



HSV et poumon

Jean-François Timsit
Université Joseph Fourier,
Grenoble
France

Herpesviridae

| Virus Humain | Nom commun | Sous-famille |
|-----------------------|-------------------------|--------------|
| Human herpesvirus 1 | Herpes simplex virus 1 | alpha |
| Human herpesvirus 2 | Herpes simplex virus 2 | alpha |
| Human herpesvirus 3 | Varicelle zona | alpha |
| Human herpesvirus 4 | Virus Ebstein-Barr | gamma |
| Human herpesvirus 5 | Cytomégalovirus | beta |
| Human herpesvirus 6/7 | Exanthème subit | beta |
| Human herpesvirus 8 | Kaposi's-sarcoma assoc. | gamma |

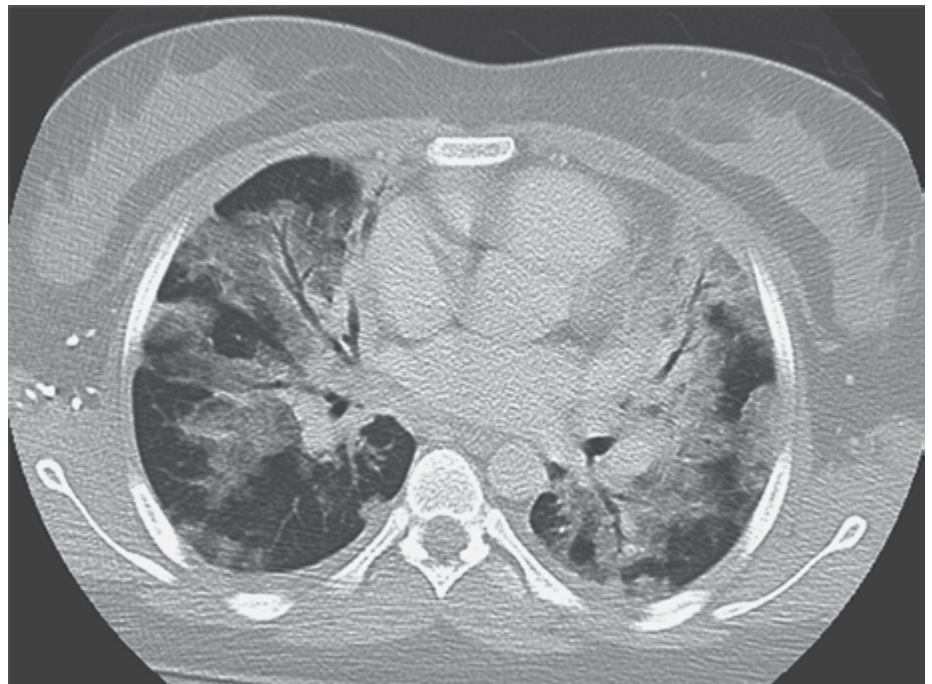
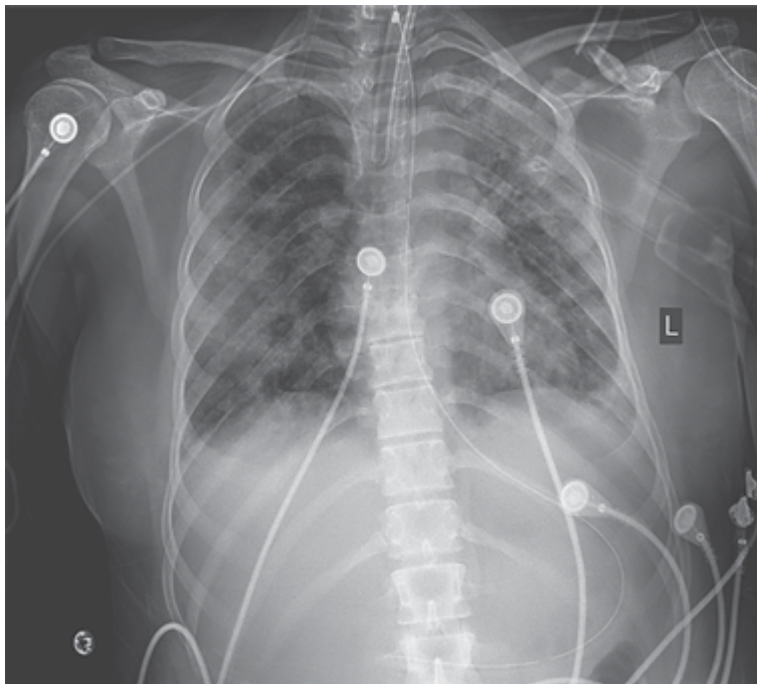
Physiopathologie

- Primo-infection (enfance)
- Latence: génome viral dans les gg trigéminés.
- Réactivation en cas d'immunodépression locale
- Passage par voie neuronale → lésions épithéliales (herpes labial, gingivostomatites)
- Développement d'anticorps +- protecteur
- Primo-infections parfois sévères

Case 12-2013:

An 18-Year-Old Woman with Pulmonary Infiltrates and Respiratory Failure *Daniel P. Hunt, M.D., Victorine V. Muse, M.D., and Martha B. Pitman, M.D.*

- T°: 39,4°C, Toux, crachats blanchâtre
- Wheezing+++
- Anorexie, diarrhée, vomissement -> echec macrolides puis beta-lactamines
- J15-21: Aggravation, SDRA, lésion crouteuse de la lèvre



Case 12-2013:

An 18-Year-Old Woman with Pulmonary Infiltrates and Respiratory Failure *Daniel*

P. Hunt, M.D., Victorine V. Muse, M.D., and Martha B. Pitman, M.D.

LBA : bronches inflammatoires

321 000 cel. (51% PNN,
18% lymphocytes, 16% monocytes, et
15% macrophages

→

- Extubée apres 2 jours d'aciclovir → tt de
15 jours

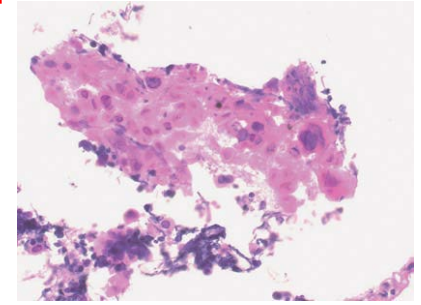
- Syndrome Guillain Barré

PL: Pt 2,2g, <5 EB/mm³

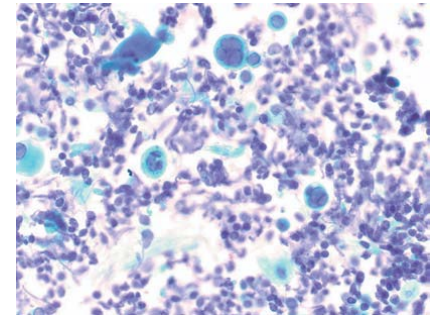
EMG: Polyneuropathie démyélinisante

Ig IV 5 jours

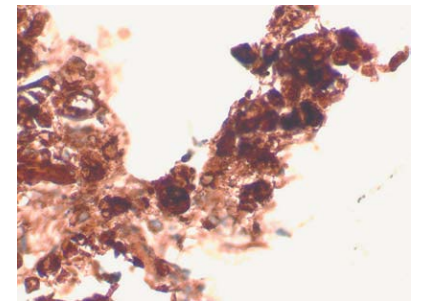
- Récupération progressive sans séquelles



Effet cytopathogene



Cellules de Tzanck



Marquage + pour HSV

Agenda

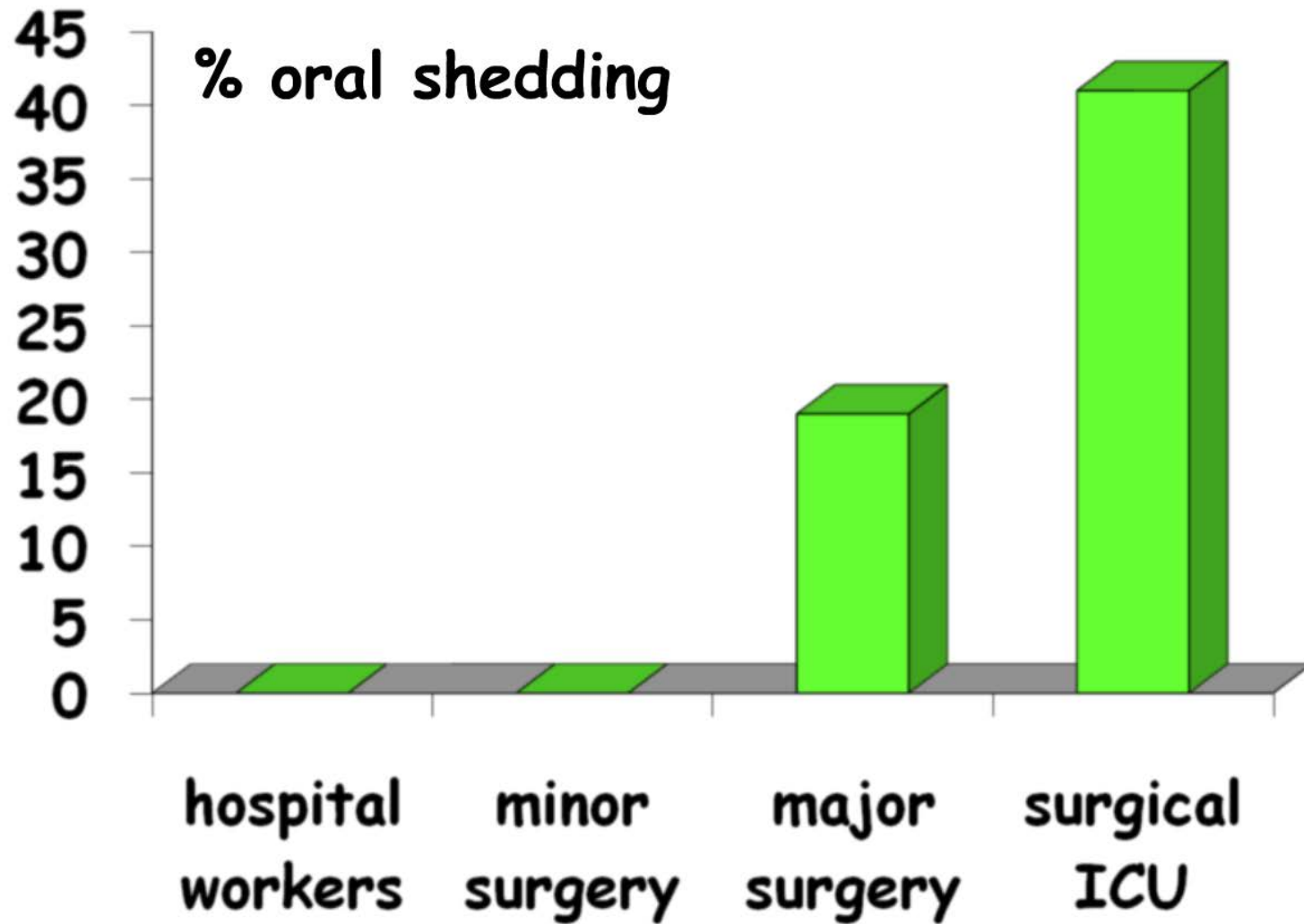
En dehors des primo-infections et de l'immunodéprimé....

- Le patient agressé est-t-il immunodéprimé?
- Prévalence de la réactivation ORL et relation avec une symptomatologie clinique
- Prévalence de la réactivation pulmonaire et relation avec des symptômes cliniques
- HSV et pronostic des patients agressés
- Chez qui traiter?

L'immunoparalysie

- De plus en plus de patients avec une immunodépression thérapeutique
 - Corticoïdes, immunosuppresseurs....
- En plus:
 - Diminution profonde des cellules dendritiques chez les patients en choc septiques
Grimaldi et al – ICM 2011
 - Diminution de l'activité cytotoxique NK et de la production IF gamma apres stimulation
Forel et al – Plos One 2012
 - Apoptose des Cellules lymphocytaires T et B chez tous les malades agressés et en particuliers les chocs septiques
Letulzo et al – Shock 2002, Boomer Jama 2011
 - Augmentation relative des T regs *Venet F et al – CCM 2004*
 - Augmentation de l'IL10 et augmentation paradoxale de l'IL15
Chiche L et al – CCM 2012
 - Expression de molécules inhibitrices dans le poumon des malades septiques (HerpesVirusEntryMediator...)
Boomer et al JAMA 2011

HSV



Réactivation oropharyngée de l'HSV en réanimation

1. 764 patients

22% avaient une réactivation HSV

Bruynseels et al - Lancet 2003

2. 201 patients ventilés depuis au moins 5 jours

54% avaient une réactivation HSV

Luyt et al - AJRCCM 2007

3. 60 patients avec un SDRA

26 % avaient une réactivation HSV à l'inclusion

57% en tout au cours du séjour

Bonadona et al - ICAAC 2005

Herpes cutané

48/201 (24%) des patients ventilés plus de 5 jours

Vésicules labiales n=29
Gingivostomatites n=19



Réactivation HSV dans les voies aériennes distales

- 764 patients en réa, 361 testés pour HSV dans le poumon
 - Bruynseels et al., Lancet 2003
- 201 patients ventilés depuis ≥ 5 j et suspects d'avoir développé une PAVM
- HSV retrouvé dans le poumon de 129 (64%)
 - Luyt et al. AJRCCM 2007



→ Eligible patients:

- ARDS or ALI with expected duration of MV > 48h
- No antiviral treatment
- Informed consent

BAL

- d0
- weekly (d7, d14,...)
 - viral cultures
 - quantitative PCR

Oropharyngeal swabs

- d0
- twice a week (d2, d5, d7, d10, d14,..)
 - viral cultures
 - quantitative PCR

Blood samples

- d0
- twice a week (d2, d5, d7, d10, d14,..)
 - quantitative PCR

→ antiviral treatment if BAL or blood positive for HSV

→ Follow up 90 days

→ Data Monitoring committee: clinical impact assessment

Flow chart and patients' characteristics

January 2002-August 2004

90 ARDS/ALI

53 enrolled
ARDS/ALI

Informed consent impossible or
refused: 9
Antiviral: 9
< 48 hours: 15
Inclusion missed: 4

| | N=53 ARDS/ALI |
|--|---------------|
| Age | 58 ± 12 |
| SAPS II | 52 ± 16 |
| PaO ₂ /FiO ₂ ratio | 106 ± 39 mmHg |
| Sex (M/F) | 36/17 |
| COPD | 11 (21%) |
| Diabetes | 11 (21%) |
| Immunocompromized | 18 (34%) |
| Cirrhosis | 6 (12%) |
| D 90 death | 24 (45.3%) |

Virologic results at time of inclusion (d0)

- HSV IgG antibodies (+): 75.4%

| HSV prevalence <i>Samples</i> | Total (%) | Cultures (%) | PCR (%) | Mean viral load (copies/ml) |
|----------------------------------|-------------------|------------------|--------------------|---|
| Throat | 13/50 (26) | 8/50 (16) | 12/48 (25) | 4.10⁷ [150 - 3.10 ⁸] |
| Blood | 2/52 (3.8) | – | 2/52 (3.8) | 3.10³ [150 - 7.10 ³] |
| BAL | 8/50 (16) | 1/50 (2) | 7/48 (14.6) | 7.10⁴ [100 -5.10 ⁵] |

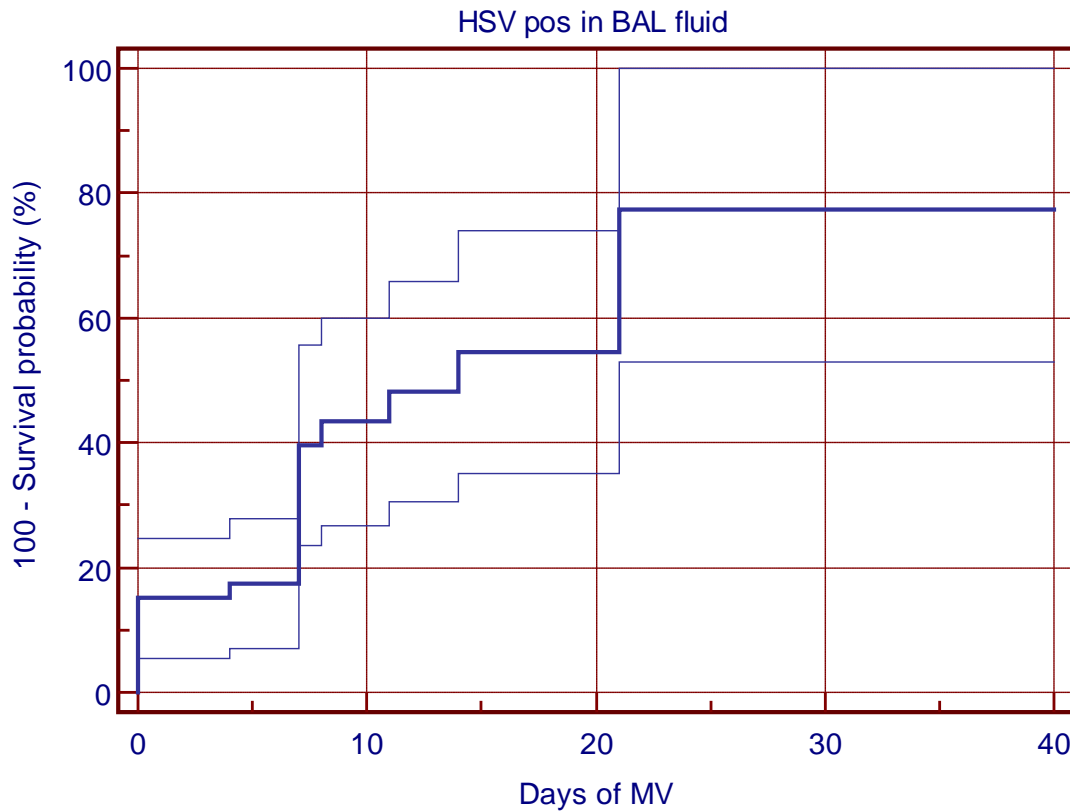
Overall, 42% patients were HSV+ in BAL

| Samples | HSV Prevalence (%) | Time to HSV reactivation (mean \pm SD) |
|---------|--------------------|--|
| Throat | 28/53 (52.8) | 4 \pm 5d |
| Blood | 22/53 (41.5) | 7 \pm 5d |
| BAL | 22/53 (42.3) | 8 \pm 7d |

- HSV₁ reactivation in all cases
- bronchoscopic findings compatible with ulcerative tracheobronchitis (1 case)

Patients with BAL HSV+: 22/53 Pts

- 12/22 patients were co-infected

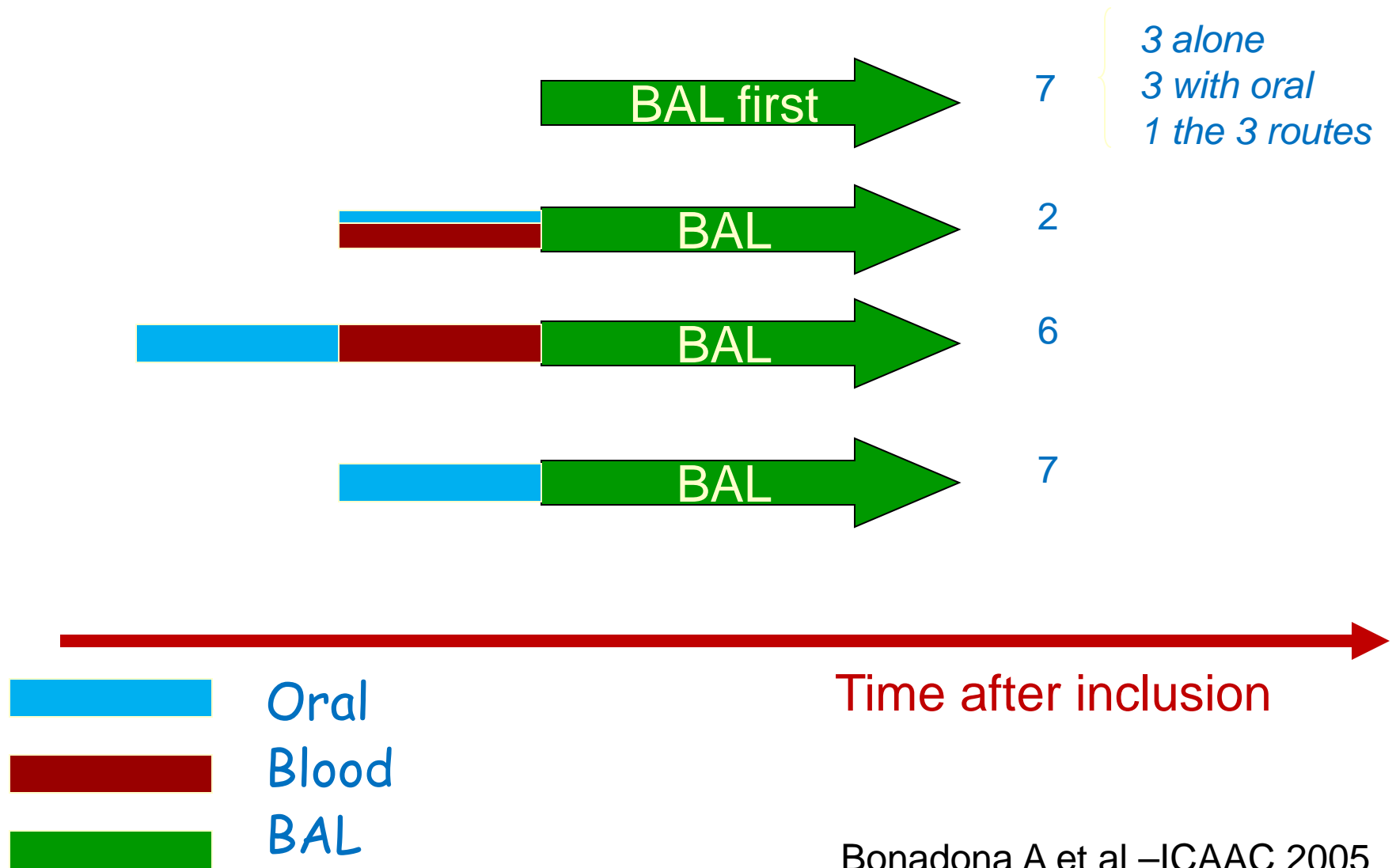


Kaplan Meier
estimate of BAL HSV
detection:

At 7 days: 39.6%
(95% CI 22.6-56.6%)

At 14 days: 54.6%
(95% CI 25.1-74.2%)

HSV route of BAL + patients



3 alone
3 with oral
1 the 3 routes

Microsatellite analysis of HSV-1 isolates: from oropharynx reactivation toward lung infection in patients undergoing mechanical ventilation.

64 patients who had multiple samples

- Oropharynx
- BAL

HSV-1 isolates from the lung genetically indistinguishable from strains isolated from the oral cavity

Also true when the microsatellite haplotypes of serial isolates were examined

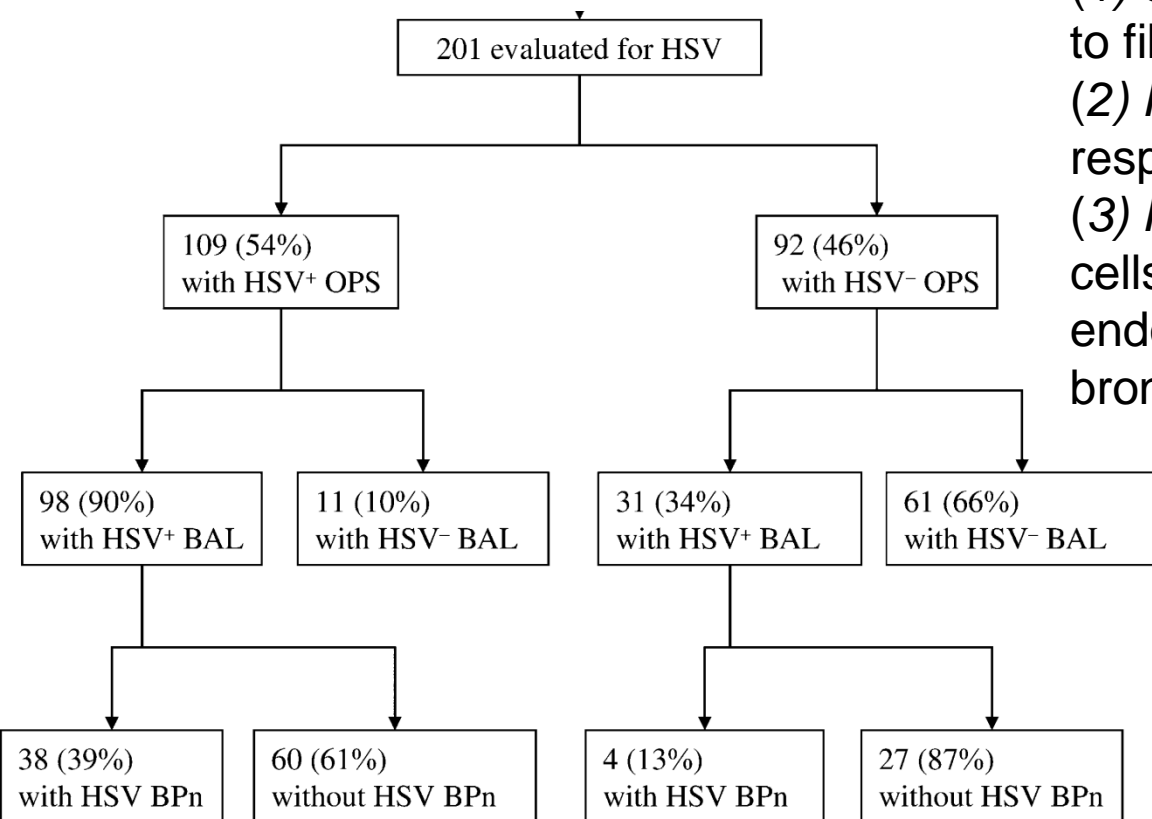
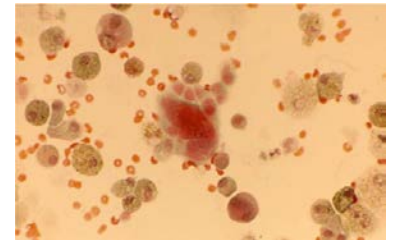
Isolation of HSV-1 in BAL always associated with or preceded by the isolation of HSV-1 from the oral cavity

Lack of evidence for a close genetic relationship among the different HSV-1 strains (no nosocomial transmission)

HSV in the lung

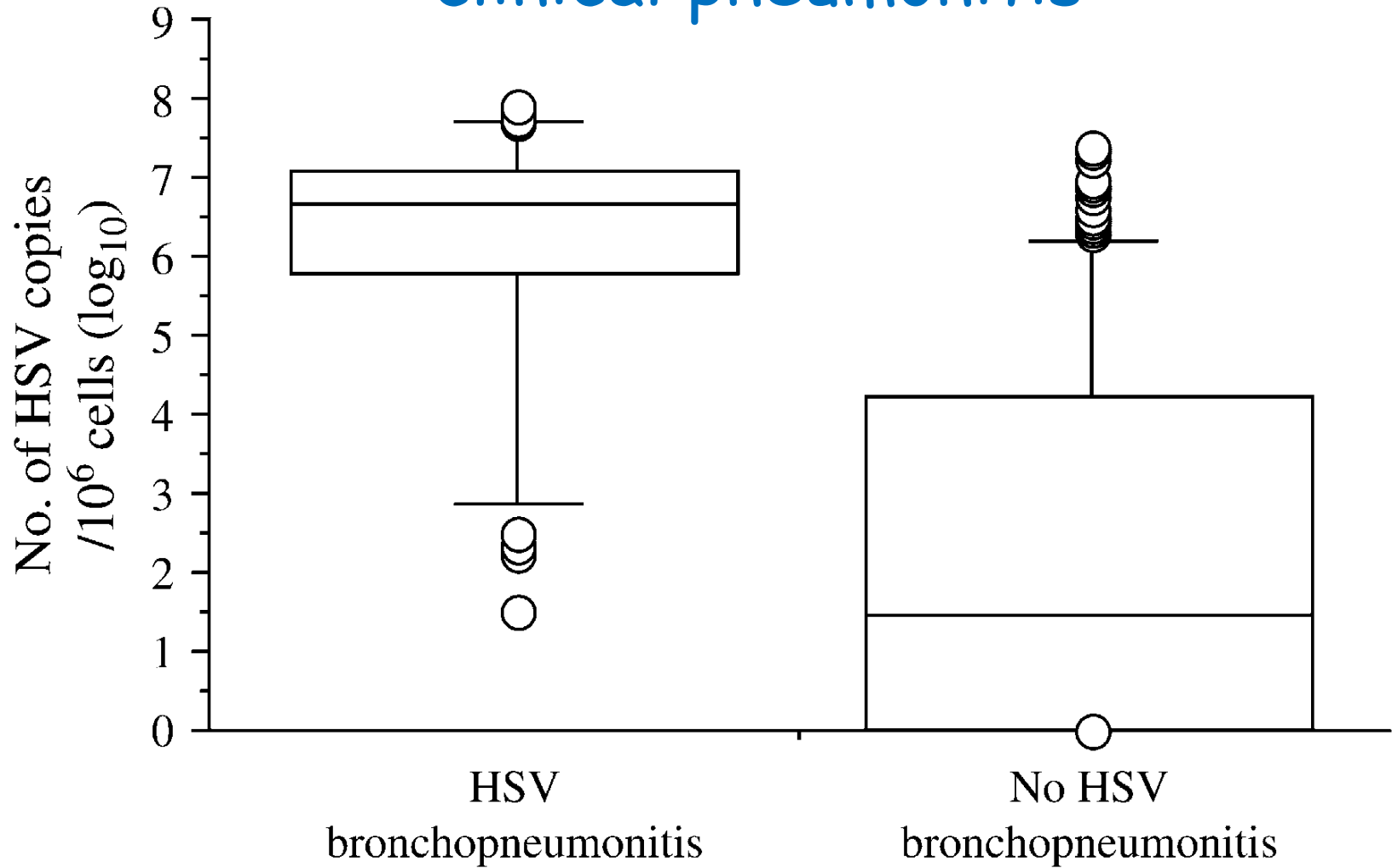
HSV Bpn: (1+2+3)

(1) *clinical deterioration, having led to fiberoptic bronchoscopy with BAL;*
(2) *HSV detection in the lower respiratory tract (PCR and/or culture);*
(3) *HSV-specific nuclear inclusions in cells collected during BAL, endotracheal aspiration, and/ or bronchial biopsy.*



→ 42/129 = 33%

HSV viral load is associated with clinical pneumonitis



Colonization or infection (IDMC)

In 5 cases the IDMC considered that VAP was probable:

- worsening clinical and radiological conditions
- HSV only pathogen isolated in BAL
- Improvement with antiviral therapy, without antibiotic change

| | Pneumonia n=5/22 (22.7%) | Colonization n=17/22 (77.3%) | p |
|---------------------------|------------------------------------|--|--------------|
| Maximal viral load | | | |
| Median | 6.8x10⁵ | 72 | 0.01* |
| [range] | [300-4.10 ⁶] | [1-2.10 ⁶] | |

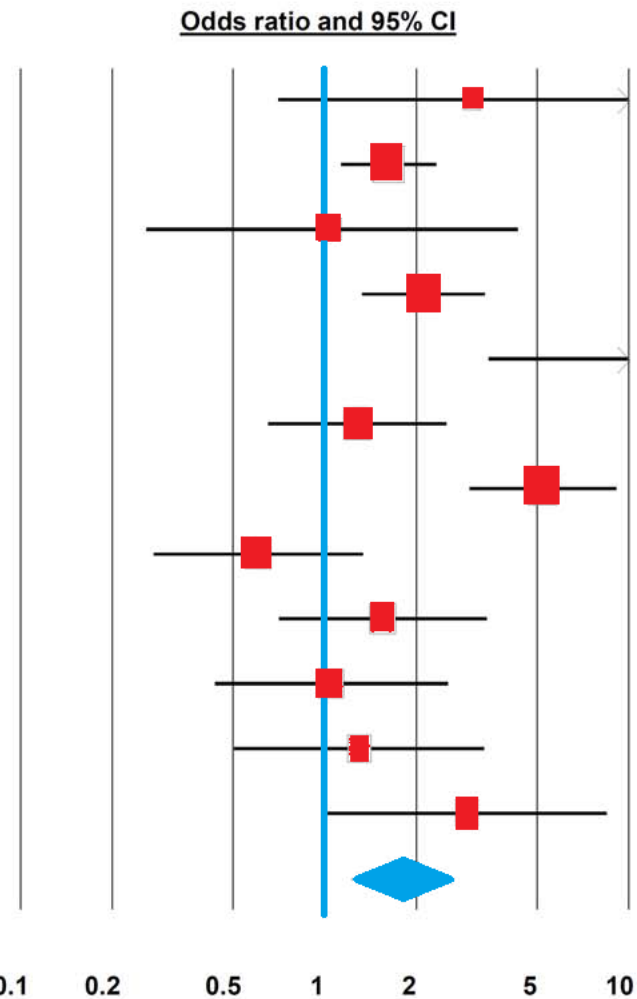
Role of HSV as a pathogen or co-pathogen for bacterias?

* Mann-Whitney test

HSV Effect on the Prognosis of Mechanically Ventilated Patients Suspected to Have Ventilator-Associated Pneumonia

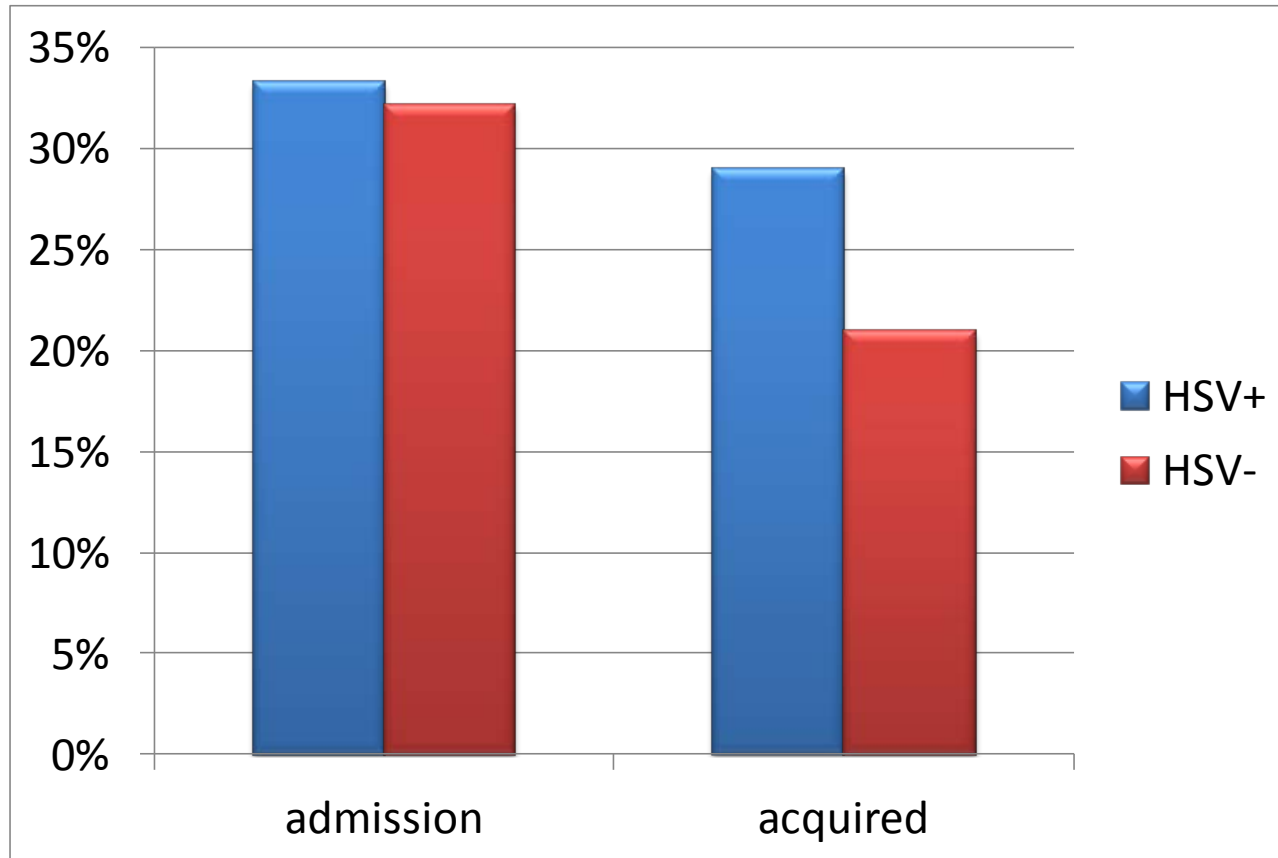
| Studies | Odds ratio | Lower limit | Upper limit | Z-value | P-value | Number of patients | |
|--------------------|--------------|--------------|--------------|--------------|--------------|--------------------|---------|
| | | | | | | HSV pos | HSV neg |
| Cook 1998 | 3.062 | 0.698 | 13.435 | 1.483 | 0.138 | 5/8 | 43/122 |
| Bruynseels 2003 | 1.622 | 1.125 | 2.338 | 2.590 | 0.010 | 59/180 | 135/584 |
| Cook 2003 | 1.057 | 0.257 | 4.343 | 0.077 | 0.939 | 3/11 | 22/84 |
| Ong 2004 | 2.116 | 1.320 | 3.393 | 3.111 | 0.002 | 43/106 | 70/287 |
| Engelmann 2007 | 66.176 | 3.436 | 1274.460 | 2.778 | 0.005 | 7/7 | 8/45 |
| Luyt 2007 | 1.281 | 0.647 | 2.536 | 0.711 | 0.477 | 20/42 | 66/159 |
| Linssen 2008 | 5.221 | 2.969 | 9.181 | 5.739 | 0.000 | 50/82 | 41/178 |
| De Vos 2009 | 0.605 | 0.271 | 1.350 | -1.227 | 0.220 | 23/65 | 19/40 |
| Scheithauer 2010 | 1.552 | 0.701 | 3.433 | 1.084 | 0.278 | 23/51 | 18/52 |
| Smith 2010 | 1.053 | 0.433 | 2.559 | 0.113 | 0.910 | 9/27 | 38/118 |
| Bouza 2011 | 1.299 | 0.500 | 3.374 | 0.537 | 0.591 | 10/19 | 71/154 |
| Coisel 2012 | 2.933 | 1.009 | 8.528 | 1.976 | 0.048 | 11/26 | 9/45 |
| All studies | 1.794 | 1.216 | 2.649 | 2.943 | 0.003 | | |

Z = 5.89 P = 0.0001 Q = 31.99 I² = 65.6%

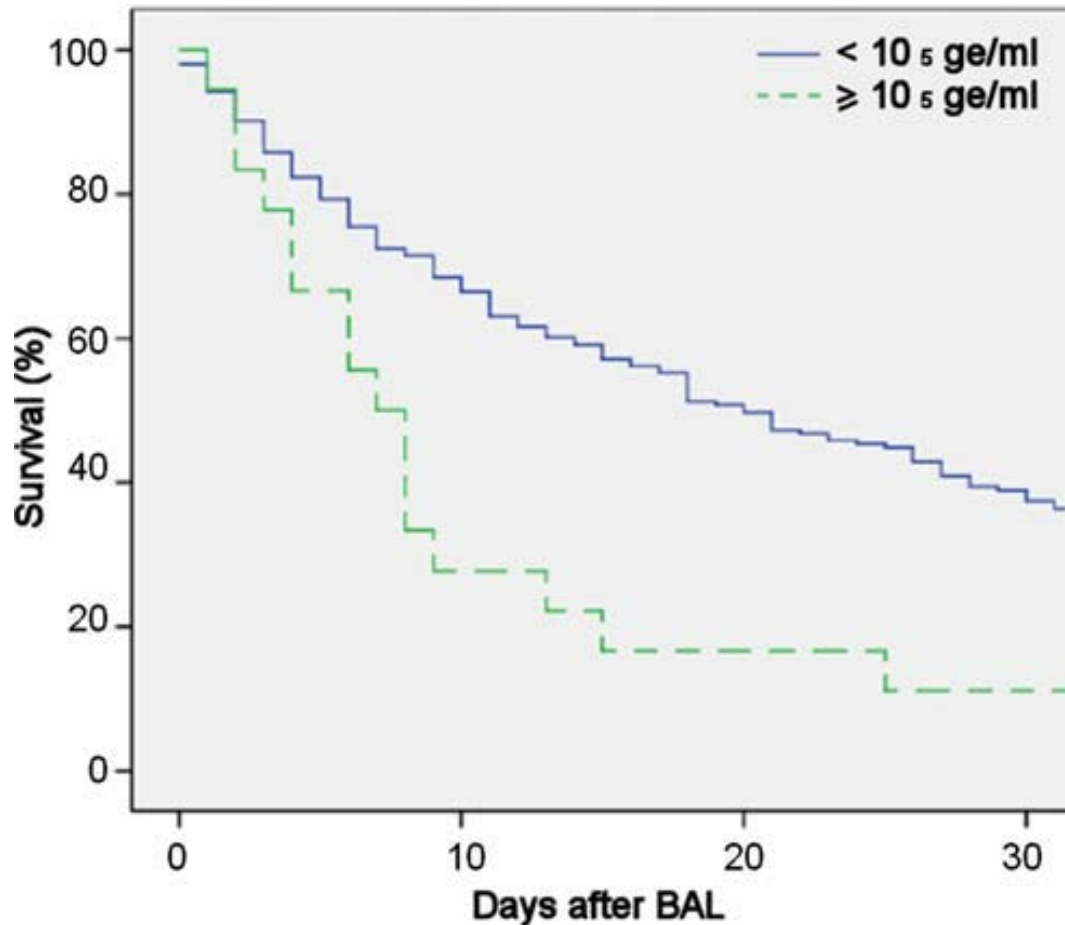


ICU mortality according to HSV status at admission or during the ICU stay

HSV PCR 3 times weekly in MV patients (tracheal aspirates)

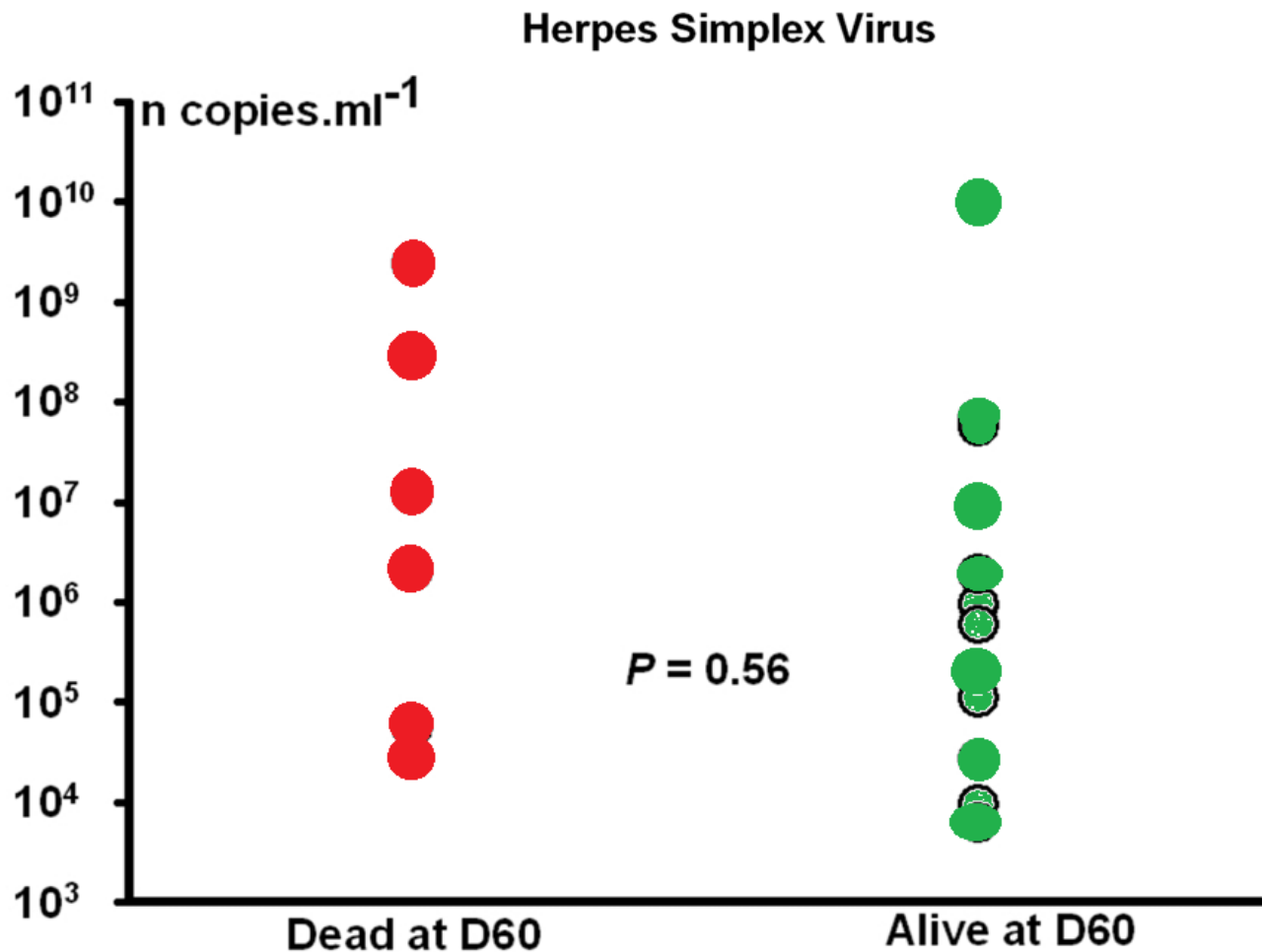


HSV viral load is associated with ICU death

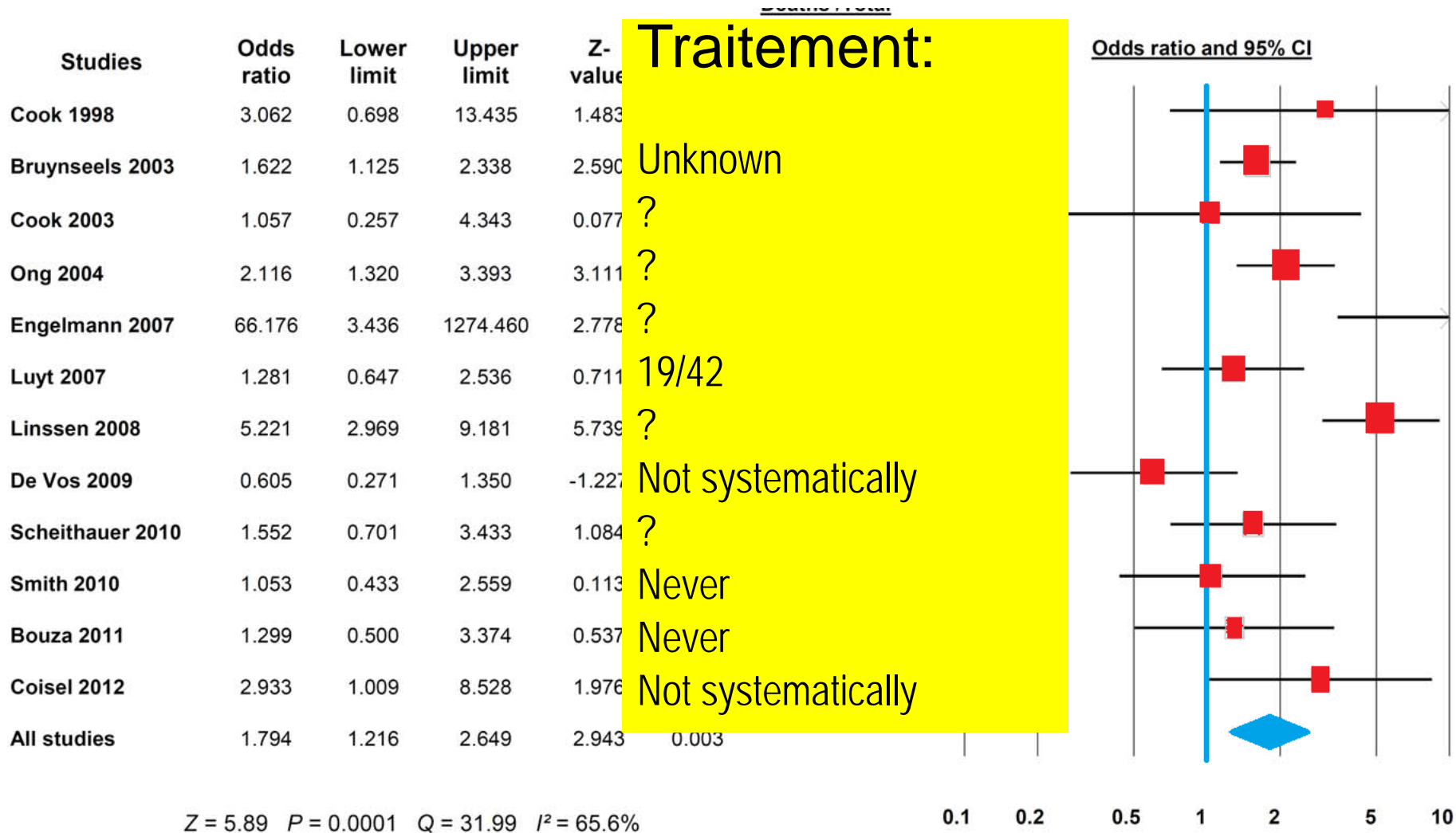


14 DC if $> 10^5$ copies
5 autopsies
5/5 pneumonia
2/5 viral inclusions

HSV Effect on the Prognosis of Mechanically Ventilated Patients Suspected to Have Ventilator-Associated Pneumonia



HSV Effect on the Prognosis of Mechanically Ventilated Patients Suspected to Have Ventilator-Associated Pneumonia



Multivariate Prognostic model

HSV BAL + was not associated with d90 mortality*..

D90 death: HSV+: 40.9% vs HSV-: 40%

- First step: age , sex, SAPS II, APACHE II, multiple organ failure, immunodepression, cirrhosis, NYHA IV...*
- *HSV in BAL was forced in the final model as a time-dependent covariate*

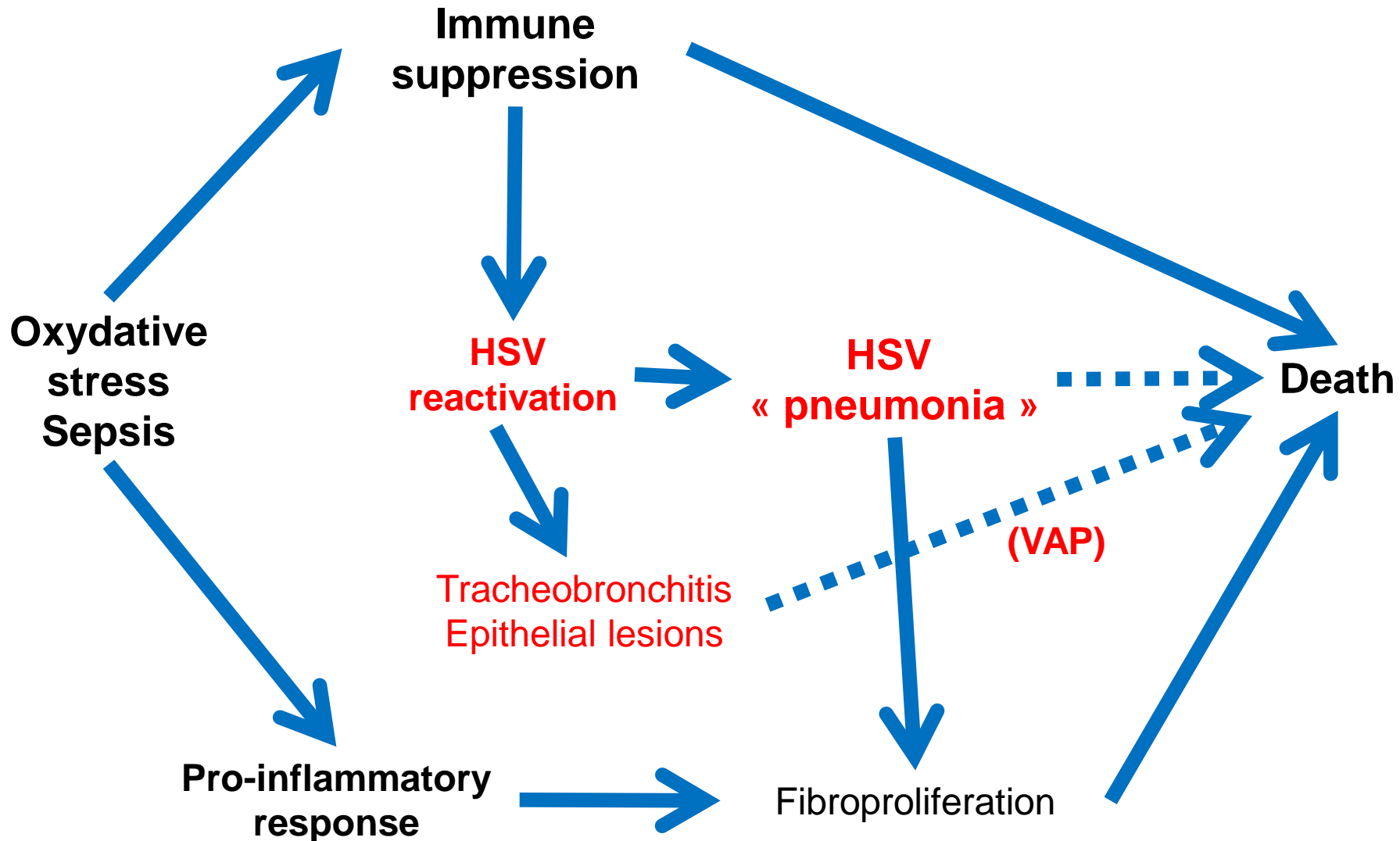
| | Hazard ratio (95% CI) | P value |
|----------------------------|--------------------------|-------------------|
| SAPS II (per point) | 1.06 (1.03-1.1) | <0.0001 |
| BAL HSV+ | 0.68 (0.27- 1.72) | 0.41 |

()...Patients were systematically treated with antiviral drugs*

Potentiel pathogènes de HSV chez l'immunocompétent patients?

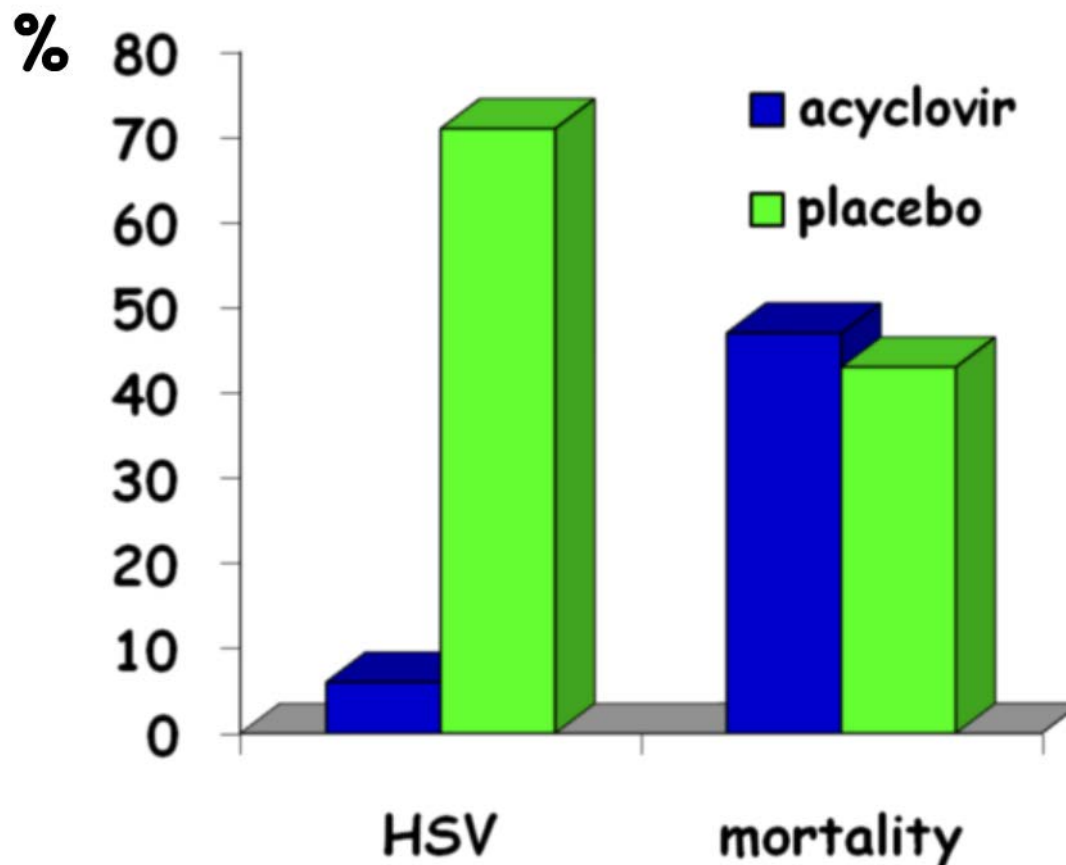
- Agression directe (pneumonie à HSV)
- Agression indirecte
 - HSV pourrait aggraver ou prolonger l'inflammation (SDRA)
 - Uprégulation des cytokines pro-inflammatoires (IL6, IL8) et d'autres médiateurs de l'inflammation
 - Co pathogène
 - Augmentation du risque d'infection bactérienne pulmonaire

HSV a respiratory pathogen, a passenger or more complex interactions...?



Prophylactic treatment of ARDS patients

- ARDS patients n=45



Conclusion: HSV

- Pathogénie connue chez l'immunodéprimés et de rares primo-infections de l'immunocompétent
- Fréquente réactivation post agressive
 - Pathogénie?
 - Direct
 - Indirect (copathogène ou lésions épithéliales)
 - Reflet du statut immunitaire défaillant
 - Traitement
 - PCR isolé → Non
 - Gingivostomatite-tracheobronchite → Oui
 - PCR haut niveau → Oui?

→ Nécessité d'un essai randomisé

Design (PTH PHRC 2011 Pr Papazian)

