

PAVM virales: mythe ou réalité?

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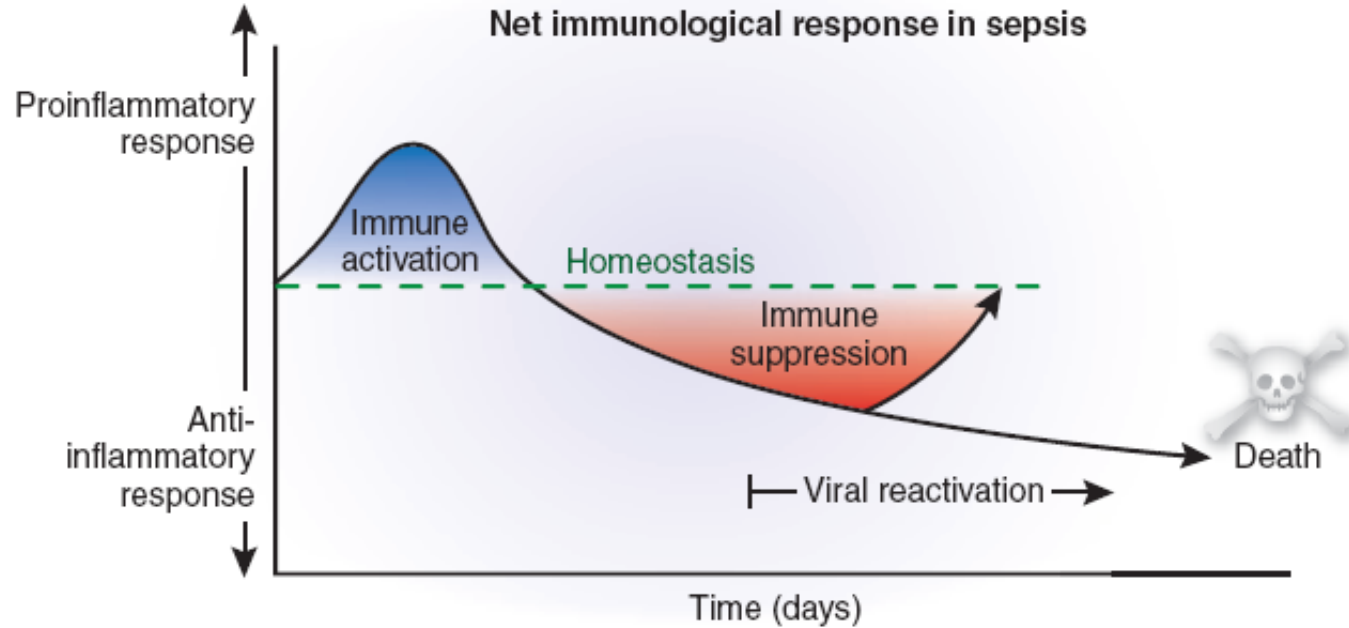
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Conflits d'intérêts

- MSD
- Aerogen
- AdvanzPharma

Tilting toward immunosuppression

Richard S Hotchkiss, Craig M Coopersmith, Jonathan E McDunn & Thomas A Ferguson



VOLUME 15 | NUMBER 5 | MAY 2009 **NATURE MEDICINE**

EST-CE QUE LA MALADIE EXISTE?

Réactivation HSV

	Population	HSV gorge	HSV poumon
Bruynseels 2003	764 malades, 361 sous VM	169 (22%)	361 (19%)
Ong 2004	393 malades sous VM	106 (27%)	
Luyt 2007	201 malades, VM >4 j, suspects PAVM	109 (54%)	129 (64%)
Linssen 2008	260 malades sous VM	—	99 (32%)
Costa 2012	127 malades suspects de PAVM		38 (31%)

Lésions cutanéomuqueuses



- Détectées chez 48/201 (24%) des patients ventilés ≥ 5 jours
 - Vésicules labiales dans 29 cas
 - Gingivostomatite dans 19 cas (HSV détecté dans les lésions dans tous les cas)

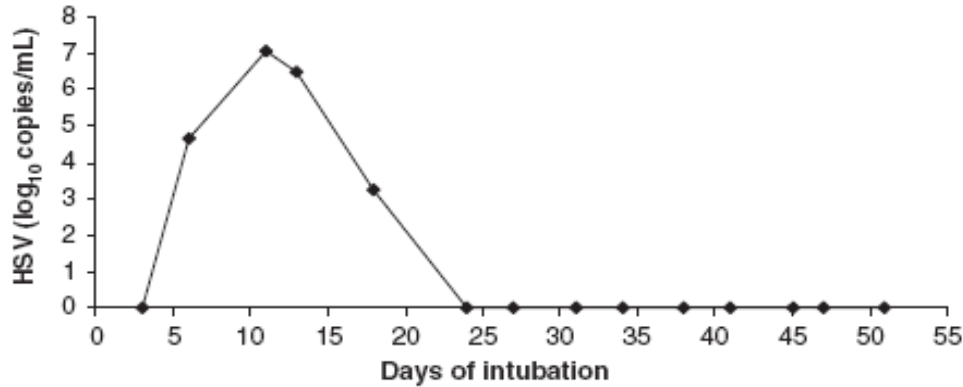


Am J Respir Crit Care Med Vol 175. pp 935–942, 2007

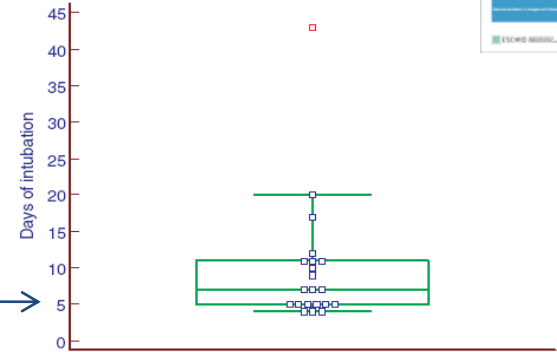
Monitoring of herpes simplex virus in the lower respiratory tract of critically ill patients using real-time PCR: a prospective study

N. De Vos^{1,*}, L. Van Hoovels^{1,*}, A. Vankeerberghen¹, K. Van Vaerenbergh¹, A. Boel¹, I. Demeyer², L. Creemers¹ and H. De Beenhouwer¹

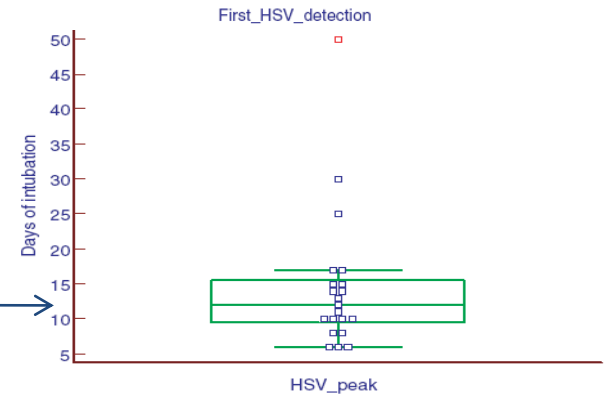
Clin Microbiol Infect 2009; **15**: 358–363



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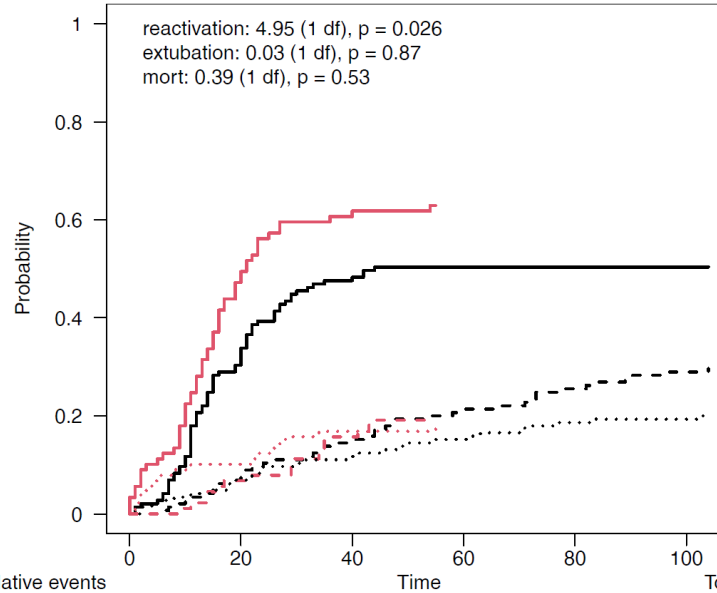


12 →



Et dans le Covid?

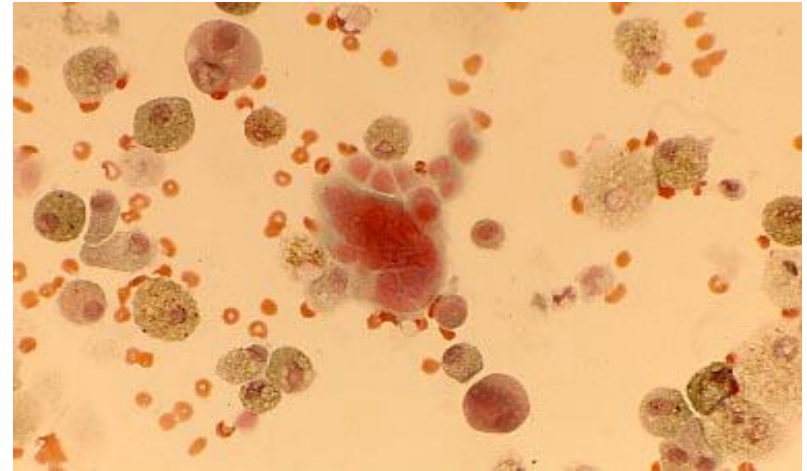
Réactivation HSV
Grippe 63%
Covid-19 50%



Bronchopneumonie HSV



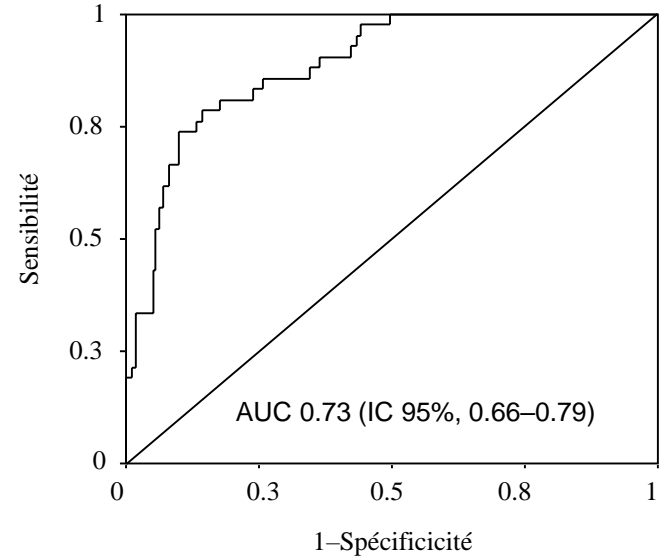
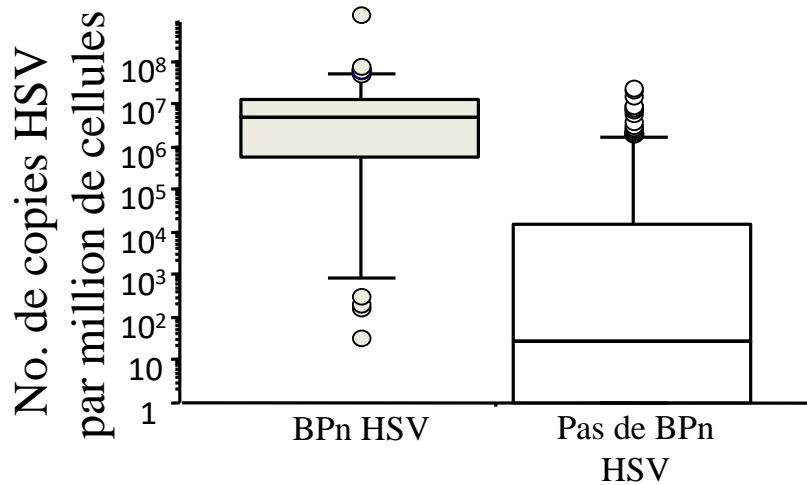
- BPn HSV chez 42/201 (21%) des patients ventilés ≥ 5 j suspects de PAVM
 - Suspicion clinique
 - Détection HSV
 - Inclusions spécifiques HSV
- Après 14 j de VM
- Associé à surmorbidity (VM plus longue, plus de PAVM bactérienne)



Am J Respir Crit Care Med Vol 175. pp 935-942, 2007

Bronchopneumonie HSV

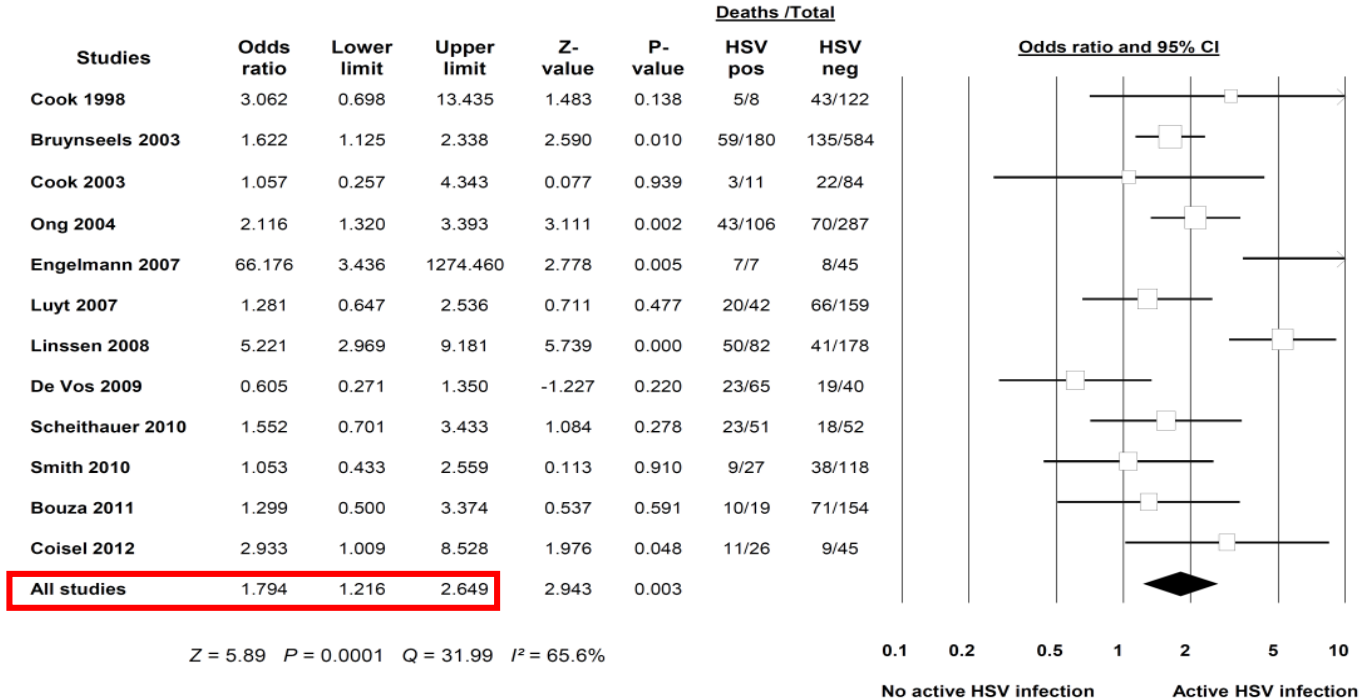
Am J Respir Crit Care Med Vol 175. pp 935–942, 2007



Charge virale $> 8 \times 10^4$ copies / 10^6 cells
Sensibilité de 81% (IC 95%, 69–90%)
Spécificité de 83% (95% CI, 71–91%)

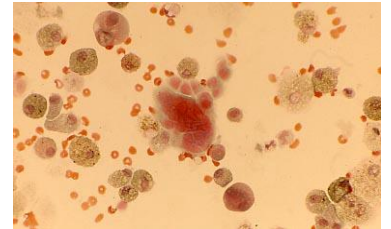
Cytomegalovirus and Herpes Simplex Virus Effect on the Prognosis of Mechanically Ventilated Patients Suspected to Have Ventilator-Associated Pneumonia

Yannael Coisel^{1*}, Sabri Bousbia², Jean-Marie Forel³, Sami Hraiech³, Bernard Lascola², Antoine Roch³, Christine Zandotti², Matthieu Million², Samir Jaber¹, Didier Raoult², Laurent Papazian³



HSV

- Réactivation HSV dans la gorge
 - Symptomatique ou non
 - 20 – 50% des patients de réanimation
 - Après 3-5 j de VM
- HSV dans les voies aériennes distales
 - 20 – 64% des patients de réanimation
 - Après 7 j de VM
 - **Associé à une évolution défavorable (charge virale élevée)**
- Bronchopneumonie à HSV
 - 20% des patients nécessitant une ventilation prolongée (>5 j)
 - Signes cliniques
 - Diagnostique cytologique (inclusions nucléaires spécifiques) ou charge virale > 5 log/millions de cellules
 - Après 14 j de VM
 - **Associée à une évolution défavorable**



Cytomegalovirus Reactivation in Critically Ill Immunocompetent Patients

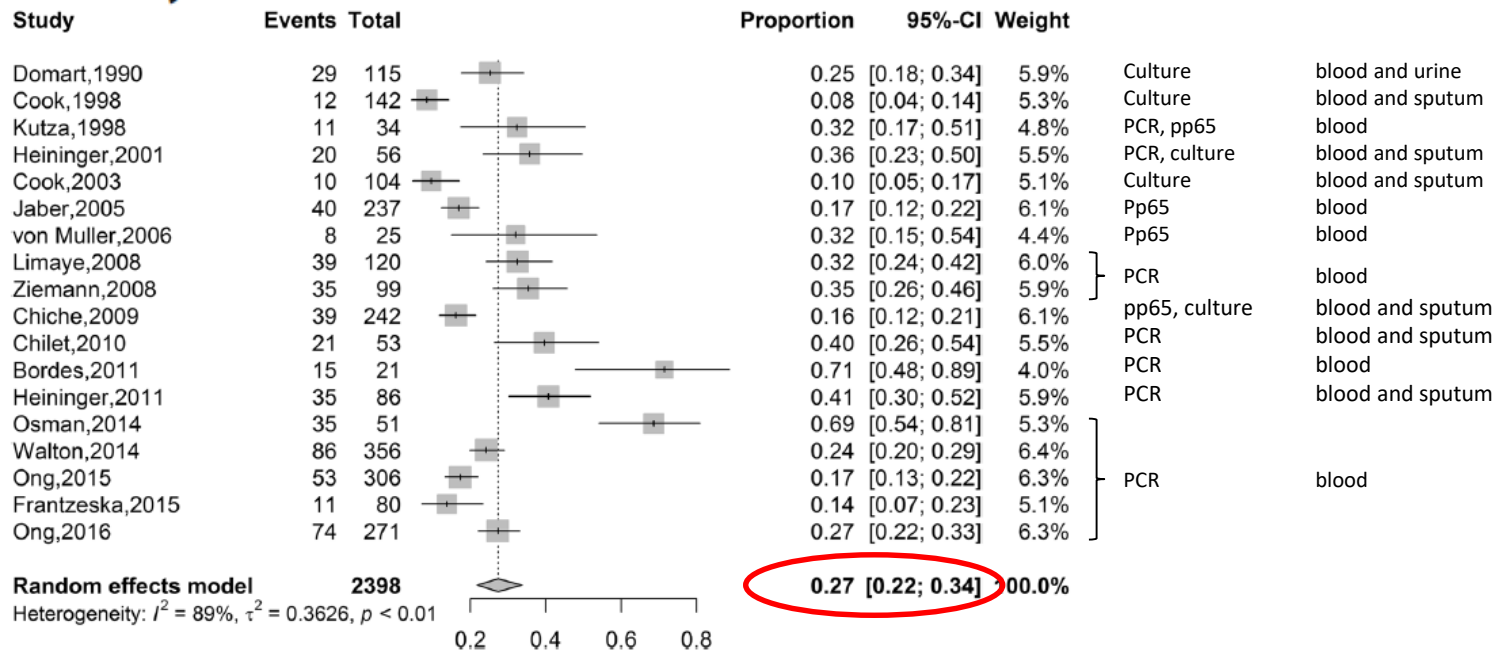
JAMA

- 120 patients « immunocompétents » séropositifs pour le CMV
- Apparition virémie chez 45 patients (35%)
 - En médiane à 12 j (3-57j)
- Virémie >1000 copies/ml chez 24 patients (20%)
 - En médiane après 26 j (9-56j)

JAMA. 2008;300(4):413-422



Cytomegalovirus infection and outcome in immunocompetent patients in the intensive care unit: a systematic review and meta-analysis



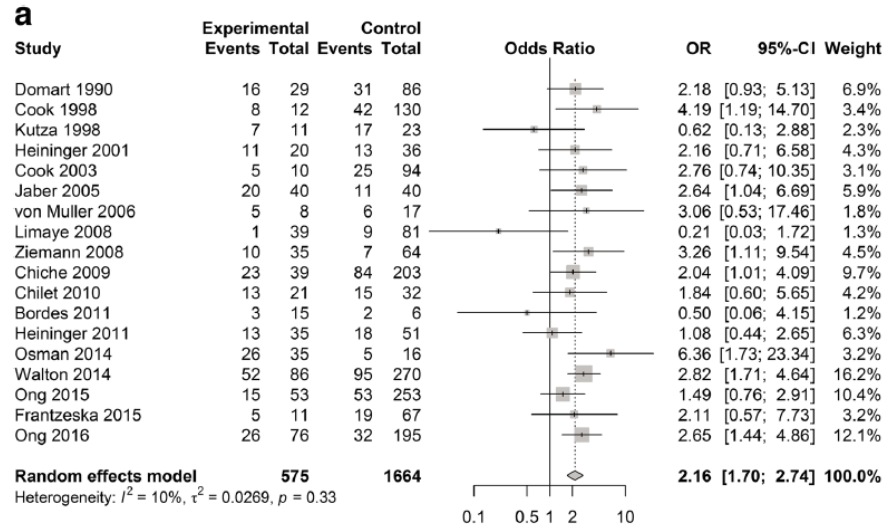
Maladie pulmonaire à CMV

Population	Fréquence de la détection virale	Manifestations de l'atteinte CMV	Tests diagnostics
Patients avec IRA ou PAVM (Papazian 1996)	25/86 (29%)	Pneumonie interstitielle diffuse	Histologie: autopsie chez 60, biopsies à thorax ouvert chez 26
Patients chir avec SAPS II>40 (Heininger 2001)	7/56 (6%)	NA	Culture virale, PCR
SDRA non expliqué (Papazian 2007)	30/100 (30%)	Pneumonie, fibrose	Histologie sur biopsies à thorax ouvert. CMV (virologie) chez 10/30
Patients sous VM (Chiche 2009)	11/242 (5%)	Pneumonie	Rapid shell-vial culture, culture cellulaire

Cytomegalovirus infection and outcome in immunocompetent patients in the intensive care unit: a systematic review and meta-analysis



Mortalité – « Infection »



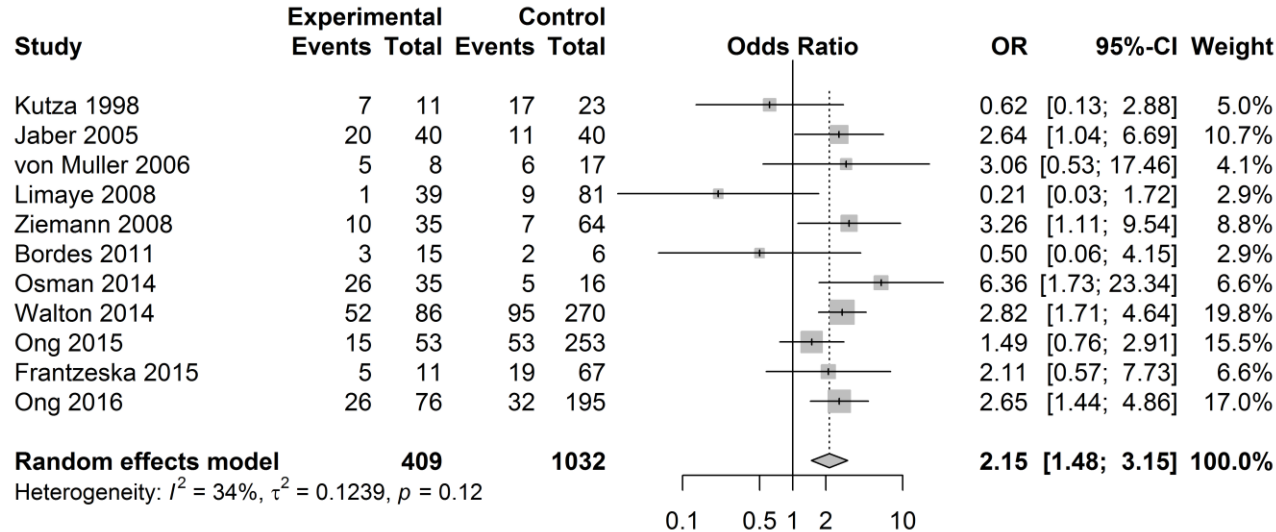
Surmortalité « infection »/pas « d'infection »



Cytomegalovirus infection and outcome in immunocompetent patients in the intensive care unit: a systematic review and meta-analysis



Mortalité – Détection dans le sang

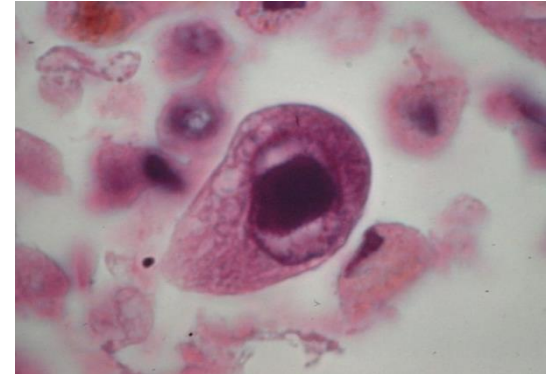


Surmortalité réactivation/pas de réactivation



CMV

- Réactivation CMV dans le sang
 - 30% des patients séropositifs
 - Diagnostic par PCR
 - Après 4-12 j en réa
 - Associé à une maladie à CMV?
 - **Associé à une évolution défavorable**
- Atteinte pulmonaire à CMV
 - 5 - 30%
 - Diagnostic par histologie/cytologie
 - Après 21 j de VM
 - Associée à une évolution défavorable ?



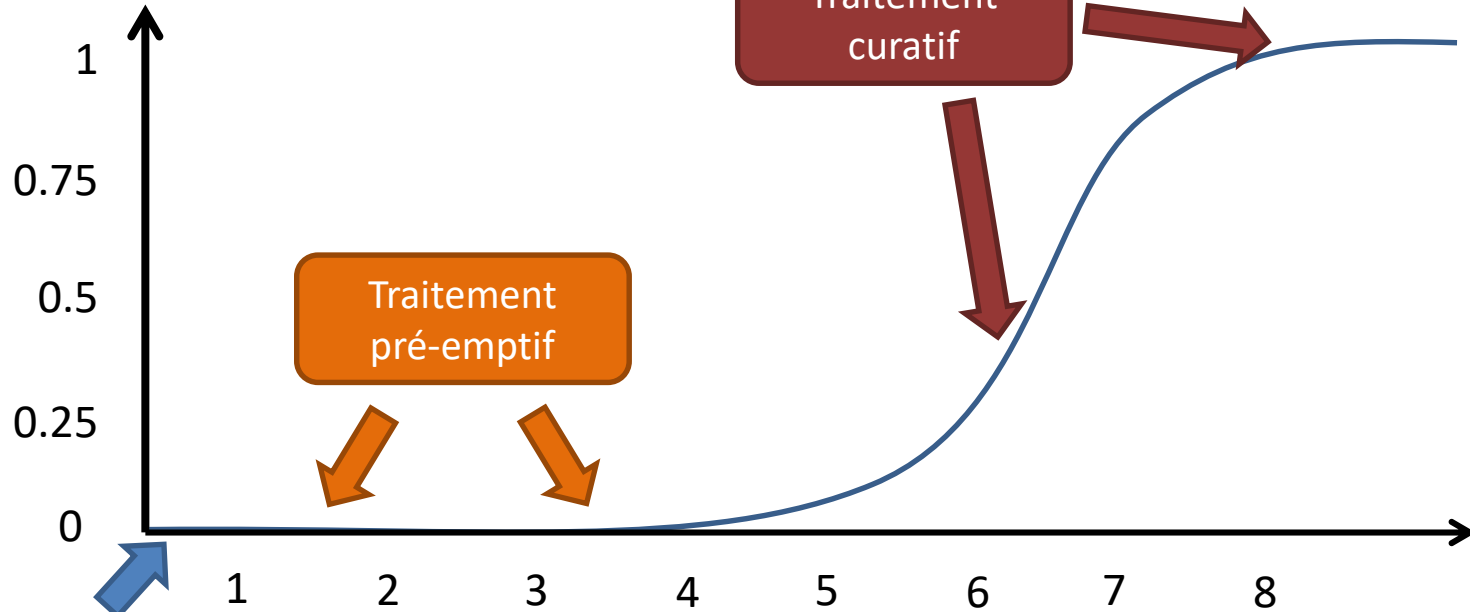
EST-CE QU'UN TRAITEMENT AMÉLIORE LE PRONOSTIC?

Les médecins passent leur vie à mettre des drogues
qu'ils ne connaissent pas dans des corps qu'ils
connaissent encore moins



François-Marie Arouet, dit Voltaire
1694 - 1778

Probabilité de maladie à CMV



Charge virale (log)



HSV et ARDS

- 45 patients avec ARDS randomisés pour recevoir un placebo (n=23) ou de l'aciclovir (n=22).
- 7 patients exclus car HSV détecté avant le traitement.
- 38 patients analysés

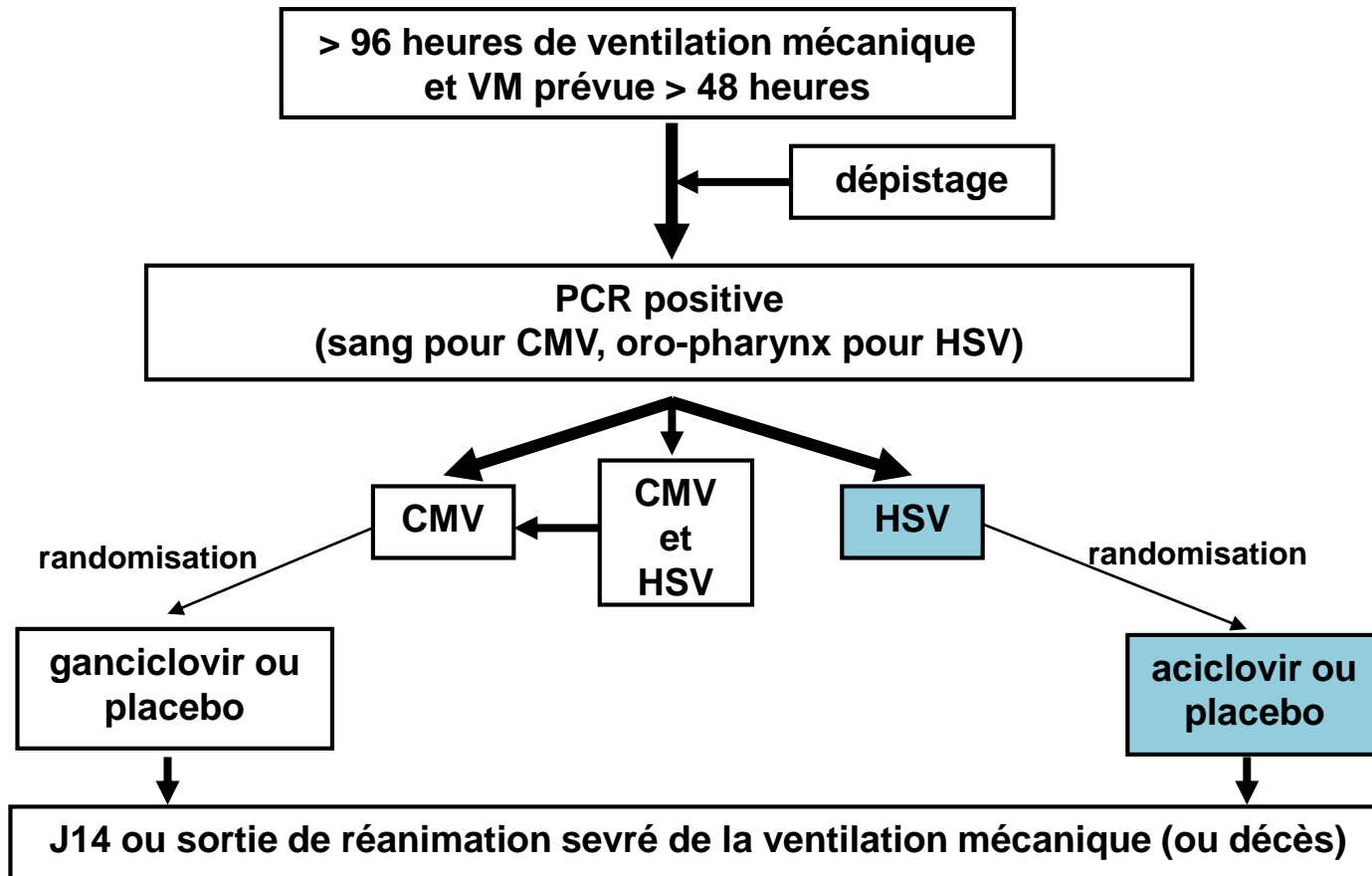
Tuxen et al., Am Rev Respir Dis 1987



HSV et ARDS

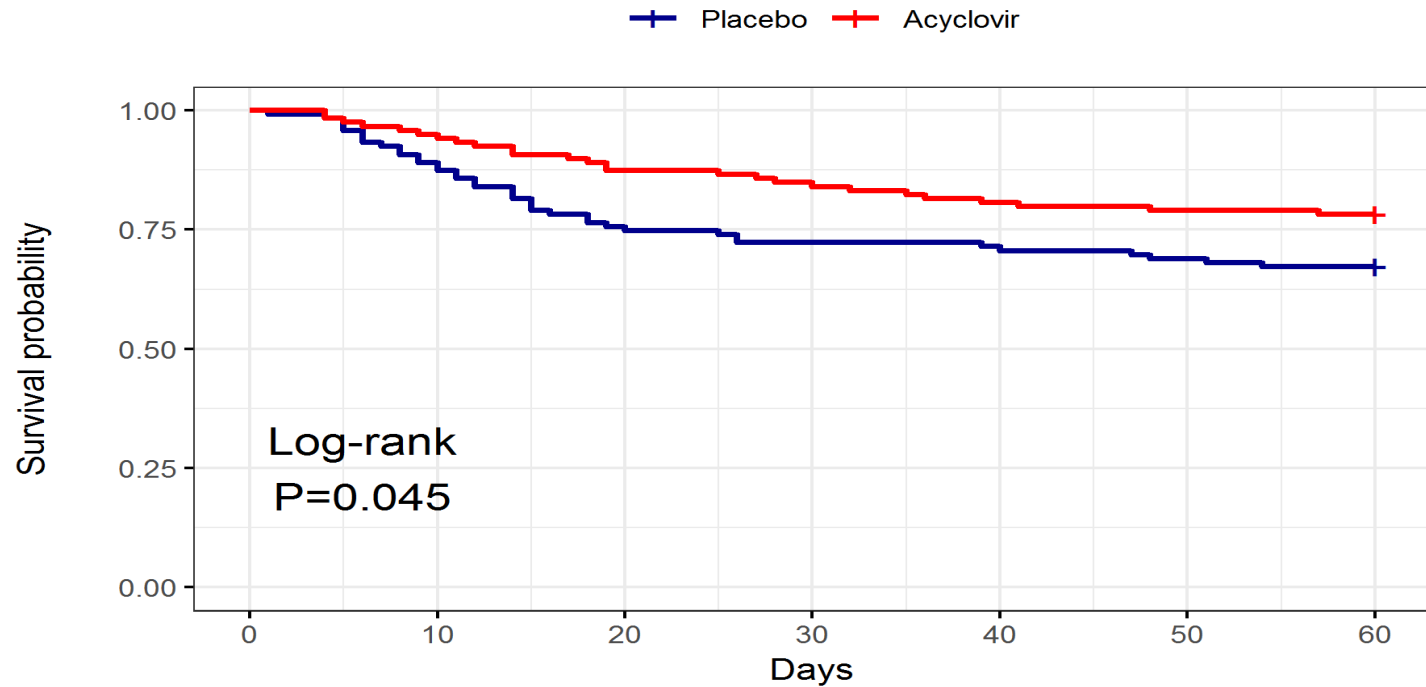
Tuxen et al., Am Rev Respir Dis 1987

	Aciclovir N = 17	Control N = 21	P
HSV dans VA	1 (6%)	13 (62%)	<0.001
HSV dans gorge ou VA	1 (6%)	15 (71%)	<0.001
Durée de VM, jours	21 ± 19	15 ± 12	NS
Mortalité	8 (47%)	9 (43%)	NS



PTH- aciclovir

	Acyclovir N = 119	Control N = 119	P value
Primary outcome			
Ventilator-free days at day 60, days	35 (0-53)	36 (0-50)	0.17
Secondary outcomes			
Day-60 mortality rate	26 (22%)	39 (33%)	0.059
HSV bronchopneumonitis	1 (1%)	4 (3%)	0.4
Active CMV infection	1 (1%)	5 (4%)	0.2
VAP	58 (49%)	53 (45%)	0.5
ARDS after randomization	14 (12%)	7 (6%)	0.1
Septic shock after randomization	22 (18%)	27 (23%)	0.4
Bacteremia/fungemia after randomization	29 (24%)	27 (23%)	0.8

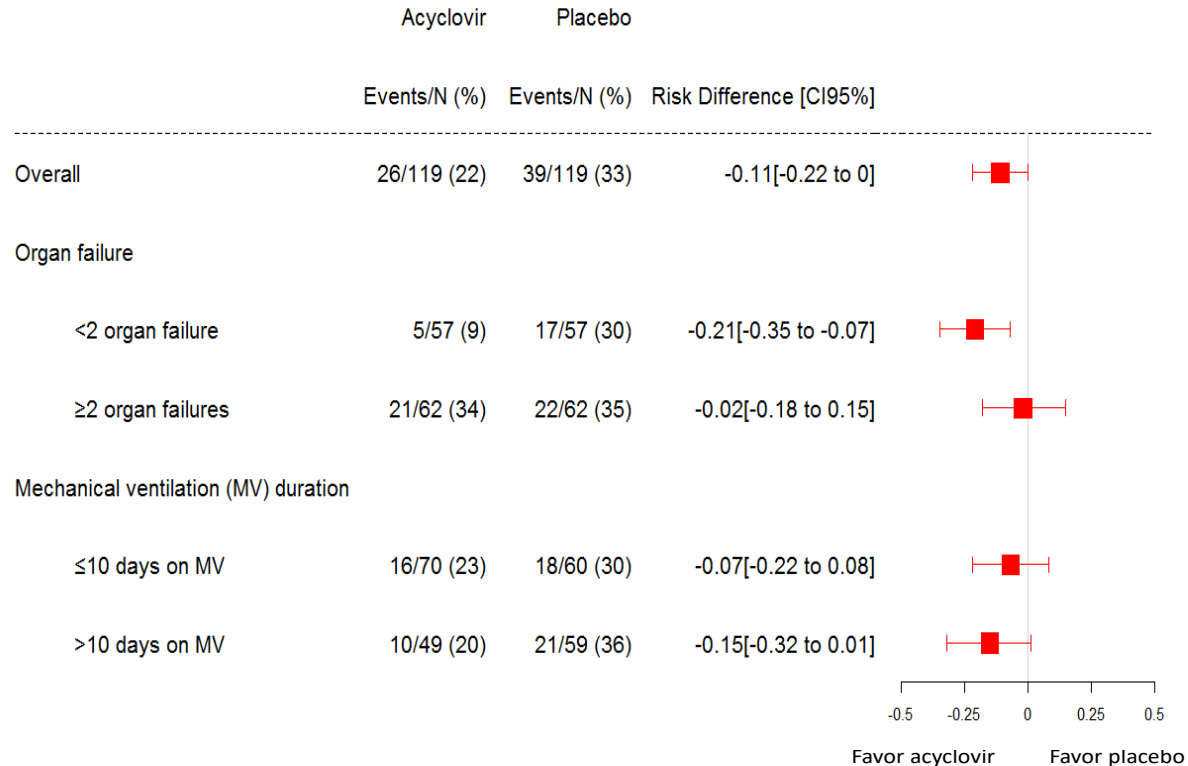


Number at risk

	0	10	20	30	40	50	60
Placebo	119	106	90	86	85	82	80
Acyclovir	119	113	104	101	96	94	93

Days

Analyse sous-groupe: mortalité à J60

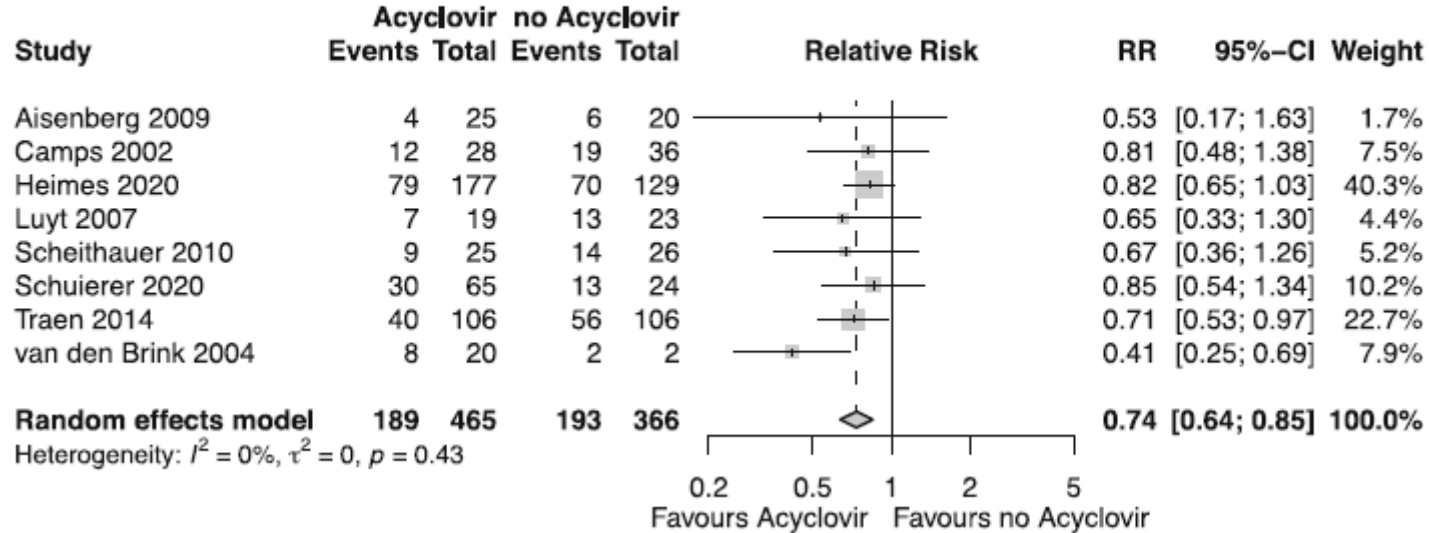


Effect of antiviral therapy on the outcomes of mechanically ventilated patients with herpes simplex virus detected in the respiratory tract: a systematic review and meta-analysis

Hagel *et al. Critical Care*

(2020) 24:584

Hospital all-cause mortality



Effect of Ganciclovir on IL-6 Levels Among Cytomegalovirus-Seropositive Adults With Critical Illness

A Randomized Clinical Trial

Ajit P. Limaye, MD; Renee D. Stapleton, MD, PhD; Lili Peng, MS; Scott R. Gunn, MD; Louise E. Kimball, PhD; Robert Hyzy, MD; Matthew C. Exline, MD; D. Clark Files, MD; Peter E. Morris, MD; Stephen K. Frankel, MD; Mark E. Mikkelsen, MD, MSCE; Duncan Hite, MD; Kyle B. Enfield, MD; Jay Steingrub, MD; James O'Brien, MD, MSc; Polly E. Parsons, MD; Joseph Cuschieri, MD; Richard G. Wunderink, MD; David L. Hotchkiss, MD; Ying Q. Chen, PhD; Gordon D. Rubenfeld, MD; Michael Boeckh, MD

JAMA. 2017;318(8):731-740.

	Placebo Group (n = 72)	Ganciclovir Group (n = 84)	Absolute Difference (95% CI) ^a	P Value
Primary Outcome at Day 14				
Difference in IL-6 level, log ₁₀ units, mean (95% CI)	-0.79 (-2.14 to 0.56)	-0.79 (-2.06 to 0.48)	0 (-0.3 to 0.2)	>.99
Secondary Outcomes at Day 28				
Any CMV reactivation, No. (%)	28 (39)	10 (12)	-27 (-40 to -14)	<.001
Mechanical ventilation days, median (IQR)	6 (3 to 12)	5 (3 to 9)	-1 (-3 to -1)	.16
VFDs, median (IQR)	20 (8 to 24)	23 (16 to 25)	3 (0 to 6)	.05
Sepsis subgroup analysis	20 (9 to 24)	23 (16 to 25)	3 (0 to 4)	.03
ICU length of stay, median (IQR), d	8 (5 to 15)	8 (4 to 14)	0 (-4 to 2)	.76
Secondary bacteremia or fungemia, No. (%)	11 (15)	13 (15)	0 (-10 to 10)	.67
Mortality, No. (%)	11 (15)	10 (12)	-3 (-14 to 7)	.54

Safety and Efficacy of Antiviral Therapy for Prevention of Cytomegalovirus Reactivation in Immunocompetent Critically Ill Patients

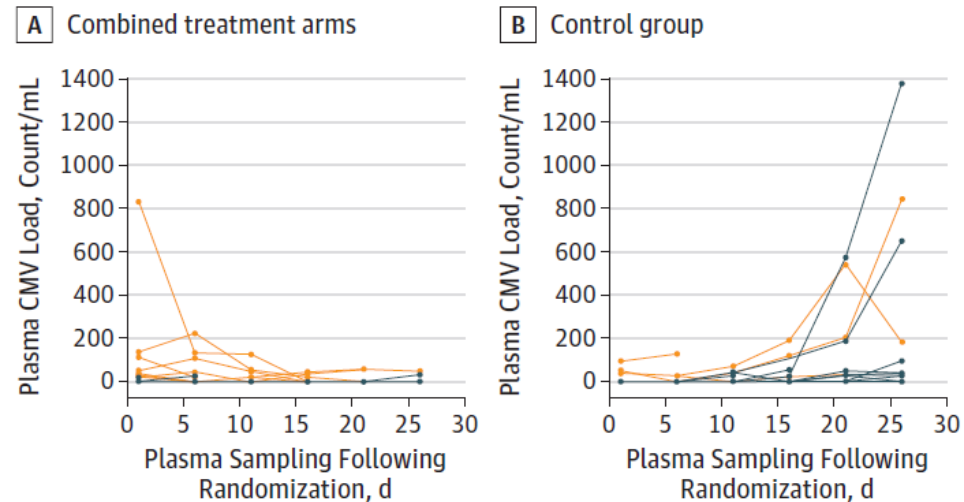
A Randomized Clinical Trial

JAMA Internal Medicine

Nicholas J. Cowley, MD; Andrew Owen, MRes; Sarah C. Shiels, BSc; Joanne Millar, PG-C; Rebecca Woolley, MSc; Natalie Ives, MSc; Husam Osman, MD, PhD; Paul Moss, MD, PhD; Julian F. Bion, MD

- Valganciclovir 450 mg/j
 - Ganciclovir IV 2,5mg/kg/j
- Valacyclovir 2g x4/j
 - Aciclovir 10 mg/kg x3/j
- Placebo

Figure 2. Cytomegalovirus (CMV) Viral Load in Blood



A, Combined valgacyclovir and valganciclovir arms. B, Control group. Each line

Safety and Efficacy of Antiviral Therapy for Prevention of Cytomegalovirus Reactivation in Immunocompetent Critically Ill Patients

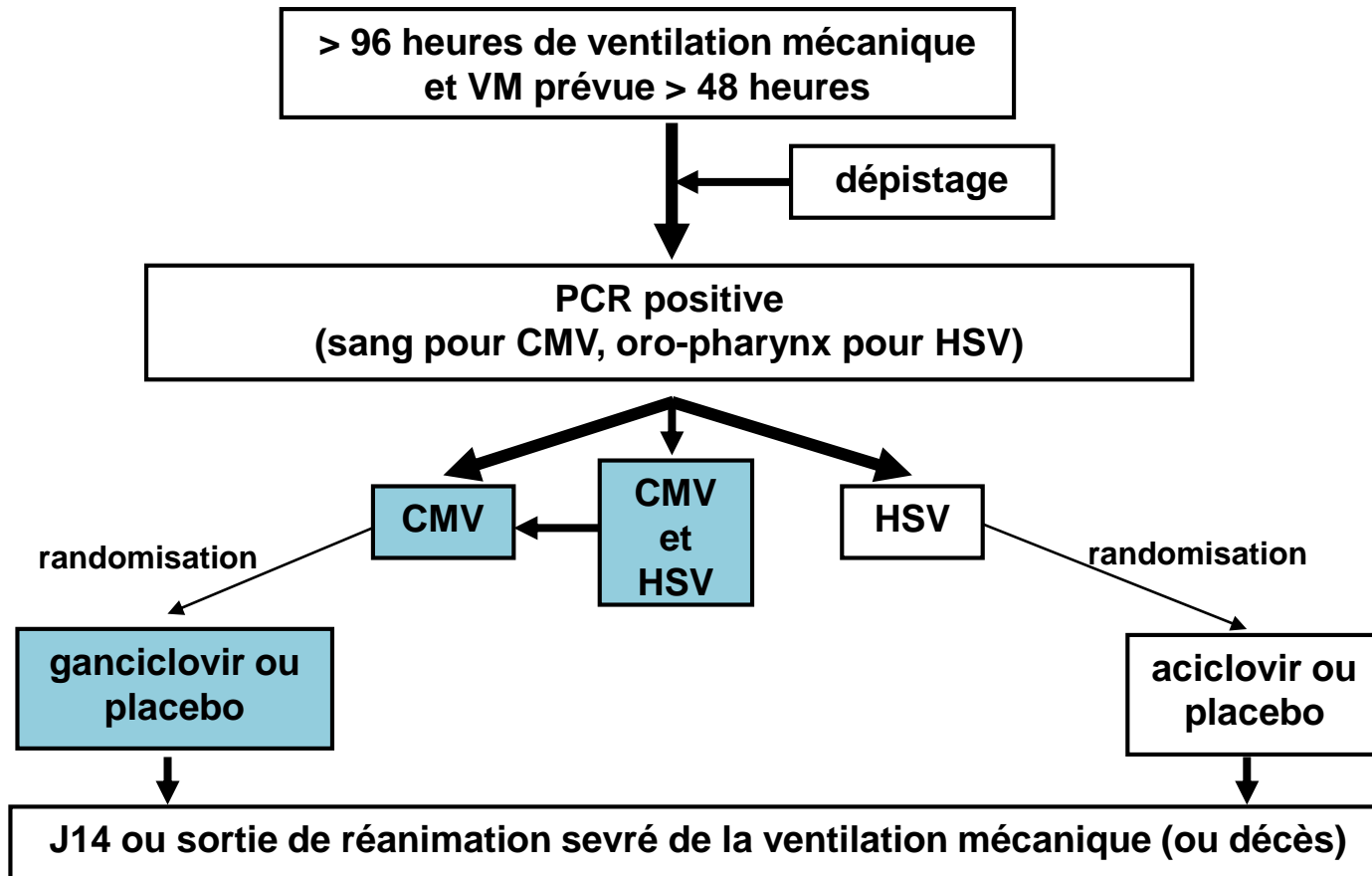
A Randomized Clinical Trial

Nicholas J. Cowley, MD; Andrew Owen, MRes; Sarah C. Shiels, BSc; Joanne Millar, PG-C; Rebecca Woolley, MSc; Natalie Ives, MSc; Husam Osman, MD, PhD; Paul Moss, MD, PhD; Julian F. Bion, MD

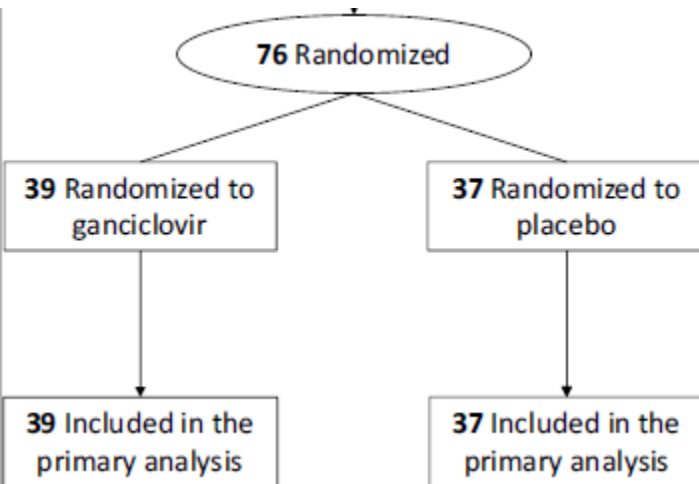
Outcome	Control (n = 44)	Valacyclovir (n = 34)	Valganciclovir (n = 46)
Secondary Clinical Measures			
Organ failure-free days (SOFA score <2), median (IQR) [range]	3.5 (0-18) [0-31]	1.5 (0-13) [0-24]	2.0 (0-11) [0-36]
Moderate organ failure-free days (SOFA score <5), median (IQR) [range]	18.0 (2-24) [0-41]	11.0 (0-22) [0-28]	16.5 (4-21) [0-44]
Discharged from ICU by 3 mo, No. (%) ^a	36 (81.8)	21 (61.8)	34 (73.9)
Discharged from hospital by 3 mo, No. (%) ^a	30 (68.2)	17 (50.0)	28 (60.9)
ICU duration of stay, median (IQR), d	11.5 (7-16)	12.0 (7-31)	16.0 (11-27)
SAEs forms returned, No.	7	12	18
Patients reporting SAEs, No. (%)	7 (15.9)	10 (29.4)	16 (34.8)
Mortality at 28 d, No. (%)	7 (15.9)	14 (41.2)	10 (21.7)
Mortality in the hospital, No. (%)	9 (20.5)	15 (44.1)	12 (26.1)

JAMA Internal Medicine





Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation



Characteristics	Placebo group (N= 37)	Ganciclovir group (N= 39)
Age, y	67.0 (59.0–72.0)	63.0 (54.0–71.0)
Male sex, no. (%)	25 (67.6)	31 (79.5)
SAPS II	45.0 (38.5–56.5)	45.0 (37.0–59.0)
SOFA score	10 (8–15)	9 (7–10)
Ongoing antimicrobial treatment, no. (%)	26 (70.3)	28 (71.8)
ECMO use, no. (%)	5 (13.5)	6 (15.4)
Renal replacement therapy, no. (%)	14 (37.8)	13 (33.3)
SOFA score	8.0 (5.0–11.0)	8.5 (4.0–10.3)
Organ/system failure, no. (%) ^a		
Cardiovascular	18 (48.6)	19 (48.7)
Respiratory	22 (59.5)	24 (61.5)
Renal	12 (32.4)	14 (35.9)
Central nervous	6 (16.2)	4 (10.3)
Hepatic	2 (5.4)	3 (7.9)
Coagulation	2 (5.4)	2 (5.1)

Durée de VM avant rando

15 (10-22)

14 (9-22)

Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation



Papazian et al. *Ann. Intensive Care*

(2021) 11:33




Parameters	Placebo group (N = 37)	Ganciclovir group (N = 39)	P Value
Primary outcome			
Ventilator-free days on day 60	0 (0–43)	10 (0–51)	0.459
Secondary outcomes (post-randomization)			
Day-60 mortality, no. (%)	16 (43.2)	16 (41.0)	0.845
Duration of MV	20 (7–40)	12 (6–29)	0.246
ICU length of stay (from admission)	44.0 (21.0–66.5)	36.0 (24.0–51.0)	0.377
ICU length of stay (from randomization)	26.0 (11.0–50.0)	17.0 (8.0–34.0)	0.318
Hospitalization length (from admission)	60.0 (33.0–75.5)	65.0 (28.0–78.0)	0.988
Hospitalization length (from randomization)	42.0 (18.5–60.0)	38.0 (13.0–60.0)	0.945
HSV bronchopneumonitis, no. (%)	1 (2.7)	0 (0)	0.487
Cytomegalovirus infection, no. (%)	5 (13.5)	1 (2.6)	0.103
Ventilator-associated pneumonia, no. (%)	15 (40.5)	13 (33.3)	0.515
Secondary bacteremia or fungemia, no. (%)	8 (21.6)	7 (17.9)	0.688
ARDS post-randomization, no. (%)	6 (16.2)	6 (15.4)	0.921
Mild ^a	0	0	
Moderate ^a	3	3	
Severe ^a	3	3	
Septic shock post-randomization, no. (%)	14 (37.8)	13 (33.3)	0.682
Renal replacement therapy until day 28, no. (%)	18 (48.6)	16 (41.0)	0.504
Number of days with study drug, no. (%)	14 (7.5–14)	14 (6.0–14)	0.991

Qui traiter? (point de vue personnel)

HSV

- Traitement prophylactique 
- Traitement préemptif 
(réactivation HSV oropharyngée)
- Traitement curatif:
bronchopneumonie HSV
(histologie, HSV >5 log)
 - Aciclovir 10 mg/kg/8h

CMV

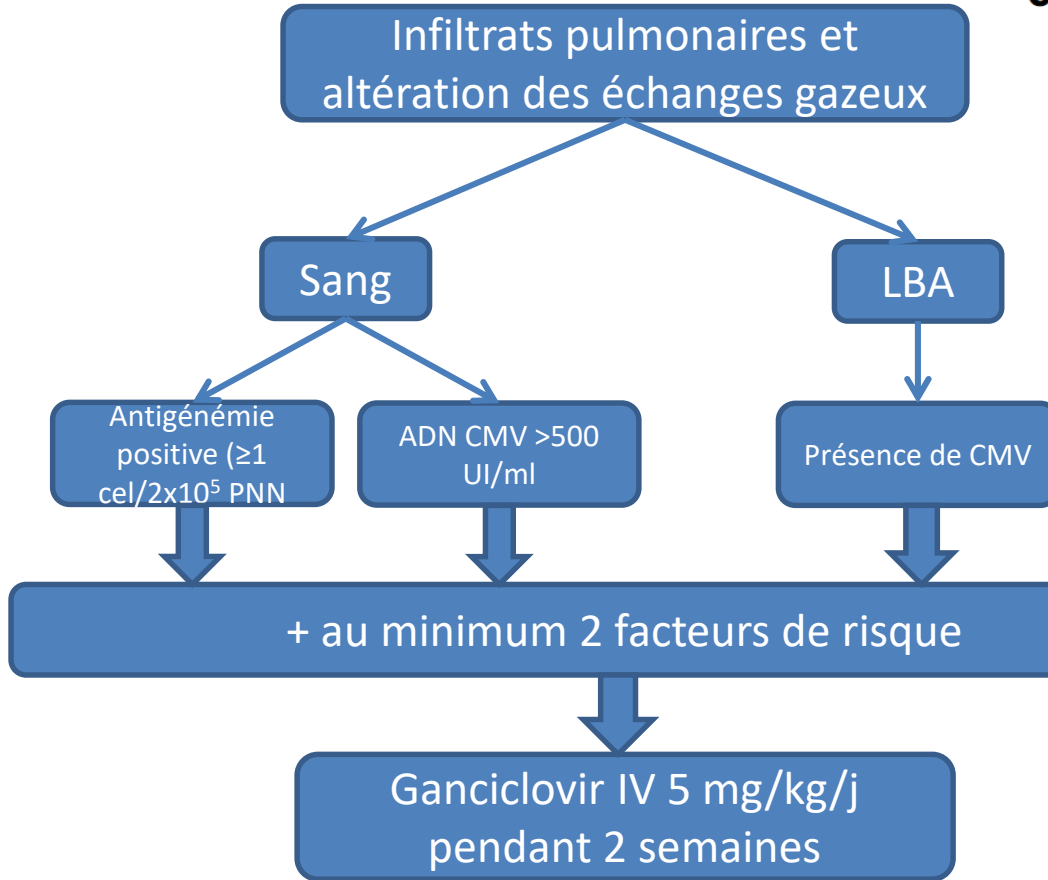
- Traitement prophylactique 
- Traitement préemptif
 - réactivation CMV dans le 
 - réactivation CMV dans les voies aériennes distales 
- Traitement curatif: pneumonie à CMV (histologie)
 - Ganciclovir 5 mg/kg/j

Cytomegalovirus reactivation in ICU patients

Laurent Papazian
Sami Hraiech
Samuel Lehingue
Antoine Roch
Laurent Chiche
Sandrine Wiramus
Jean-Marie Forel



Intensive Care Med (2016) 42:28–37



- Leucopénie
- Hémophagocytose
- Absence de cause bactérienne retrouvée
- VM >2 semaines
- ALAT/ASAT \nearrow (1,5-3 x N)
- Bilirubine \nearrow (1,5-3 x N)
 - Fièvre
 - Diarrhée

CONCLUSION

- Réactivation virale (HSV, CMV) sont fréquentes en réanimation et associées à un pronostic défavorable
- Traitement: plus avis d'expert qu'autre chose