the throat of 2% healthy volunteers and 3% pts not admitted at ICU compared to 22% in ICU patients ($P < 0.001$)

Bruynseels P et al. *Lancet* 2003, 362: 1536-41

Association between HSV in the respiratory tract and clinical features



Bruynseels P et al. *Lancet* 2003, 362: 1536-41

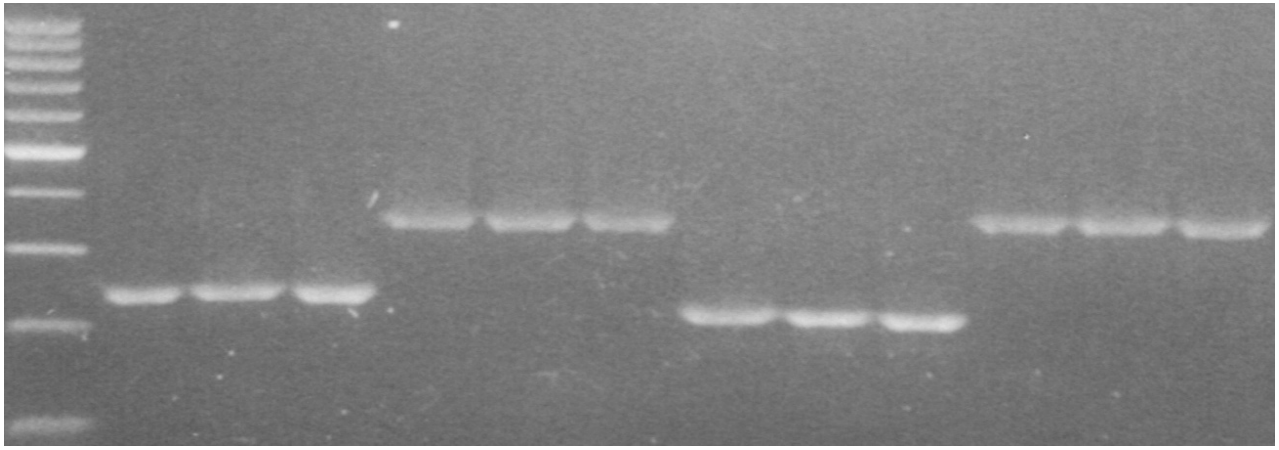
Outcome in patients with HSV in the respiratory tract : a prospective study

	All patients (n=764)	Throat culture HSV+ (n=169)	HSV- (n=595)	*P*
ICU LOS	8.5 (3-162)	16 (3-162)	7 (3-93)	<0.001
UZA LOS	24.5 (3-254)	32 (3-208)	22 (3-254)	< 0.001
mortality	194 (25%)	25 (34%)	136 (23%)	0.003
	All patients (n=361)	**LRT culture HSV+ (n=58)**	**HSV- (n=303)**	***P***
ICU LOS	14 (3-162)	24 (4-106)	13 (3-162)	<0.001
UZA LOS	32 (3-254)	40.5 (12-208)	28 (3-254)	<0.001
mortality	121 (34%)	22 (38%)	99 (33%)	0.45

Bruynseels P et al. *Lancet* 2003, 362: 1536-41

HSV reactivation in the throat and aspiration? Genotyping of HSV isolates

- Typing of multiple isolates from the same patient: What is the genetic variability of multiple HSV strains
  - 68 ptn with multiple isolates from throat and/or LRT
  - No genetic differences between isolates, infection/reactivation probably caused by only one strain.

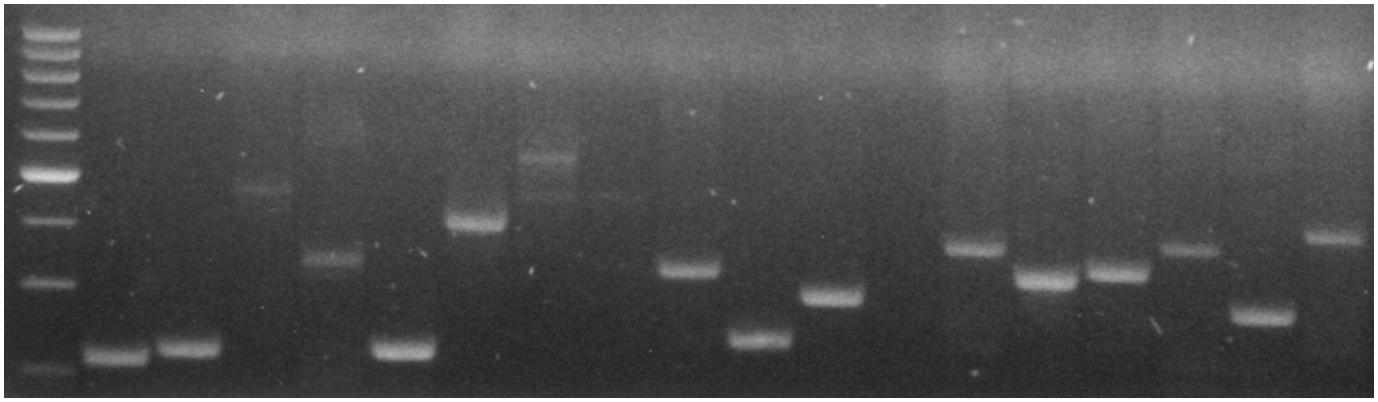


- **These data support the theory that infection of the LRT is acquired by aspiration of the virus from the throat**

M. Ieven et al . 44th ICAAC, Washington, Nov 2, 2004.

HSV reactivation in the throat and aspiration? Genotyping of HSV isolates

- Typing of isolates between patients: genetic heterogenity: nosocomial transmission?
  - 131 different HSV genotypes can be identified in 143 patients.
  - The genotype within one patient remains stable during the 6 weeks of observation
  - Only in 3/143 patients, nosocomial transmission could not be excluded



- **There is little evidence of noscomial HSV transmission**

M. Ieven et al . 44th ICAAC, Washington, Nov 2, 2004.

HSV lung infection in patients undergoing prolonged mechanical ventilation

- Design: prospective study including all ICU patients with MV ≥ 5d
- BAL, OPS + biopsy if clinical deterioration
- HSV by culture and Q-PCR
- Bronchopneumonitis defined by:
  - Clinical deterioration
  - HSV pos in BAL by PCR and/or culture
  - HSV-specific nuclear inclusions

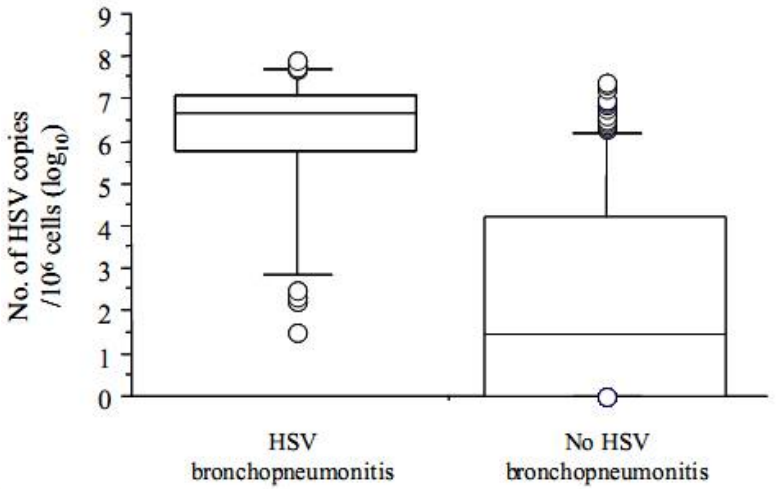
Luyt C et al. Am J Resp Crit Care Med 2007; 175: 935-942

HSV lung infection in patients undergoing prolonged mechanical ventilation

- Results
  - HSV bronchopneumonitis diagnosed in 42/201 (21%)
- Risk factors for HSV BPn
  - Oral-labial lesions
  - HSV-positive throat

• HSV BPn is a descending infection and impacts outcome
•Only an interventional trial will be able to determine its true impact in an ICU setting!!

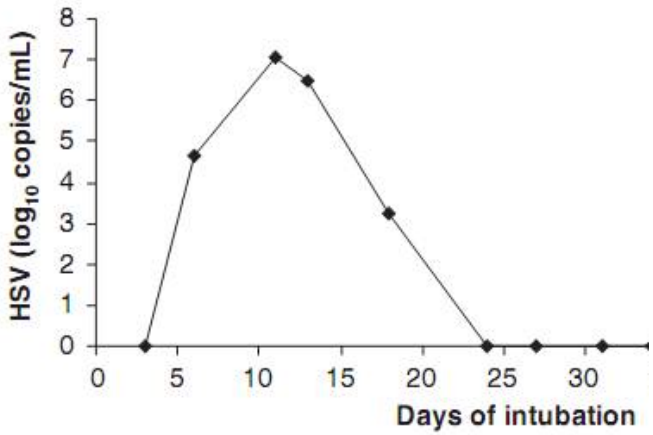
  - Prolonged ICU stay: 40 vs 32d: *P* = 0.01
  - VAP episodes: 1.5 vs 1.1 *P* = 0.03
  - In hospital mortality: 48% vs 42% NS
- Virus loads
  - Mean ⇧ in pts with HSV BPn



Luyt C et al. Am J Resp Crit Care Med 2007; 175: 935-942

Monitoring of HSV in LRT of critically ill patients by PCR

- Prospective observational study in ICU patients mechanically ventilated for at least 48h
- Monitoring of HSV by quantitative PCR
- Results:
  - HSV common in MV patients: 65/105 (62%)
  - Detection of HSV significantly associated with:
    - Prolonged mechanical ventilation: $P < 0.01$
    - Prolonged ICU stay: $P < 0.01$
    - Development of VAP: $P = 0.02$
  - Monitoring viral loads in the LRT:
    - HSV pos after a mean of 7days of intubation
    - Exponential ⇧ to HSV peaks 10^{6}-10^{8} copies/ml



De Vos N et al, Clin Microbiol Infect 2009; 15: 358-363

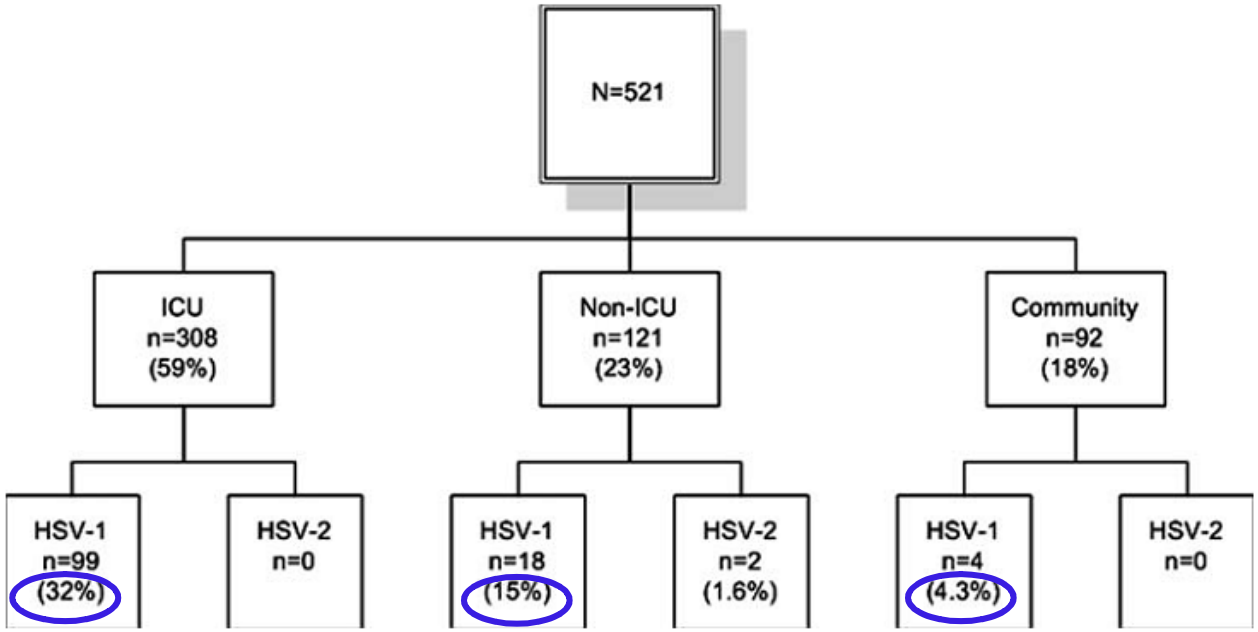
Monitoring of HSV in LRT of critically ill patients by PCR

- Based on suspicion of possible high viral load and clinical deterioration: 46% of HSV positive patients received acyclovir at the physician's discretion
  - No significant difference in patient outcome
  - No significant decrease in HSV viral load
- Conclusions:
  - Q-PCR is reliable for the detection of HSV in the LRT
  - No strong conclusions on impact of HSV on morbidity and mortality
  - **Further studies are needed with antivirals vs placebo to analyse the outcome of HSV positive patients**

De Vos N et al, Clin Microbiol Infect 2009; 15: 358-363

HSV viral load in BAL and outcome in critically ill patients

- Objective: evaluate HSV loads in BAL and clinical outcome
- Design:462 pts



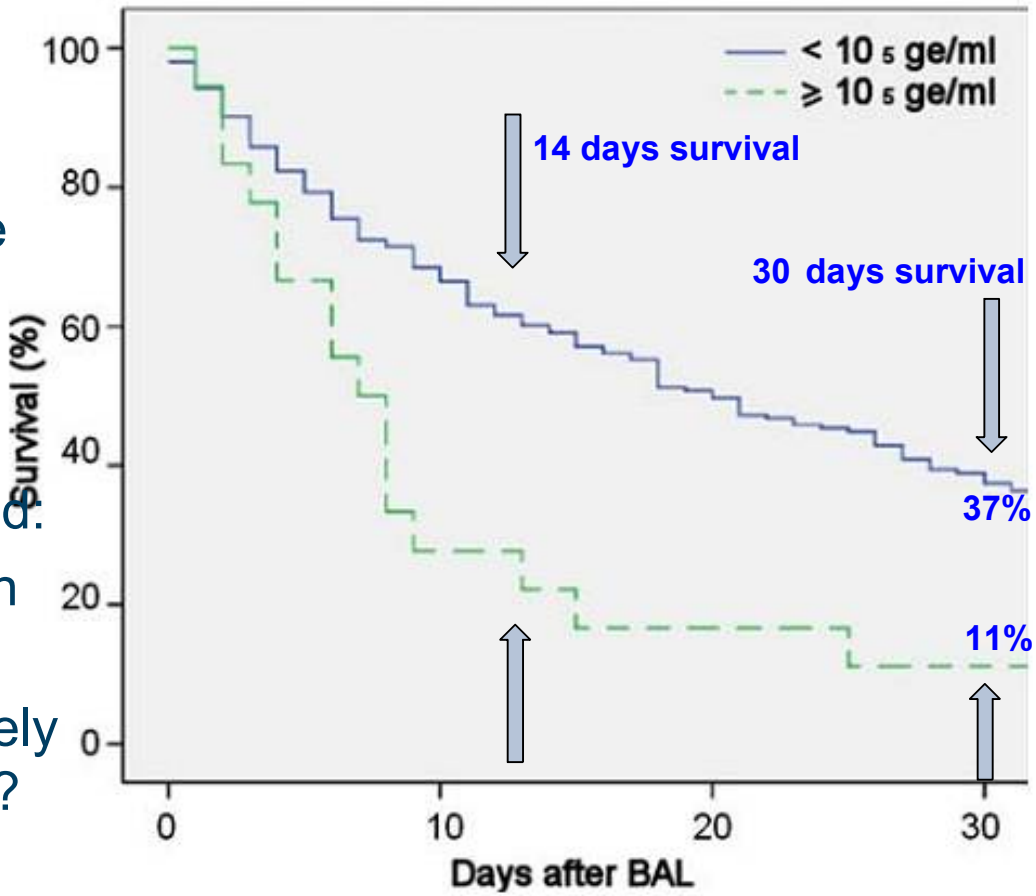
- Results
  - Prevalence:
  - Less HSV in age <50 yrs: 12% vs 25% in age >50 yrs: $p< 0.001$
  - HSV loads $>10^5$ ge/ml: 14-day mortality: 41% vs 20%: $p = 0.001$

Linssen C et al, Intensive Care Med 2008; 34: 2202-2209

HSV viral load in BAL and outcome in critically ill patients

- 2/4 pts with loads >10^5 ge/ml: post-mortem HSV pneumonia

  BUT
- No data on underlying disease
- Design of study insufficient to prove HSV to be the cause of death in all but 2 pts
- What remains to be determined:
  - is HSV causally linked with low survival? or
  - is HSV a marker of severely disturbed immune system?
- **A large prospective, randomized intervention study is needed!**



Linssen C et al, Intensive Care Med 2008; 34: 2202-2209

HSV: a marker of severity in bacterial ventilator associated pneumonia

- Prospective study: all patients with VAP (n= 177) in 14 months
- Bacterial VAP with HSV compared with those without HSV
- Results
  - HSV in 13.4% of patients with confirmed bacterial VAP
  - Outcome:

• Only a randomized trial evaluating a specific antiviral treatment could answer this question !!

- Conclusions:
  - A significant percentage of bacterial VAP patients shed HSV
  - HSV is a marker of severity
  - BUT the exact significance of HSV in the LRT of critically ill patients is still open for debate

Bouza E et al. J Critical Care 2010

Impact of HSV detection in respiratory specimens of patients with suspected viral pneumonia

- Between 2007 and 2009, all patients with suspected viral pneumonia tests for herpes viruses
- Case-control study: 51 HSV pos and 52 HSV neg patients
- Results:
  - Viral load> 10^5 geq/ml associated with:
    - Mechanical ventilation: 20/21 vs 17/29: $p = 0.004$
    - ARDS: 19/21 vs 18/29: $p = 0.005$
    - Sepsis: 18/21 vs 14/29: $p = 0.008$
    - Bacterial pathogen 19/21 vs 4/29: $p = 0.01$

• HSV-1 viral loads in respiratory symptoms are a symptom of a clinically poor condition rather than a cause of it !!
•Longitudinal and therapy studies are needed !!

  - Patients treated with acyclovir and those who were not treated

Scheithauser S et al., Infection 2010; 38: 401-405

HSV: What we do know...

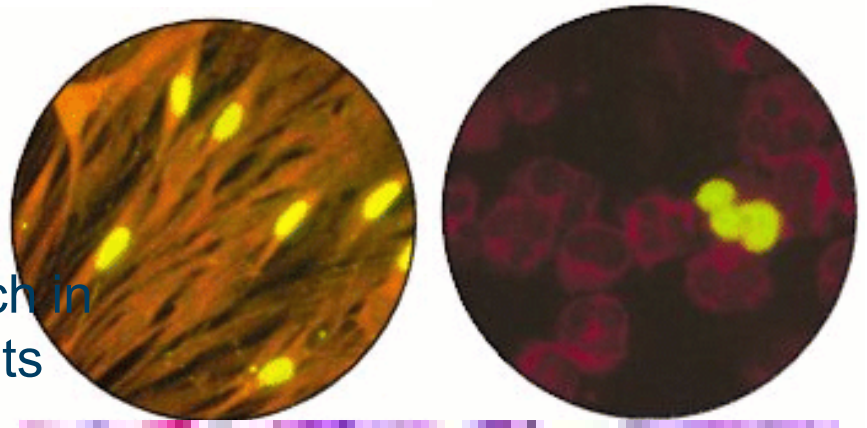
- Prevalence of HSV at ICU: between <10% to >50%.
- HSV in the throat is a significant and independant risk factor for the presence of HSV in the LRT: aspiration from the URT is most likely.
- HSV positive patients have impaired outcome (increased ICU and hospital lenght of stay) as compared to HSV negative patients, even after adjustment for disease severity.

HSV: What we do not know...

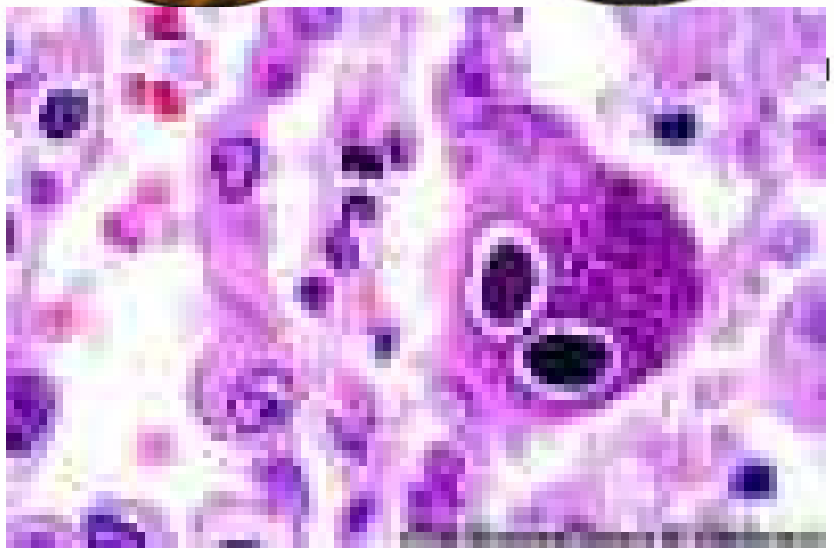
- The role of systematic ACV therapy in case of HSV isolation
  - Prevention of LRT infections with HSV?
  - Improve outcome in these patients?

CMV in non-immunosuppressed critically ill patients:pathogen or bystander?

- Incidence of CMV infection:
  - Well known in immunocompromised patients
  - Not part of routine diagnostic approach in non-immunocompromised ICU patients



- Origin of the virus in the LRT?
  - Endogenous reactivation
    - Reactivation in LRT?
    - Hematogenous spread?



- Pathogen or bystander?

CMV infection in the ICU in non-immunocompromised adults

- Systematic review of 13 studies:
  - 9 prospective cohorts
  - 4 retrospective studies
- Overall rate of active CMV infection in the non-immunocompromised ICU patients: 17%
  - varying between 1% and 36%
- Limitations:
  - Relatively small sample size
  - Inclusion of only selected ICU patients
  - Different diagnostic methods
  - Limited control for confounding factors

Kalil A Crit Care Med 2009, 37:2350-2358
Limaye et al Rev. Med. Virol. 2010; 20:372-379

How common is CMV infection in non-immunocompromised adults in the ICU?

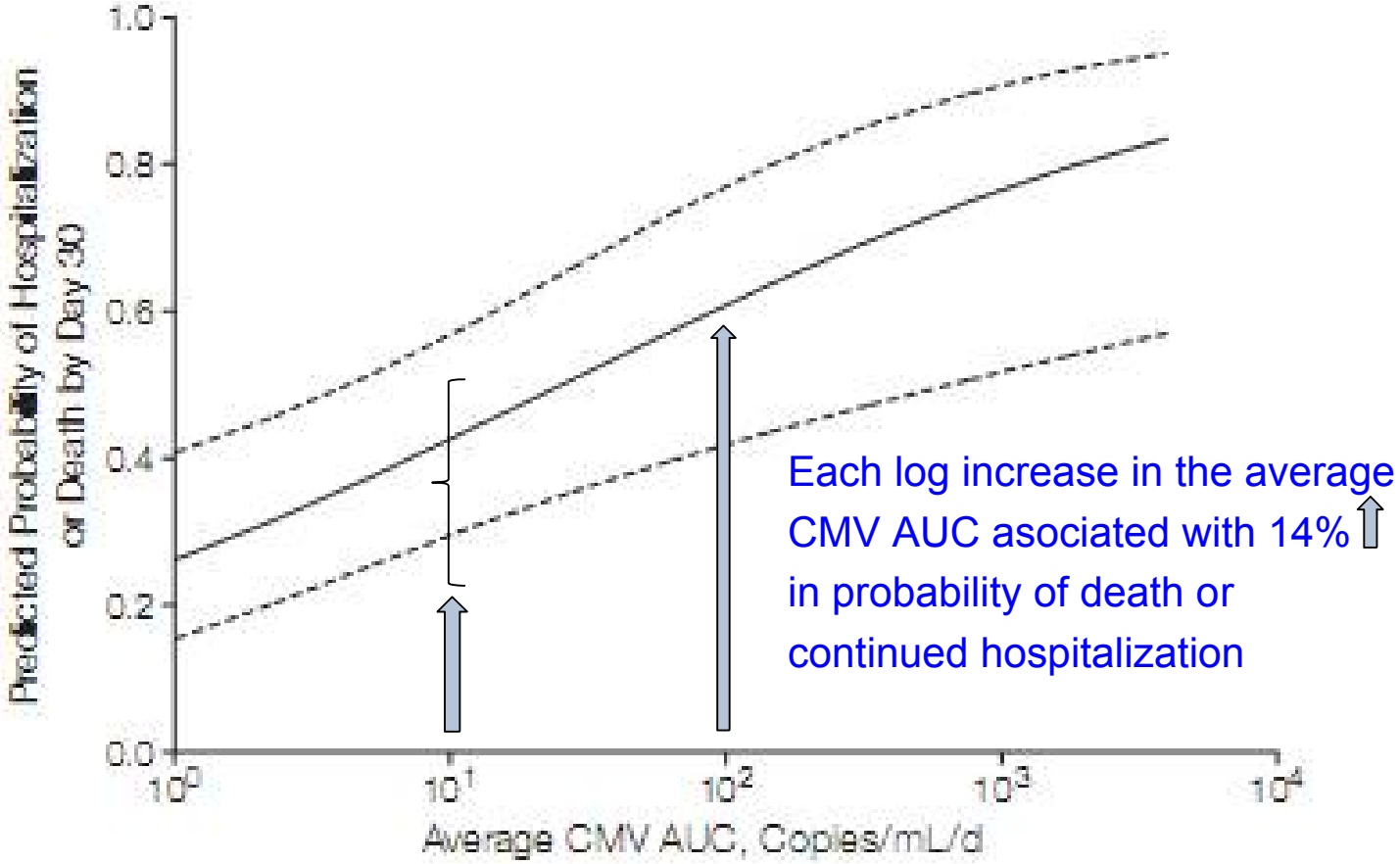
Refs.	Viral culture	Refs.	Viral DNA or antigen
Cook et al, 1998	12/142 (8.5%)	Razonable et al, 2002	1/120 (0.8%)
Papazian et al 1996	8/86 (9.3%)	Desachy et al, 2001	1/96 (1.0%)
Cook et al, 2003	10/104 (10%)	Stephan et al, 1996	1/24 (4.2%)
Domart et al, 1990	29/115 (25%)	Jaber et al, 2005	40/237 (17%)
		Von Muller et al, 2006	8/25 (32%)
		Kutza et al, 1998	11/34 (32%)
		Limaye et al, 2008	39/120 (33%)
		Ziemann et al, 2008	35/99 (35%)
		Heininger et al, 2001	20/56 (36%)
Pooled	**59/447 (13%)**	Pooled	**156/811 (19%)**

Kalil A Crit Care Med 2009, 37:2350-2358

Limaye AP Rev. Med. Virol. 2010; 20: 372-379

Monitoring CMV infection in ICU patients by quantitative PCR?

- 120 seropos CMV pts in 6 ICU's: 33% reactivation based on PCR in plasma
- Prolonged hospitalizaition & higher mortallity rate in CMV reactivators



Limaye A et al, JAMA 2008; 300: 413-422

Adverse clinical outcomes associated with CMV infection in non-immunocompromised

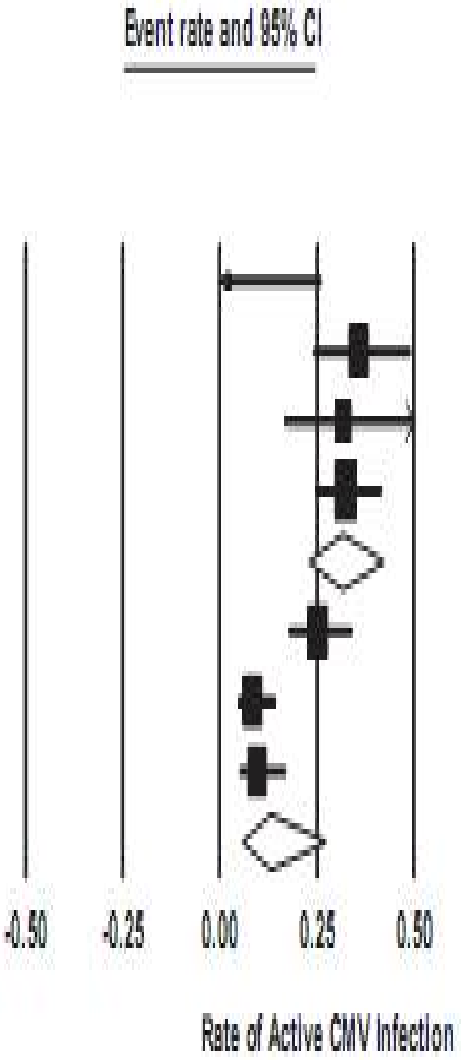
Adverse outcome	nr of studies
All-cause mortality	Investigated in 8/13 6/8 found association
Increased lenght of hospital and/or ICU stay	8/13 studies
Increased duration of mechanical ventilation	5/13 studies
Increased nosocomial infections	3/13 studies

Pooled data from 8 studies showed 75/192 deaths in Active CMV group vs 119/441 in pts with non active CMV infection (*P* = 0.001)

Limaye AP Rev. Med. Virol. 2010; 20: 372-379

Active CMV Infection Rate by Disease Severity

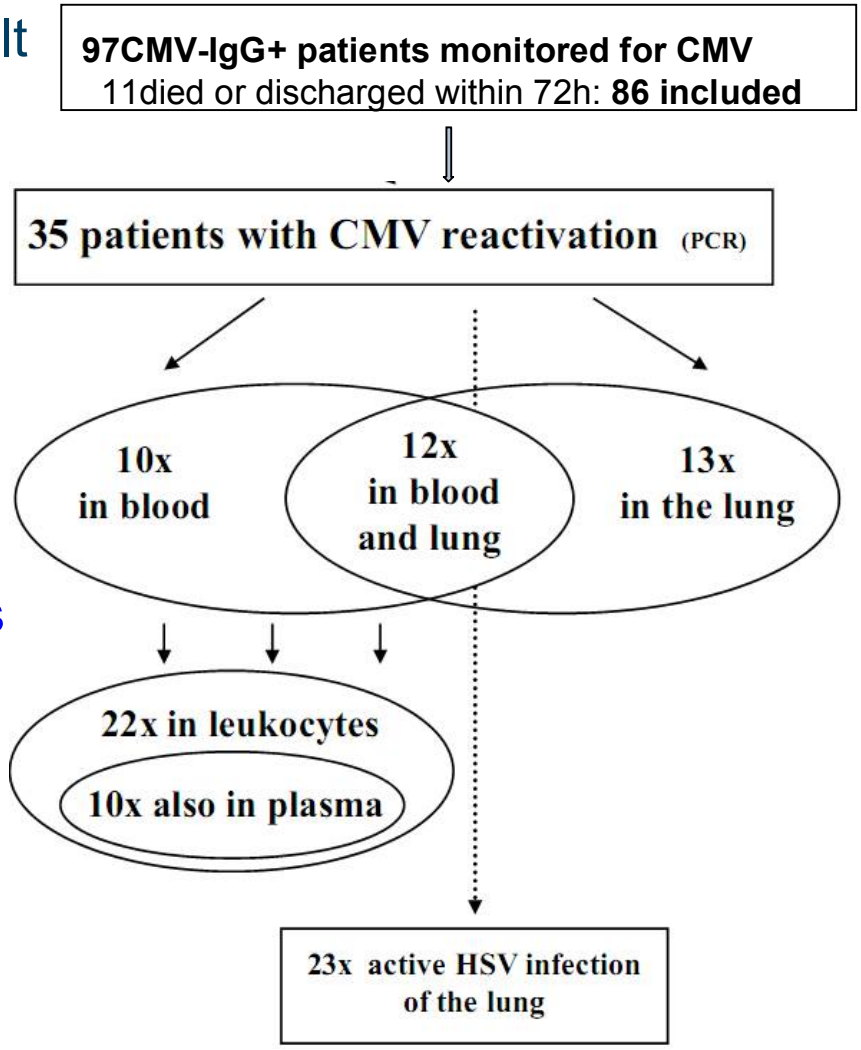
References	By Disease Severity	Total (%)
Stephan F 1996	High	1/24 (4.2%)
Heininger A 2001	High	20/56 (36%)
von Muller L 2006	High	8/25 (32%)
Limaye A 2008	High	39/120 (33%)
	High	**68/225 (31%)**
Domart Y 1990	Low	29/115 (25%)
Cook CH 1998	Low	12/142 (8.5%)
Cook C 2003	Low	10/104 (10%)
	Low	**51/361 (15%)**



*High Severity: APACHE II>20, SAPS>40, SOFA>10. Z=6.26; P<0.0001; Q=11; I2=85%

CMV reactivation and outcome of critically ill patients with severe sepsis

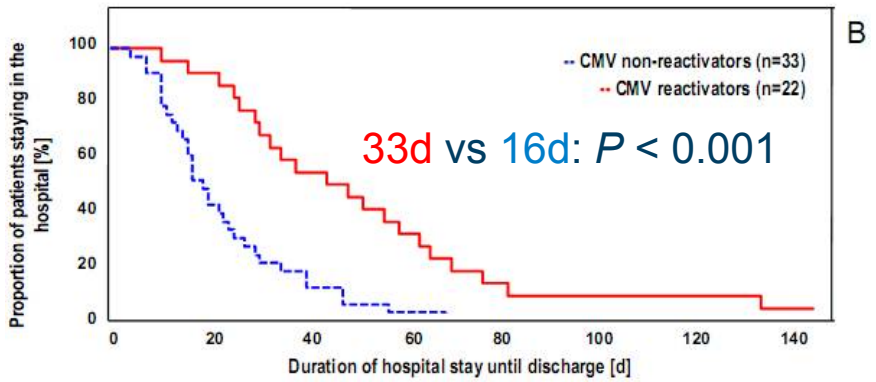
- Prospective longitudinal study in 97 adult CMV+ pts with new onset of sepsis
- Leucocytes, plasma and tracheal secretions examined weekly for CMV, tracheal secretions also for HSV
- CMV occured in 35/86 (40.7%)
  - 13/35 cases exclusively in the lungs
- Median CMV reactivation after 21 days
- Also HSV reactivation:
  - More in patients with CMV reactivation



Heininger A et al, Crit Care 2011; 15: R77 e-pub ahead of print

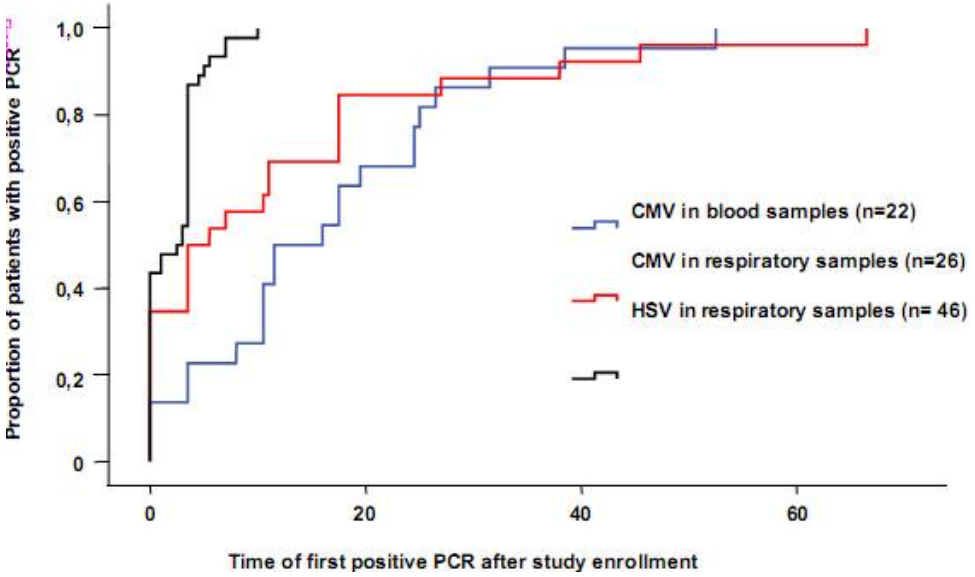
CMV reactivation and outcome of critically ill patients with severe sepsis

- Increased morbidity
  - LOS in ICU
  - Hospital stay
  - Mechanical ventilation



- CMV reactivation: obvious earlier in tracheal secretions than in blood
- HSV even more frequently and earlier than CMV
- NS difference in mortality
  - 37.1% vs 35.3%: *P* = 0.86
- Even when adjusted for
  - Severity of illness
  - Presence of septic shock
  - HSV reactivation

➡ **No ⇧ in hospital mortality**



Heininger A et al, Crit Care 2011; 15: R77 e-pub ahead of print

Important factors influencing the rate of CMV infection

- Sensitivity of diagnostic methods used:
  - Viral culture
  - CMV antigenemia or PCR
- Time of screening for CMV after admission to ICU
  - 21% if > 5 days vs 1% if < 5 days
- Type of patients included
  - Medical vs surgical ICU patients
- Baseline CMV serostatus
  - Higher rates if only seropositive patients are included
- Reactivation in blood and/or in the lung
  - earlier, more frequently, higher levels in lung?
- Disease severity
  - 32% in APACHE ≥ 20 vs 13% in low severity

Kalil A Crit Care Med 2009, 37:2350-2358
Limaye AP Rev. Med. Virol. 2010; 20:372-379

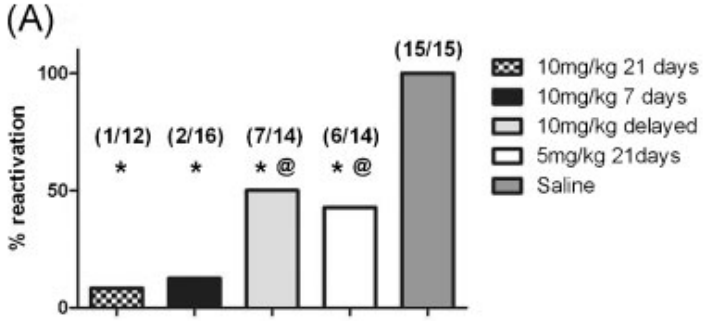
Adverse clinical outcomes with CMV: biologically plausible mechanisms?

- Direct CMV-mediated lung injury (i.e. CMV pneumonia)
  - CMV detected histopathology in 30% biopsies in 3 studies
- dysregulated inflammation in ALI/ ARDS patients
  - Upregulation of key cytokines IL-6, IL-8
- Immunomodulatory properties
  - Increased rate of bacterial, fungal or other nosocomial infection
- severe septic patients:
  - Can develop immunoparalysis or compensatory anti-inflamatory response syndrome
  - Bacterial sepsis itself can reactivate latent CMV infection through endotoxin release by bacteria

Kalil A Crit Care Med 2009, 37:2350-2358
Limaye AP Rev. Med. Virol. 2010; 20:372-379

Next steps to further define relationship CMV & adverse outcome in ICU patients?

- Controlled trial of CMV prevention in ICU
- Most appropriate study population:
  - CMV seropositive patients with
  - either sepsis or pneumonia associated ALI/ARDS
- Two major approaches:
  - Antiviral prohylaxis
  - Preemptive therapy



- Emerging data in a murine model:
  - In sepsis-induced CMV reactivation suggest significantly better effect with early (prophylactic) Tx with ⇧ dose ganciclovir
  - but likely higher risk for toxicity, cost and potential for R

Limaye AP Rev. Med. Virol. 2010; 20: 372-379

Should HSV and CMV in non-immunocompromised ICU patients be considered in a different way?

- **Histological data**
  - Open-lung biopsies in ARDS patients: more histologic findings compatible with CMV disease, only a few with HSV pneumonia
  - Recent study: also HSV bronchopneumonitis but BAL and biopsy only positive in limited nr of patients

- **Clinical outcome data**
  - CMV: +/- always associated with⇧ duration of both mechanical ventilation and ICU stay, sometimes⇧ mortality rate
  - Most HSV studies also associated with longer mechanical ventilation and hospital stays, less impact on mortality (??)

Chiche L et al., Curr Opin Infect Dis 2011; 24: 152-156

Should HSV and CMV in non-immunocompromised ICU patients be considered in a different way?

- **Physiopathologic data**
  - For CMV lung is considered as the main site of latency and reactivation
  - HSV: viral reactivation in the oropharynx and lower respiratory tract involvement by aspiration

- **Therapeutic data**
  - No trials done for CMV; in a murine model, prophylaxis with ganciclovir prevented postseptic CMV reactivation
  - Only one prospective double-blind randomized prophylactic acyclovir study in ARDS patients: prevention of HSV reactivation but no improvement of respiratory failure, duration of ventilator support or mortality

Chiche L et al., Curr Opin Infect Dis 2011; 24: 152-156

Herpes virus reactivation in the ICU: Conclusions

- Both HSV and CMV occur in 0 to > 30% of critically ill patients at ICU and may be associated with poor outcome.
- HSV in the throat is a significant and independant risk factor for the presence of HSV in the LRT: aspiration from the URT is most likely; CMV occurs especially in sepsis patients.
- Further studies are needed to identify subsets of patients who are at risk of developing HSV and/or CMV infections.
- The “bystander or pathogen” debate concerns both HSV and CMV: definitive proof of causality demonstrating CMV and /or HSV as pathogens awaits controlled clinical trials with specific antiviral therapies.