JN 23es Journées Nationales d'Infectiologie
Bordeaux
et la région Aquitaine
Palais des Congrès
du mercredi 15 juin 2022
au vendredi 17 juin 2022

Que faire des réactivations virales chez le patient de réanimation?

Pr Charles-Edouard Luyt
Médecine Intensive Réanimation
Institut de Cardiologie
Groupe Hospitalier Pitié-Salpêtrière
Sorbonne Université
Paris

charles-edouard.luyt@aphp.fr

Conflits d’intérêts

- MSD
- Aerogen
- AdvanzPharma

charles-edouard.luyt@aphp.fr

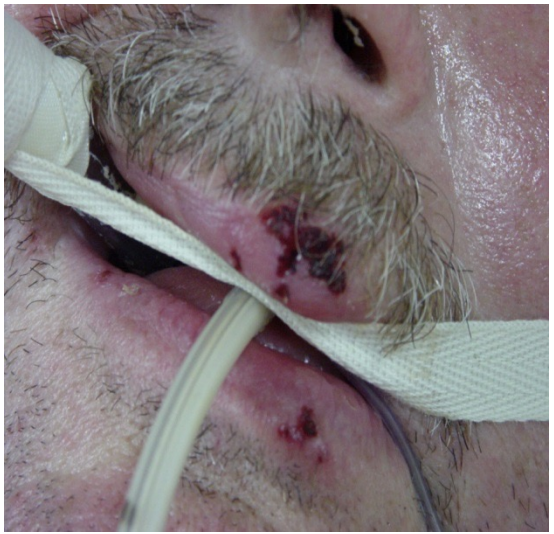
REACTIVATION VIRALE EN REANIMATION: EPIDEMIOLOGIE

charles-edouard.luyt@aphp.fr

Réactivation labiale

- Détectées chez 48/201 (24%) des patients ventilés ≥5 jours et suspects de PAVM
  - 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

charles-edouard.luyt@aphp.fr

Réactivation HSV

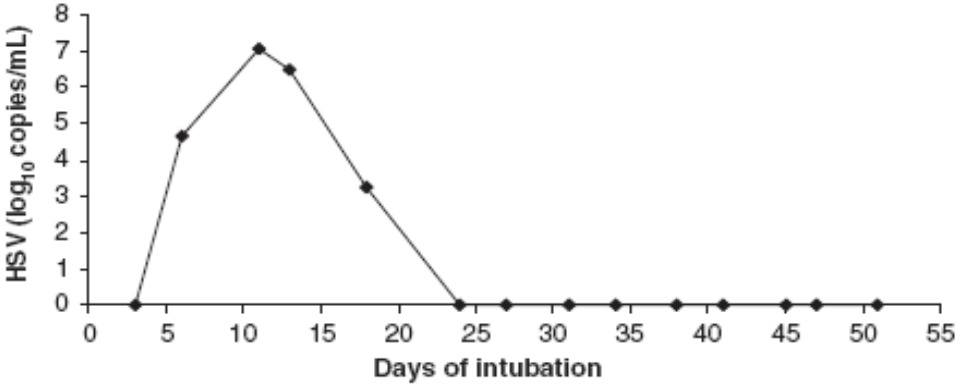
	Population	HSV gorge	HSV poumon
Bruynseels 2003	764 malades, 361 sous VM	169 (22%)	361 (19%)
Ong 2004	393 malades sous VM	106 (27%)	
Luyt 2007	201 malades, VM >4 j, suspects PAVM	109 (54%)	129 (64%)
Linssen 2008	260 malades sous VM	—	99 (32%)
Costa 2012	127 malades suspects de PAVM		38 (31%)

charles-edouard.luyt@aphp.fr

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. Vankeerberghen[1], K. Van Vaerenbergh[1], A. Boel[1], I. Demeyer[2], L. Creemers[1] and H. De Beenhouwer[1]

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



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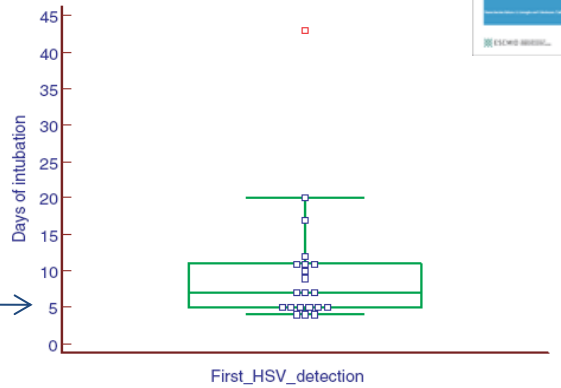

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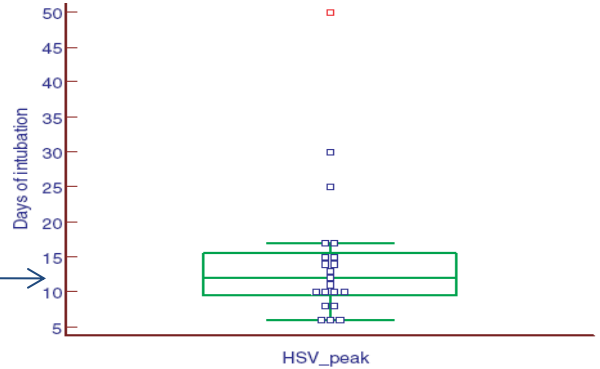
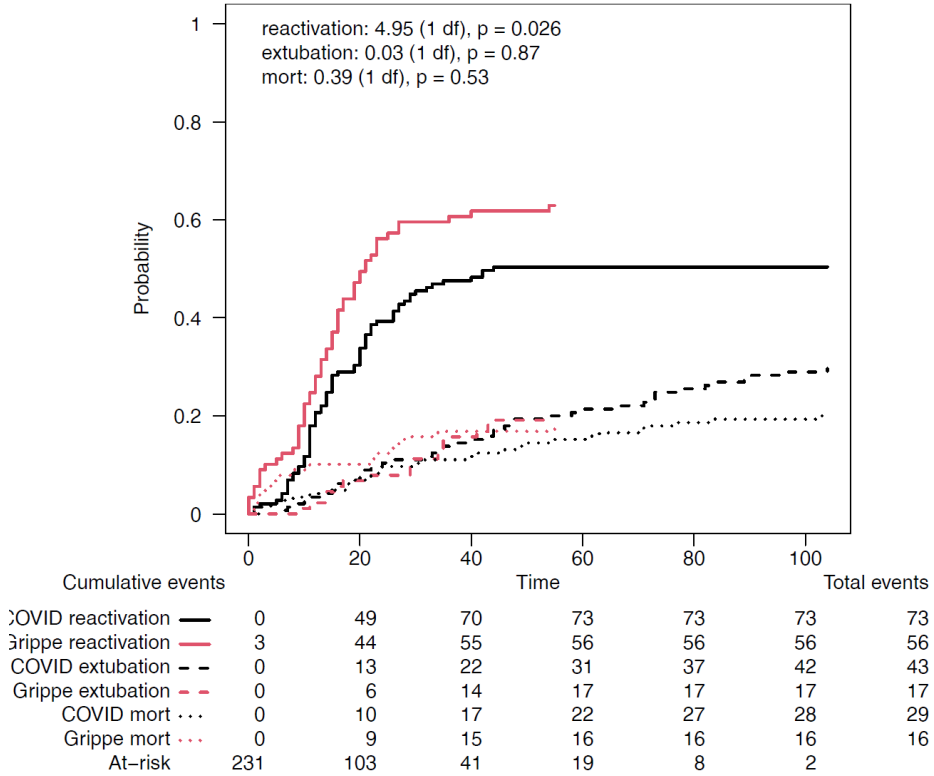


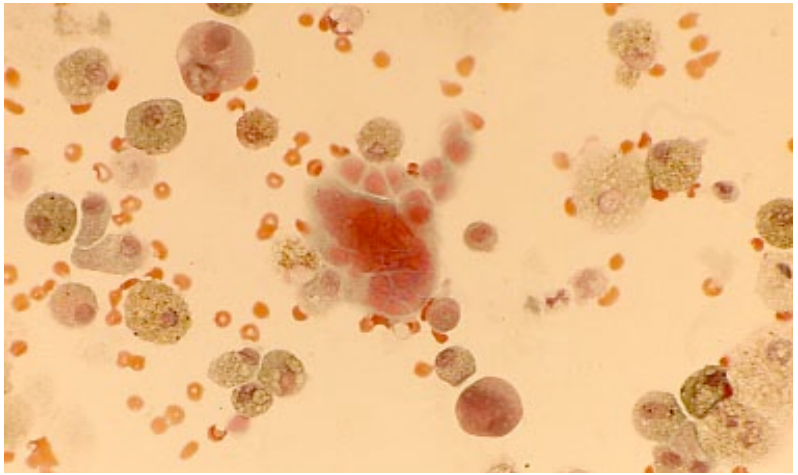
Et dans le Covid?

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 surmorbidité (VM plus longue, plus de PAVM bactérienne)

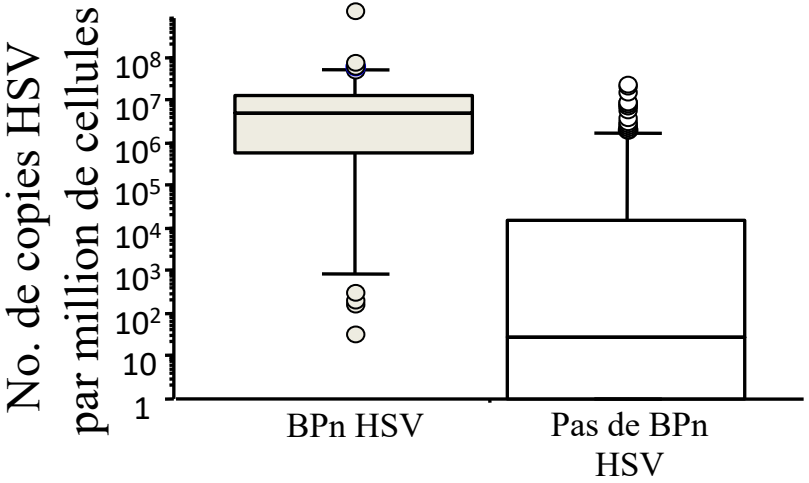


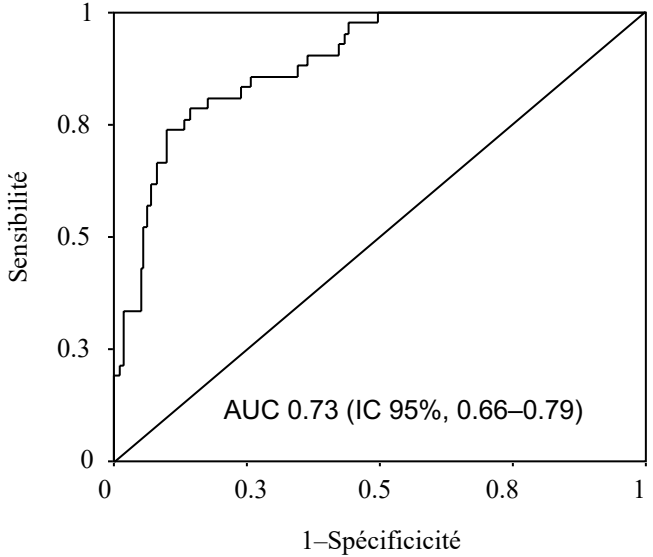
Am J Respir Crit Care Med Vol 175. pp 935–942, 2007

charles-edouard.luyt@aphp.fr

Bronchopneumonie HSV

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





Charge virale > 8 × 10^4 copies /10^6 cells

Sensibilité de 81% (IC 95%, 69–90%)

Spécificité de 83% (95% CI, 71–91%)

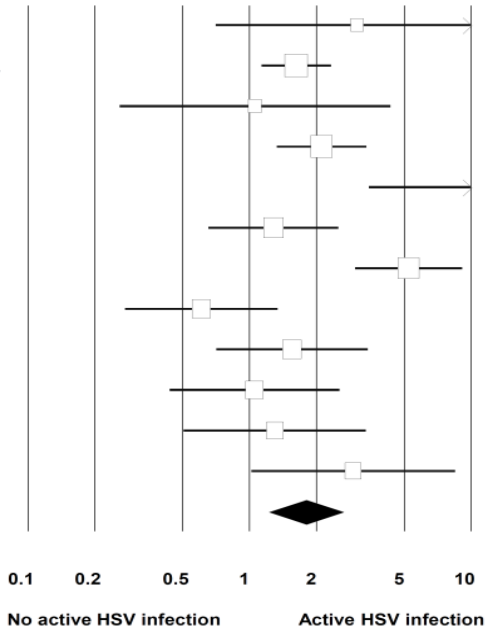
Cytomegalovirus and Herpes Simplex Virus Effect on the Prognosis of Mechanically Ventilated Patients Suspected to Have Ventilator-Associated Pneumonia

Yannael Coisel[1]*, Sabri Bousbia[2], Jean-Marie Forel[3], Sami Hraiech[3], Bernard Lascola[2], Antoine Roch[3], Christine Zandotti[2], Matthieu Million[2], Samir Jaber[1], Didier Raoult[2], Laurent Papazian[3]

PLOS ONE

Studies	Odds ratio	Lower limit	Upper limit	Z-value	P-value	Deaths /Total HSV pos	Deaths /Total 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		

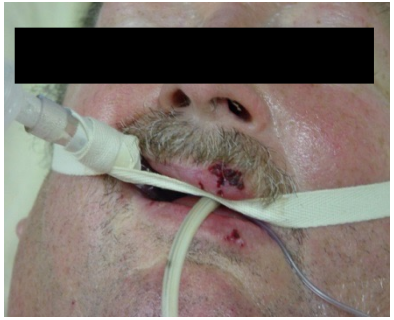
$Z = 5.89$ $P = 0.0001$ $Q = 31.99$ $I^2 = 65.6\%$

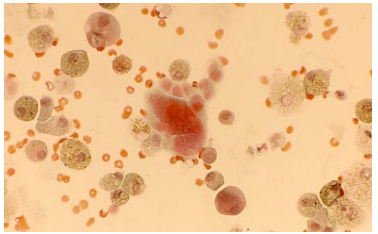


charles-edouard.luyt@aphp.fr

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**





charles-edouard.luyt@aphp.fr

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)

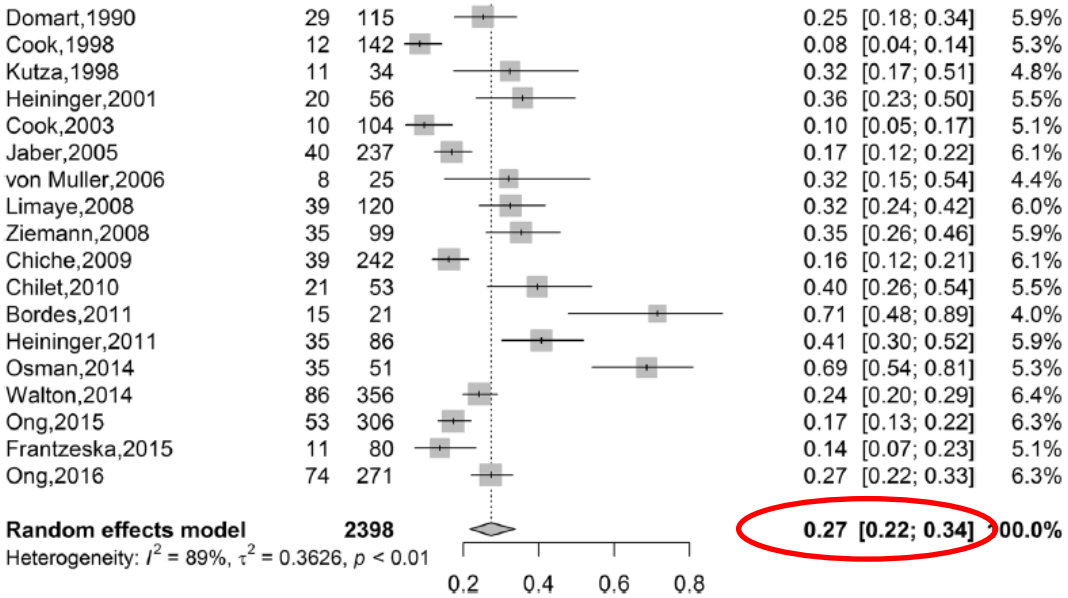
JAMA. 2008;300(4):413-422

charles-edouard.luyt@aphp.fr

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

BMC Infectious Diseases

Li et al. BMC Infectious Diseases (2018) 18:289



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

charles-edouard.luyt@aphp.fr

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BMC Infectious Diseases

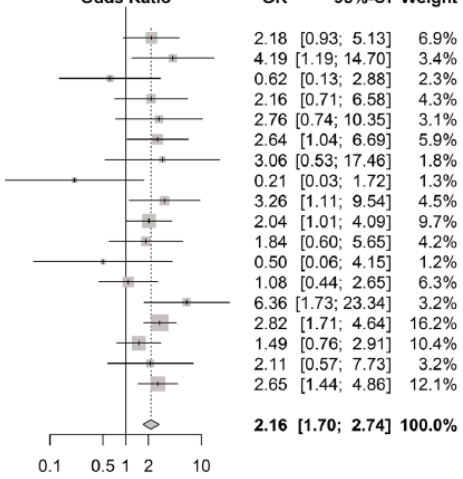
Li et al. BMC Infectious Diseases (20

Mortalité – « Infection »

a

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight
Domart 1990	16	29	31	86	2.18	[0.93; 5.13]	6.9%
Cook 1998	8	12	42	130	4.19	[1.19; 14.70]	3.4%
Kutza 1998	7	11	17	23	0.62	[0.13; 2.88]	2.3%
Heininger 2001	11	20	13	36	2.16	[0.71; 6.58]	4.3%
Cook 2003	5	10	25	94	2.76	[0.74; 10.35]	3.1%
Jaber 2005	20	40	11	40	2.64	[1.04; 6.69]	5.9%
von Muller 2006	5	8	6	17	3.06	[0.53; 17.46]	1.8%
Limaye 2008	1	39	9	81	0.21	[0.03; 1.72]	1.3%
Ziemann 2008	10	35	7	64	3.26	[1.11; 9.54]	4.5%
Chiche 2009	23	39	84	203	2.04	[1.01; 4.09]	9.7%
Chilet 2010	13	21	15	32	1.84	[0.60; 5.65]	4.2%
Bordes 2011	3	15	2	6	0.50	[0.06; 4.15]	1.2%
Heininger 2011	13	35	18	51	1.08	[0.44; 2.65]	6.3%
Osman 2014	26	35	5	16	6.36	[1.73; 23.34]	3.2%
Walton 2014	52	86	95	270	2.82	[1.71; 4.64]	16.2%
Ong 2015	15	53	53	253	1.49	[0.76; 2.91]	10.4%
Frantzeska 2015	5	11	19	67	2.11	[0.57; 7.73]	3.2%
Ong 2016	26	76	32	195	2.65	[1.44; 4.86]	12.1%
Random effects model		**575**		**1664**	**2.16**	**[1.70; 2.74]**	**100.0%**

Heterogeneity: I^2 = 10%, τ^2 = 0.0269, p = 0.33



Surmortalité « infection »/pas « d'infection »

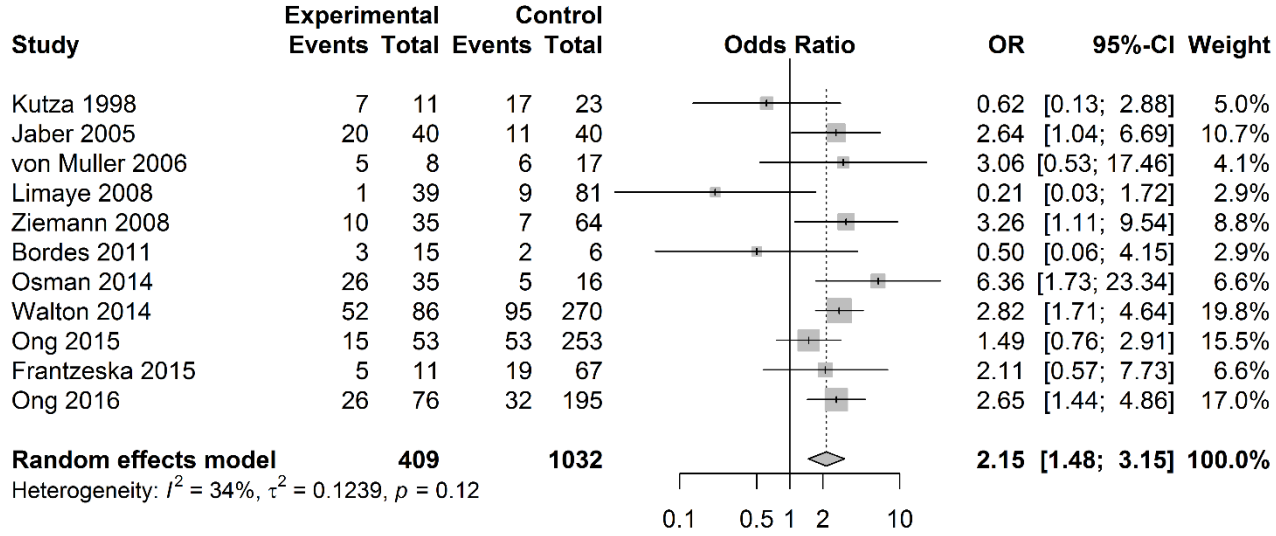
charles-edouard.luyt@aphp.fr

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

BMC Infectious Diseases

Li et al. BMC Infectious Diseases (2018) 18:289

Mortalité – Détection dans le sang



Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight
Kutza 1998	7	11	17	23	0.62	[0.13; 2.88]	5.0%
Jaber 2005	20	40	11	40	2.64	[1.04; 6.69]	10.7%
von Muller 2006	5	8	6	17	3.06	[0.53; 17.46]	4.1%
Limaye 2008	1	39	9	81	0.21	[0.03; 1.72]	2.9%
Ziemann 2008	10	35	7	64	3.26	[1.11; 9.54]	8.8%
Bordes 2011	3	15	2	6	0.50	[0.06; 4.15]	2.9%
Osman 2014	26	35	5	16	6.36	[1.73; 23.34]	6.6%
Walton 2014	52	86	95	270	2.82	[1.71; 4.64]	19.8%
Ong 2015	15	53	53	253	1.49	[0.76; 2.91]	15.5%
Frantzeska 2015	5	11	19	67	2.11	[0.57; 7.73]	6.6%
Ong 2016	26	76	32	195	2.65	[1.44; 4.86]	17.0%
Random effects model		**409**		**1032**	**2.15**	**[1.48; 3.15]**	**100.0%**

Heterogeneity: I^2 = 34%, τ^2 = 0.1239, p = 0.12

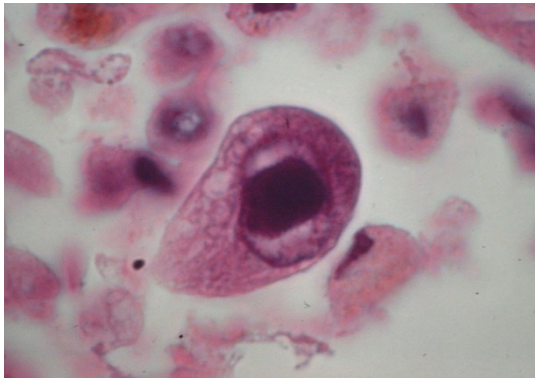
Surmortalité réactivation/pas de réactivation

charles-edouard.luyt@aphp.fr

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 ?



charles-edouard.luyt@aphp.fr

REACTIVATION VIRALE EN REANIMATION: QUI TRAITER?

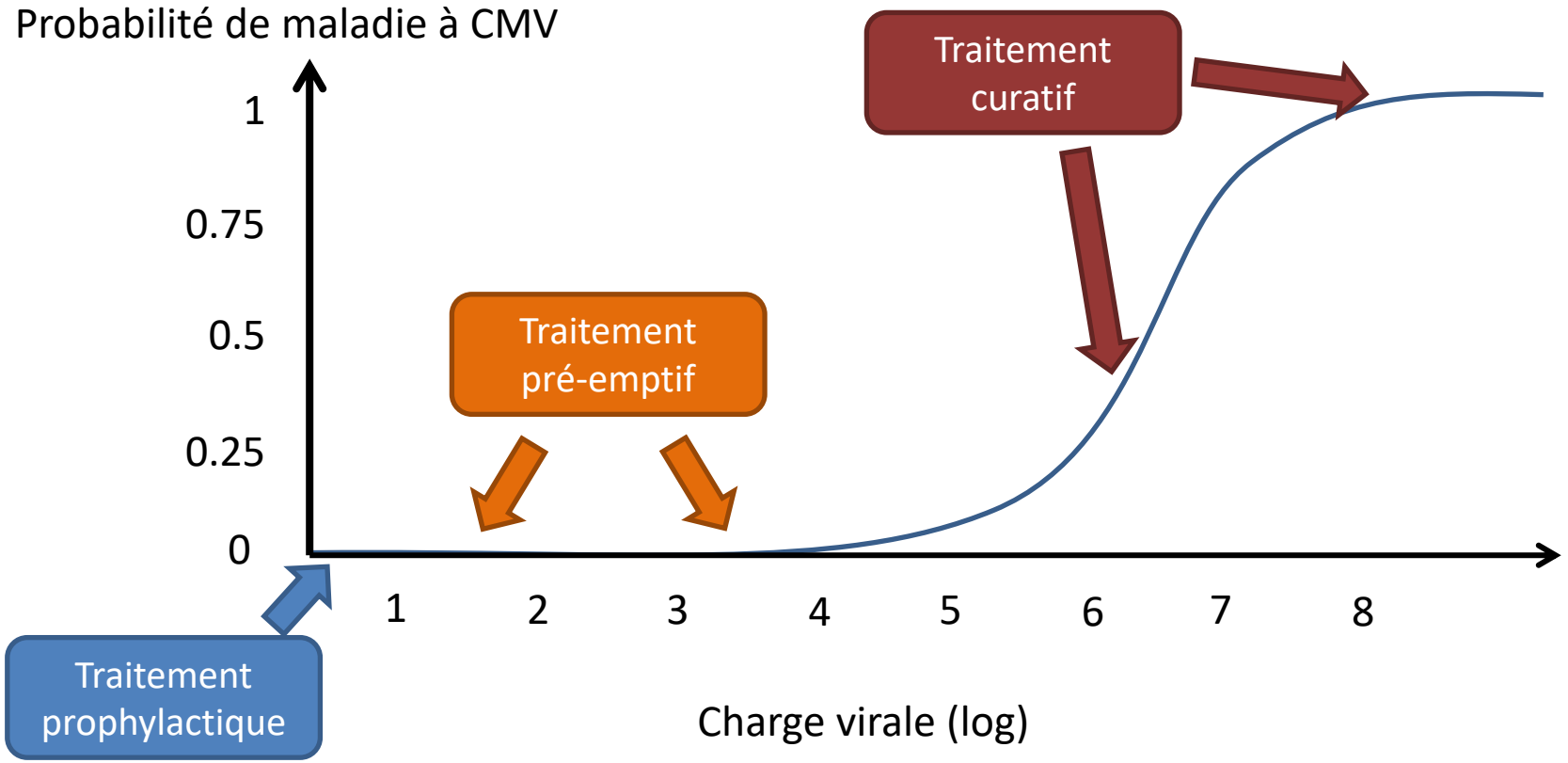
charles-edouard.luyt@aphp.fr

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

charles-edouard.luyt@aphp.fr


Probabilité de maladie à CMV
1
0.75
0.5
0.25
0
1
2
3
4
5
6
7
8
Traitement curatif
Traitement pré-emptif
Traitement prophylactique
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

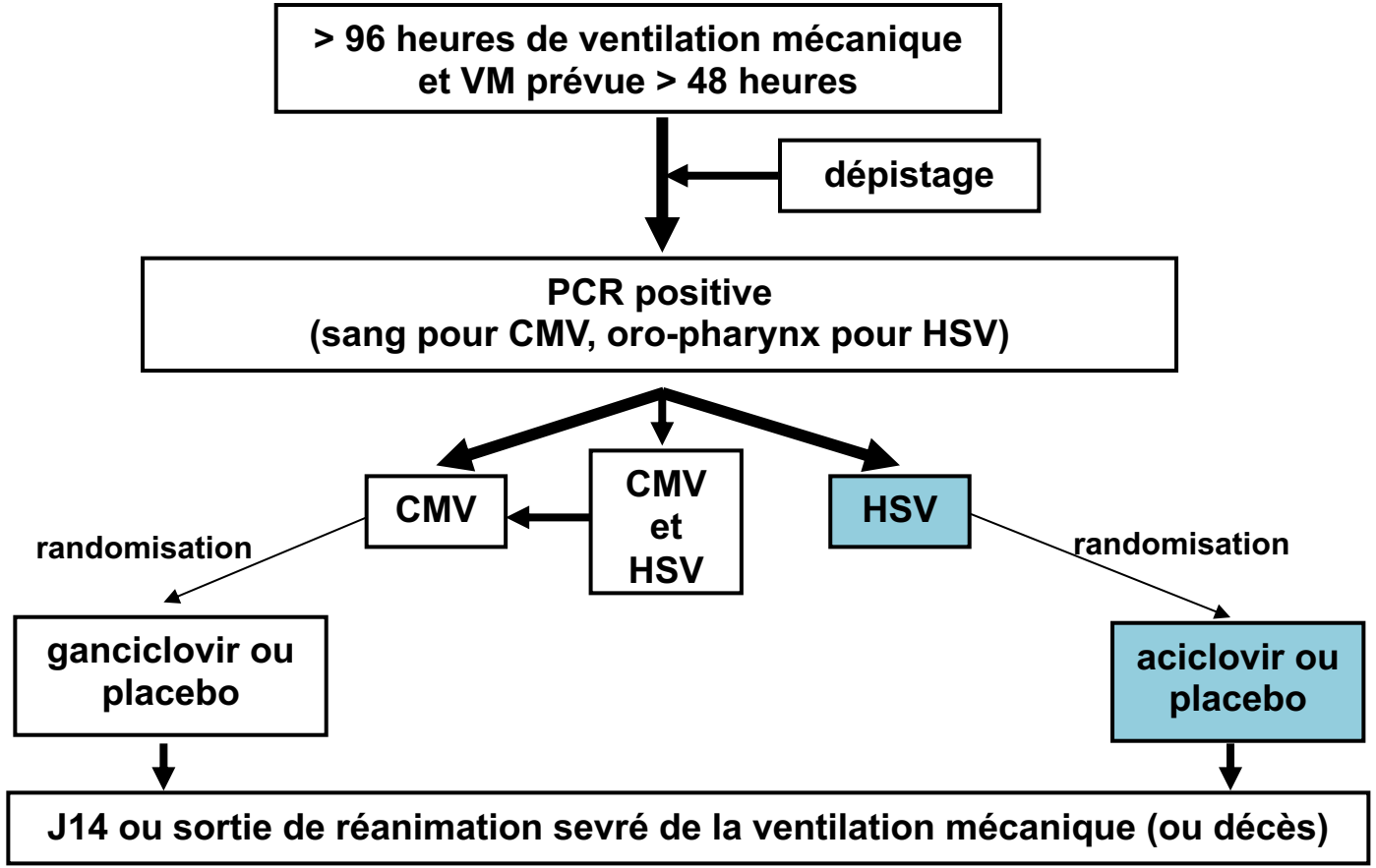
charles-edouard.luyt@aphp.fr

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

charles-edouard.luyt@aphp.fr


> 96 heures de ventilation mécanique
et VM prévue > 48 heures
dépistage
PCR positive
(sang pour CMV, oro-pharynx pour HSV)
CMV
CMV
et
HSV
HSV
randomisation
randomisation
ganciclovir ou
placebo
aciclovir ou
placebo
J14 ou sortie de réanimation sevré de la ventilation mécanique (ou décès)

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

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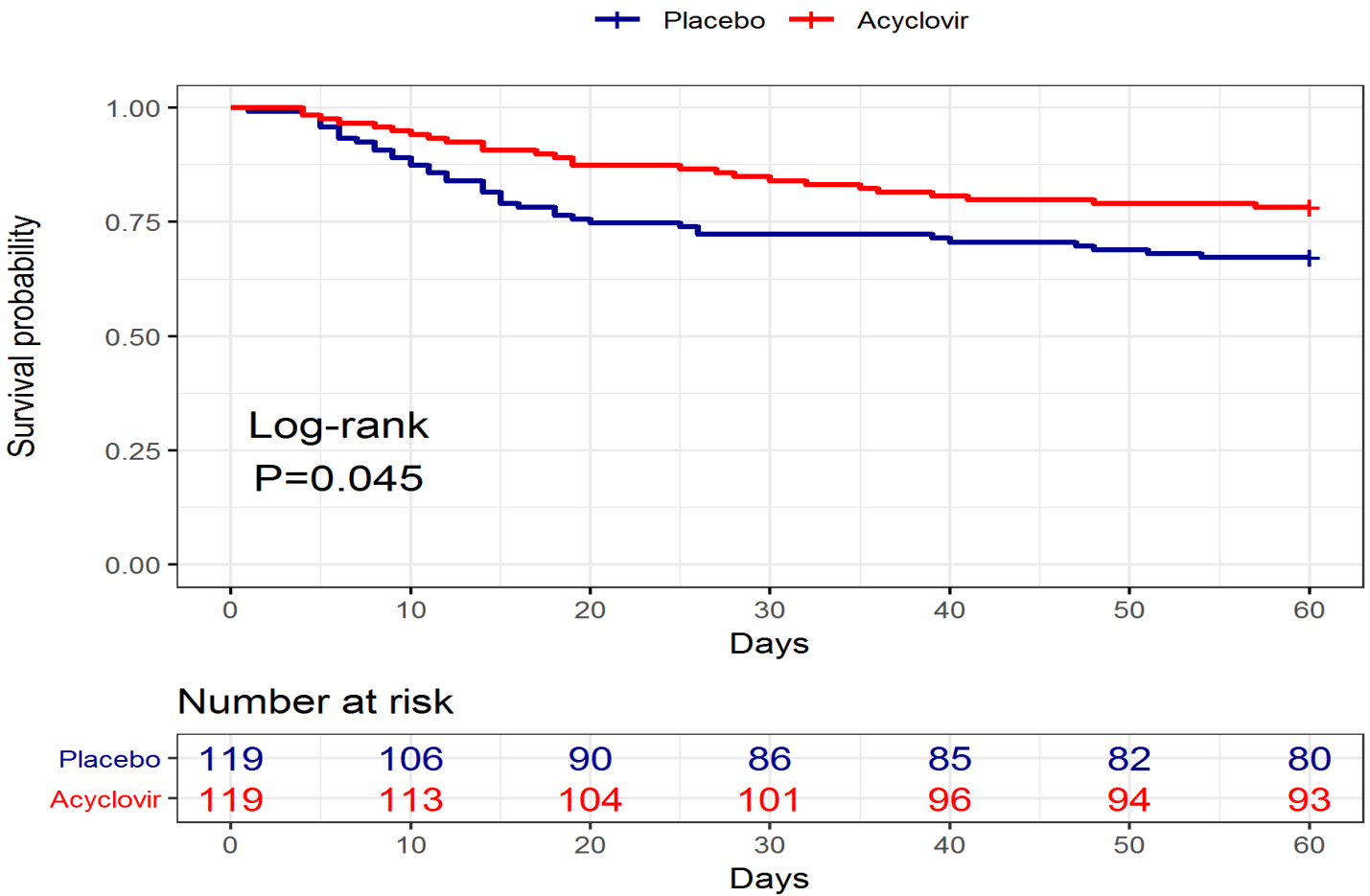
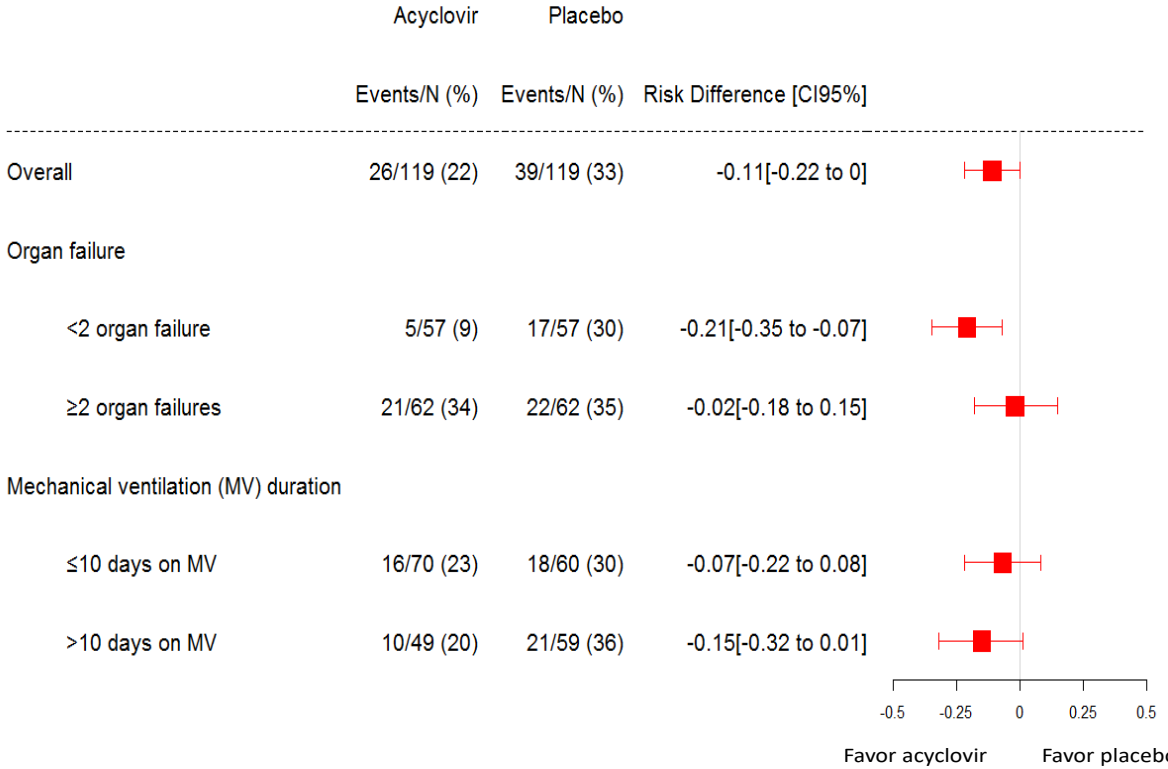

Placebo
Acyclovir
Survival probability
1.00
0.75
0.50
0.25
0.00
Log-rank
P=0.045
0
10
20
30
40
50
60
Days
Number at risk
Placebo 119 106 90 86 85 82 80
Acyclovir 119 113 104 101 96 94 93
0
10
20
30
40
50
60
Days

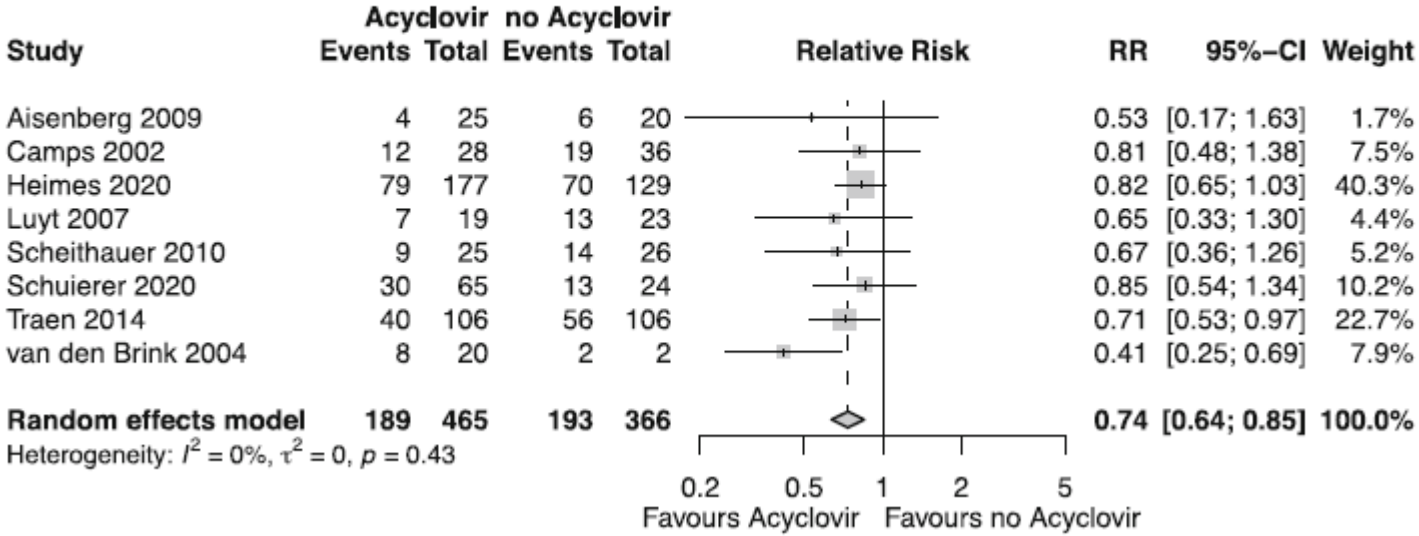
Analyse sous-groupe: mortalité à J60



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. Hotchkin, 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

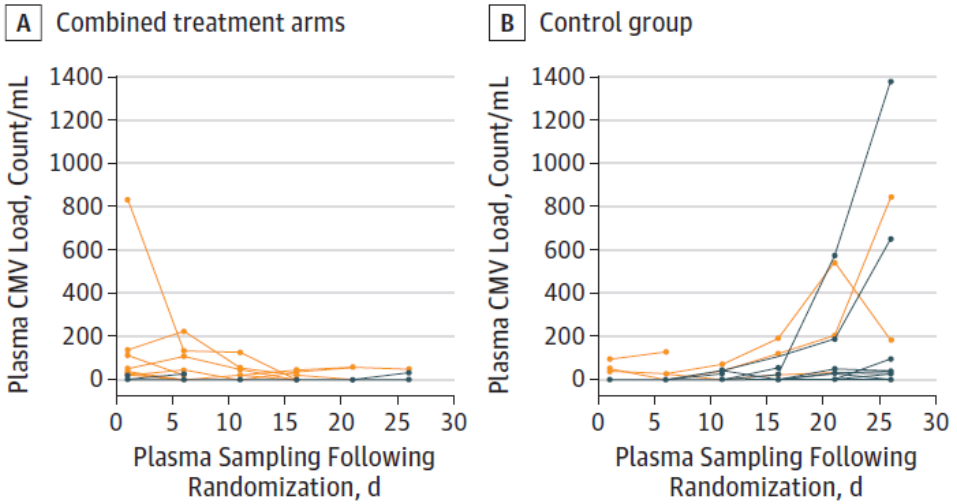
A Randomized Clinical Trial

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 valacyclovir 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)

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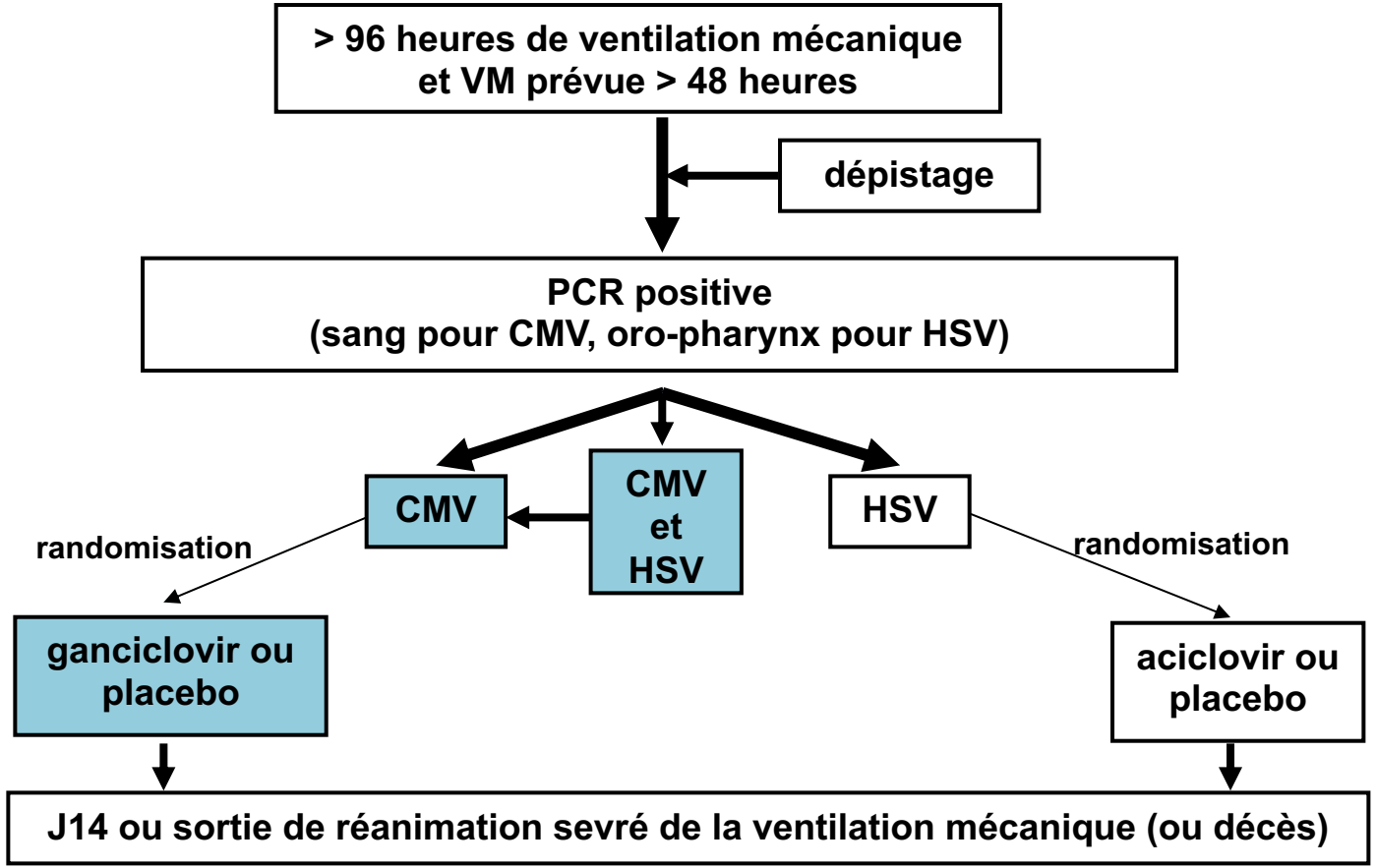
charles-edouard.luyt@aphp.fr



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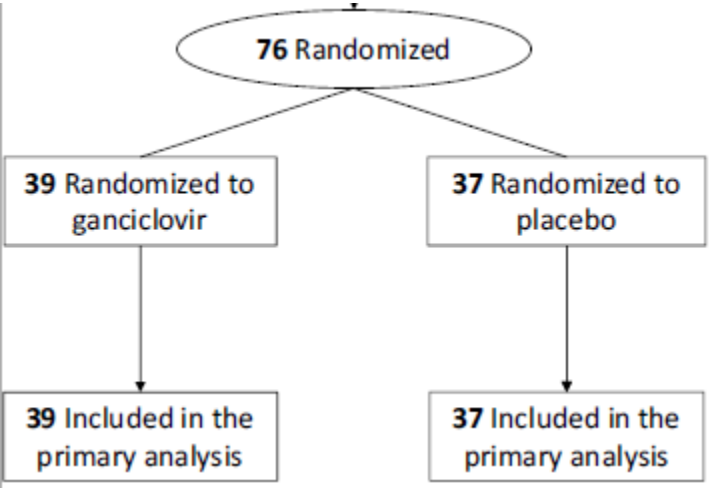
Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation



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)

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charles-edouard.luyt@aphp.fr

Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation

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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

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Qui traiter ?

HSV

- Traitement prophylactic
- 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 sar
  - réactivation CMV dans les voie aériennes distales
- Traitement curatif: pneumonie à CMV (histologie)
  - Ganciclovir 5 mg/kg/j

charles-edouard.luyt@aphp.fr

Cytomegalovirus reactivation in ICU patients

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

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Infiltrats pulmonaires et altération des échanges gazeux

- Sang
  - Antigénémie positive (≥1 cel/2x10^5 PNN
  - ADN CMV >500 UI/ml
- LBA
  - Présence de CMV

+ au minimum 2 facteurs de risque

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

Ganciclovir IV 5 mg/kg/j pendant 2 semaines

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CONCLUSION

- Réactivation virale (HSV, CMV) sont fréquentes en réanimation et associées à un pronostic défavorable
- Traitement
  - Pas de traitement prophylactique
  - Pas de traitement pré-emptif
  - Traitement curatif en cas de bronchopneumonie herpétique ou pneumonie à CMV

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