Infections à CMV en réanimation: faut-il traiter ?

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Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Papazian Laurent

Titre : Infections à CMV en réanimation: faut-il traiter ?

Consultant ou membre d'un conseil scientifique	☐ OUI	☑ NON
Conférencier ou auteur/rédacteur rémunéré d'articles ou documents	☐ OUI	☑ NON
Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations SRLF/ESICM	☑ OUI	☐ NON
Investigateur principal d'une recherche ou d'une étude clinique PTH PHRC	☑ OUI	☐ NON

Why???

- Viruses = emerging infectious diseases in ICU
- Many publications in MV patients
- Microbiological diagnosis

- Are herpesviruses pathogenics in ICU patients?
- Do HSV and CMV have the same pathogenicity?

Anesthesiology
1996; 84:280–7
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Cytomegalovirus

An Unexpected Cause of Ventilator-associated Pneumonia

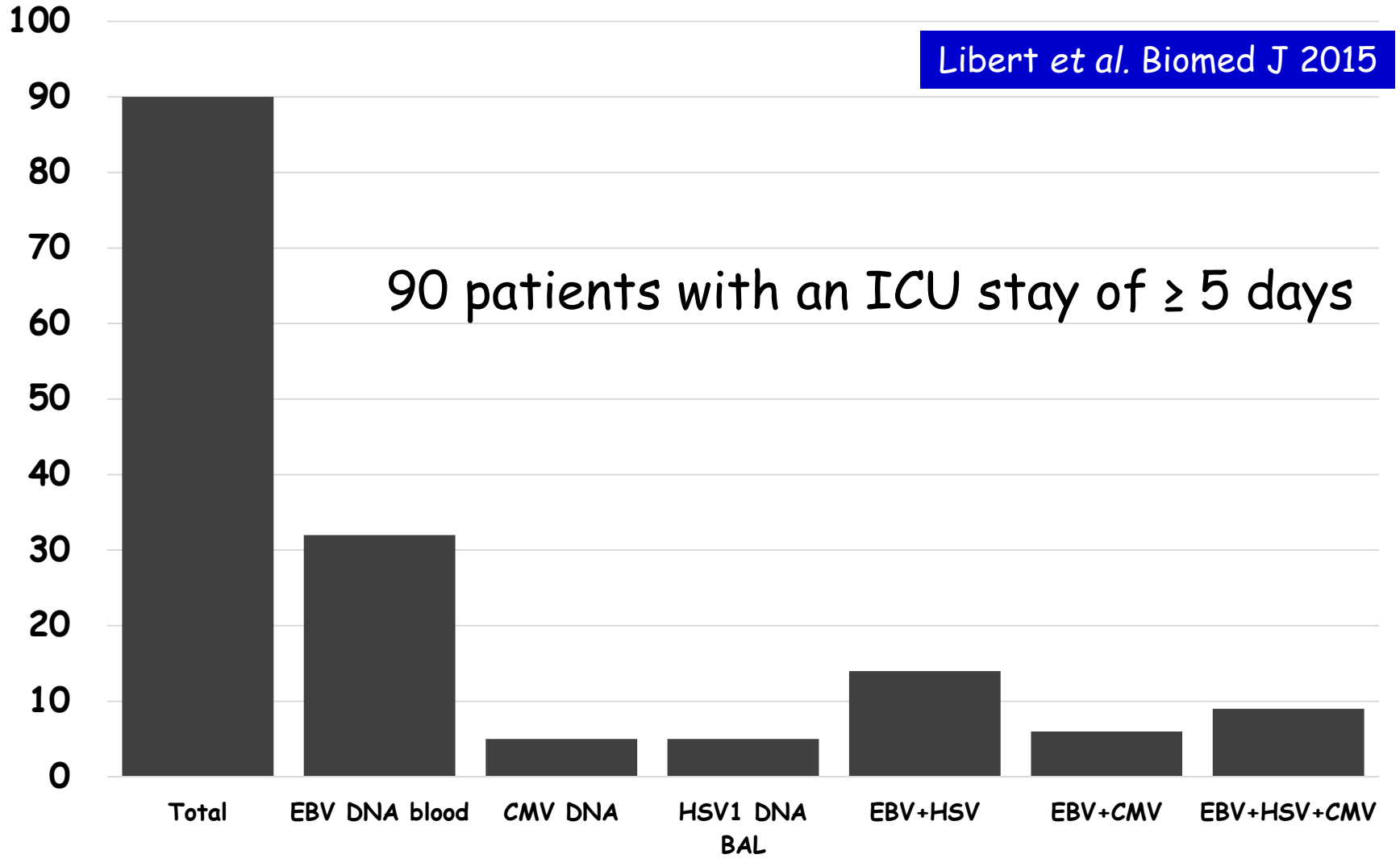
Laurent Papazian, M.D., Alain Fraisse, M.D.,† Louise Garbe, M.D.,‡ Christine Zandotti, M.D.,§ Pascal Thomas, M.D.,‖ Pierre Saux, M.D.,* Gilles Perrin, M.D.,* François Gouin, M.D.#*

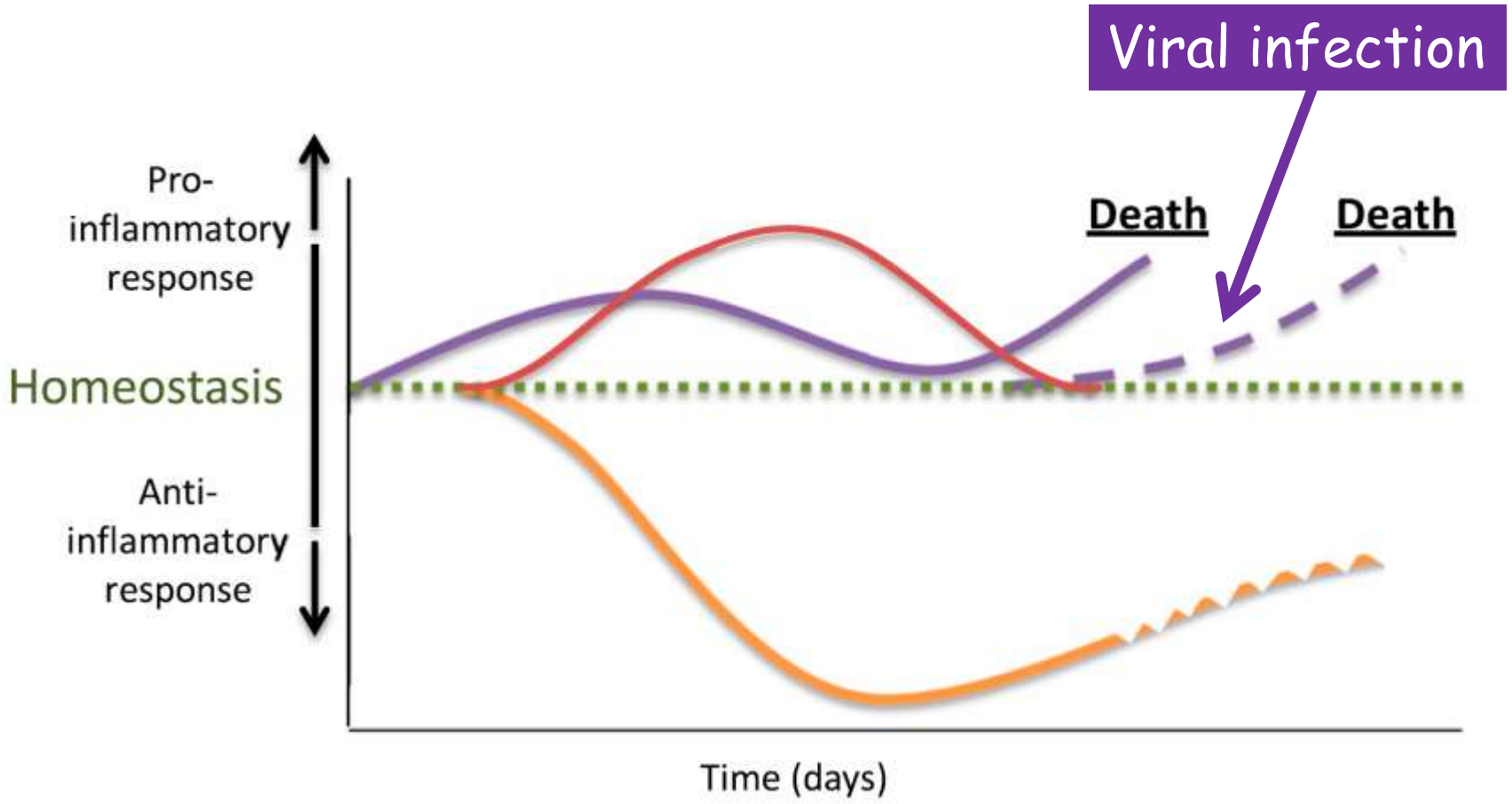
- **Retrospective study** (n = 2,795)
- **ARDS** and ventilation of more than 7 days + histology
- **Exclusion criteria**: leukemia, AIDS, steroids, chimiotherapy
- **Autopsies (n = 60), OLB (n = 26)**

  25 histologically-proven CMV pneumonia

- CMV sole pathogen in 88%

Multiple viral reactivations in ICU immunocompetent patients





Leentjens *et al.* AJRCCM 2013

CMV reactivation

- Lung is a major site of CMV latency and recurrence

Balthesen *et al.* J Virol 93

- CMV is carried in myeloid lineage progenitor cells in the BM and is maintained in the cells as they divide down the myeloid lineage into 0.01 % of peripheral mononuclear cells
- CMV reactivates when blood monocytes differentiate into macrophages into tissues under the influence of cytokines

Sissons *et al.* J Infect 2002

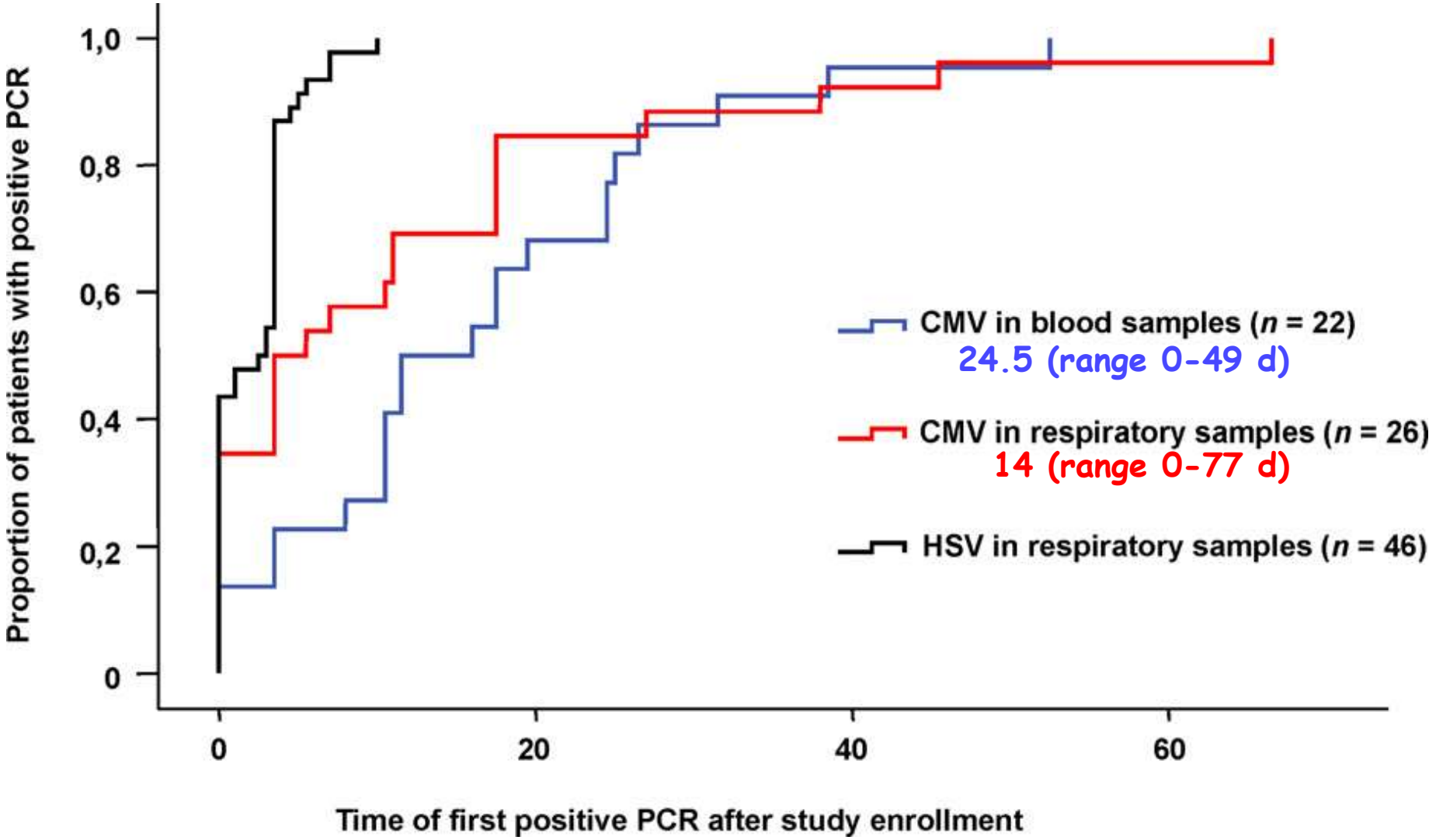
CMV PCR in blood and TA

Variable	Specimen	
	Tracheal aspirate	Plasma
Patients with positive CMV PCR result no. (%)	19 (100)[a]	14 (76)
Initial CMV DNA load (copies/ml)	124 (11–57,042)	18 (10–2,660)
Peak CMV DNA load (copies/ml)		
Overall	239 (11–132,754)	67 (10–2,799)
Deceased	357 (11–132,754)	59.5 (10–2,779)
Survivors	164 (38–8,103)	81.5 (10–2,779)
Samples with CMV DNA load >1,000 copies/ml, no. (%)	8 (19)	4 (12)
Time to first positive PCR after admission, days	11 (0–34)	16.5 (0–28)
Time to resolution (negative PCR) of the episode, days[c]	28 (18–35)	20 (10–35)

Chilet *et al.* J Med Virol 2010

CMV and HSV PCR

Heininger *et al.* Crit Care 2011



What kind of patients ?

Variables	CMV Group (n = 40)
Surgical	24
Oesogastrectomy	3
Duodenopancreatectomy	2
Colonic surgery	7
Peritonitis	9
Miscellaneous	3
Medical	13
ARDS	4
Necrotizing pancreatitis	2
Digestive bleeding	3
Cirrhotic decompensation	3
Miscellaneous	1
Trauma	3
Cranial	1
Thoracic	1
Abdominal	1

Jaber *et al.* Chest 2005

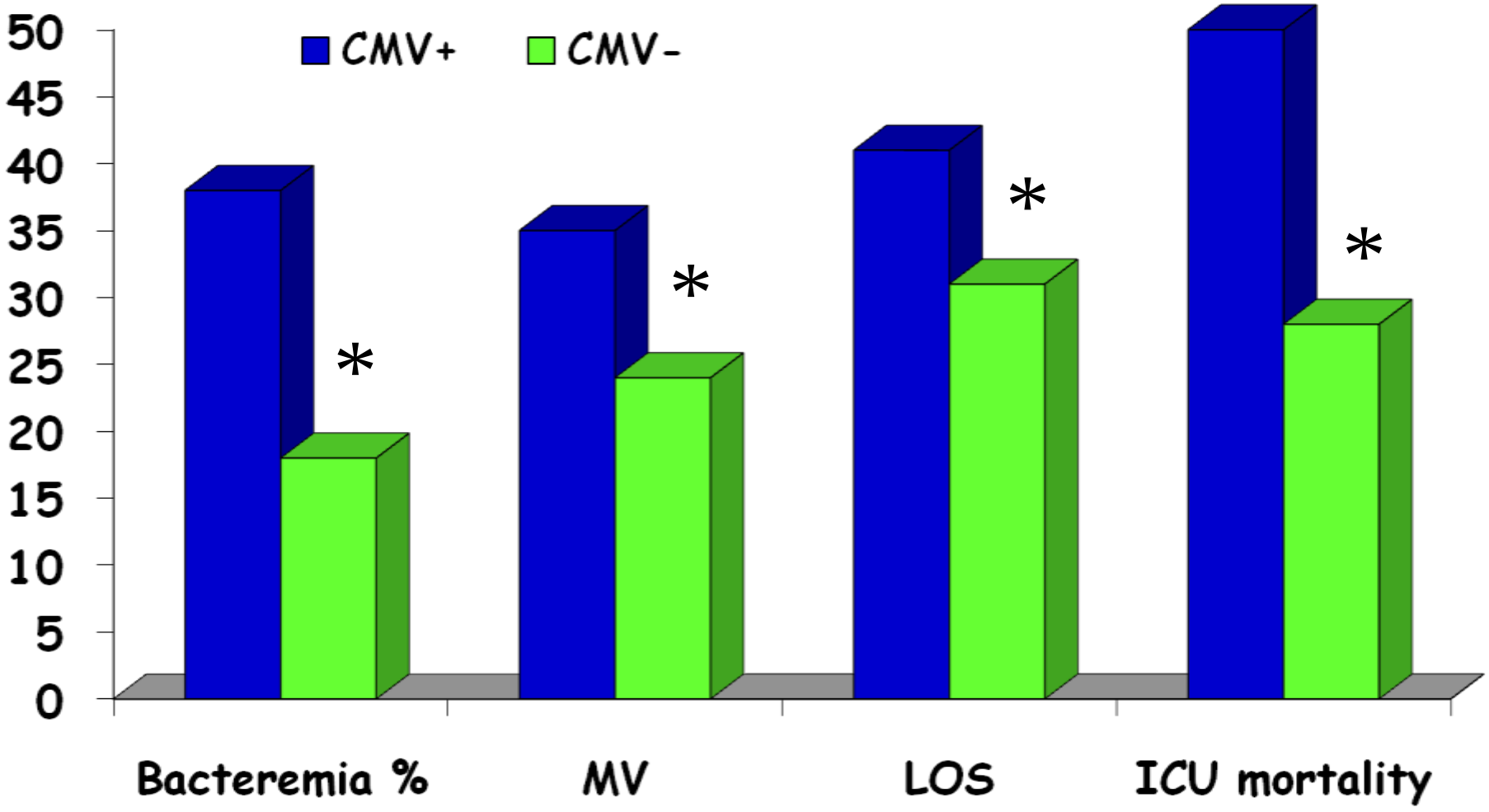
CMV: clinical significance?

- 237 patients: at least 1 positive antigenaemia
- Incidence: 40/237 (17%)

Variables	Exact Matched Pairs, No. (%)	Mean Difference	Maximal Difference
Gender equal	39/40 (97.5)		
Age (± 10), yr	40/40 (100)	5	10
SAPS II (± 7)	35/40 (87.5)	4	10
To ICU admission time (± 12), mo	35/40 (87.5)	9	29
Type of admission equal	35/40 (87.5)		

Jaber *et al.* Chest 2005

Morbidity – ICU mortality



Jaber *et al.* Chest 2005

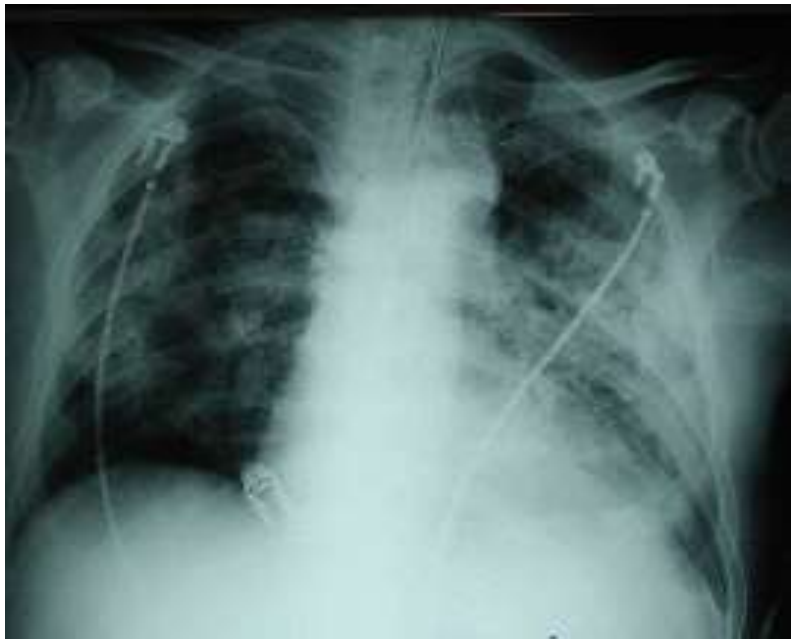
Risk factors for CMV disease in critical care setting and their strength of association

Risk factor	Strength of association
Immune compromised	Strong association [49]
Age	No evidence [8]
Gender	Inconsistent data [8]
Mechanical ventilation	Strong association [1, 8]
Sepsis	Strong association [8, 47]
Corticosteroids use	Weak evidence [27]
Blood transfusion	Weak association [1, 27, 28]
Disease severity scores	No association [1, 24, 27–31]
Active malignancy	No association [2, 24, 28]
Stress (catecholamines surge)	Weak association [25]

Al-Omari *et al.* Ann Intensive Care 2016

Clinical presentation

- t° = 36.6 ± 2.4 °C
- GB = 13.9 ± 5.8 G/l
- Weinberg = 5 (3-7)
- PaO2/FiO2 = 195 (139-277)



- Cholestasis
- ASAT, UI.L^{-1} = 30 (19-40)
- ALAT, UI.L^{-1} = 35 (20-99)

Other sites of CMV infection

- Colitis
  - From January 2000 to March 2013
    - Patients with a histopathological diagnosis of CMV colitis
    - 158 ICU beds
  - 14 cases
  - Mortality rate, 71.4%

Siciliano *et al.* Int J Infect Dis 2014

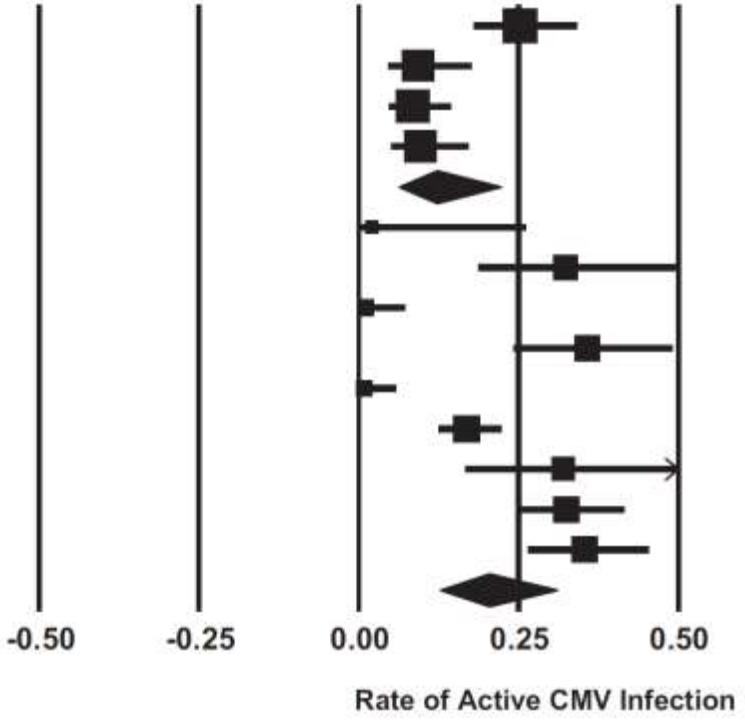
Chan *et al.* J Crit Care 2014

Incidence of active CMV infection

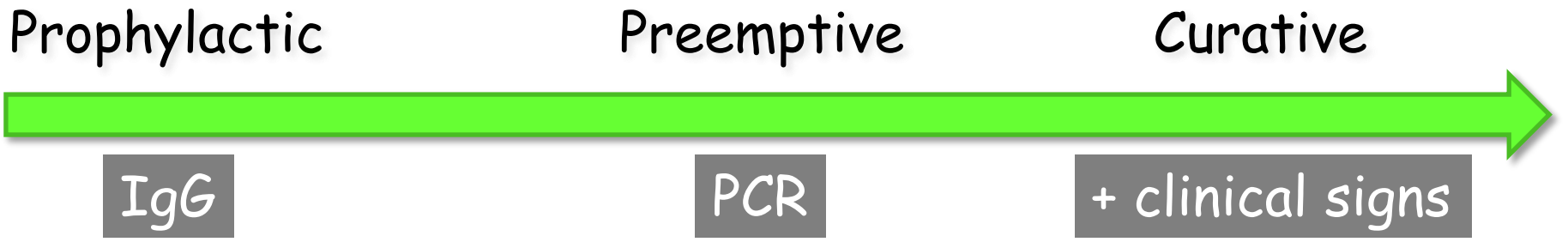
Kalil & Florescu Crit Care Med 2009

Active CMV* Infection Rate by Diagnostic Method

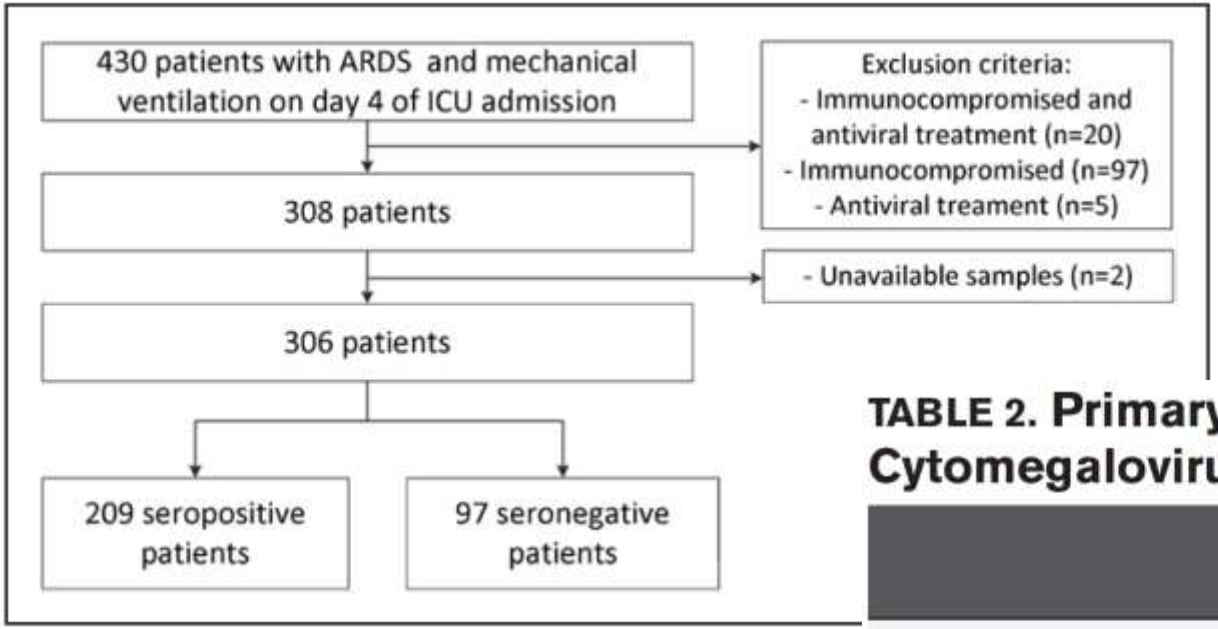
Group by CMV Diagnostic Method	Study name	Event rate	Lower limit	Upper limit	Total
Viral Culture	Domart Y 1990	0.25	0.18	0.34	29 / 115
Viral Culture	Papazian L 1996	0.09	0.05	0.18	8 / 86
Viral Culture	Cook CH 1998	0.08	0.05	0.14	12 / 142
Viral Culture	Cook C 2003	0.10	0.05	0.17	10 / 104
Viral Culture		0.12	0.06	0.22	59 / 447
Viral DNA or Antigen	Stephan F 1996	0.02	0.00	0.26	1 / 24
Viral DNA or Antigen	Kutza A 1998	0.32	0.19	0.50	11 / 34
Viral DNA or Antigen	Desachy A 2001	0.01	0.00	0.07	1 / 96
Viral DNA or Antigen	Heininger A 2001	0.36	0.24	0.49	20 / 56
Viral DNA or Antigen	Razonable R 2002	0.01	0.00	0.06	1 / 120
Viral DNA or Antigen	Jaber S 2005	0.17	0.13	0.22	40 / 237
Viral DNA or Antigen	von Muller L 2006	0.32	0.17	0.52	8 / 25
Viral DNA or Antigen	Limaye A 2008	0.33	0.25	0.41	39 / 120
Viral DNA or Antigen	Ziemann M 2008	0.35	0.27	0.45	35 / 99
Viral DNA or Antigen		0.20	0.13	0.31	156 / 811



When to treat?



Is the serologic status relevant?



Ong et al. CCM 2015

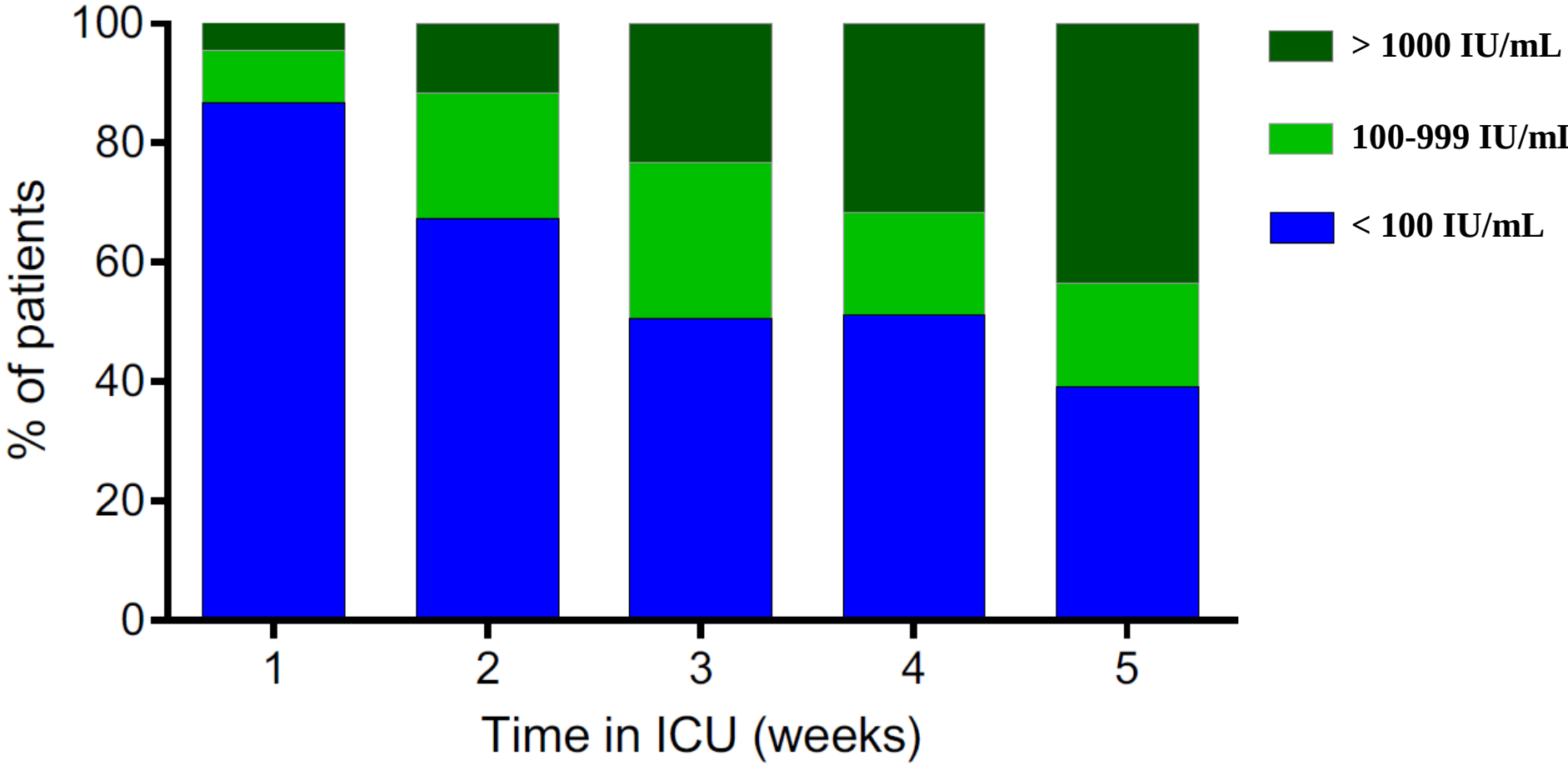
TABLE 2. Primary Outcome by Cytomegalovirus Serostatus

	Seronegative ($n = 97$)	Seropositive ($n = 209$)
Ventilator-free days[a]		
0[b]	28 (29)	72 (34)
1–18	36 (37)	63 (30)
19–24	33 (34)	74 (35)

- CMV reactivation 53 of 209 patients (26%)
- 28-day mortality was 28%
  - compared to 24% in seropositive patients without reactivation
  - and 16% (p=0.09) in seronegative patients

CMV reactivation in seropositive ARDS patients

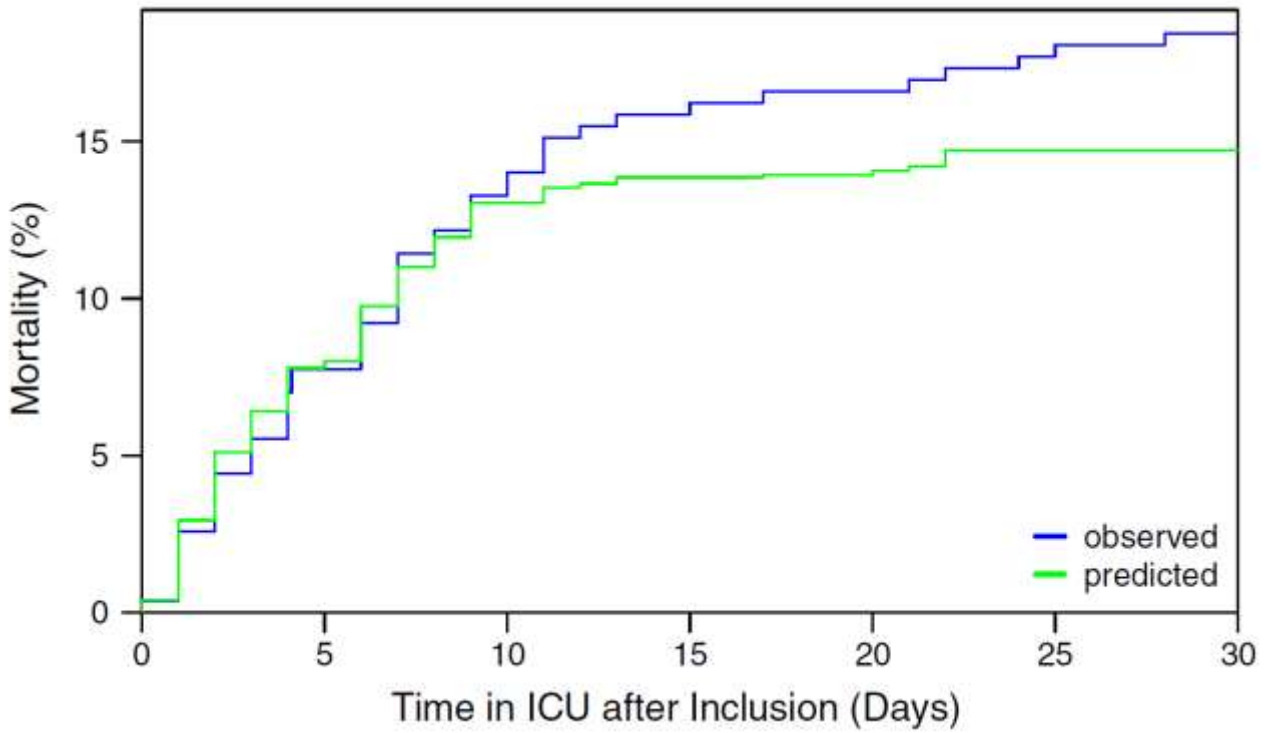
Ong et al. Intensive Care Med 2016



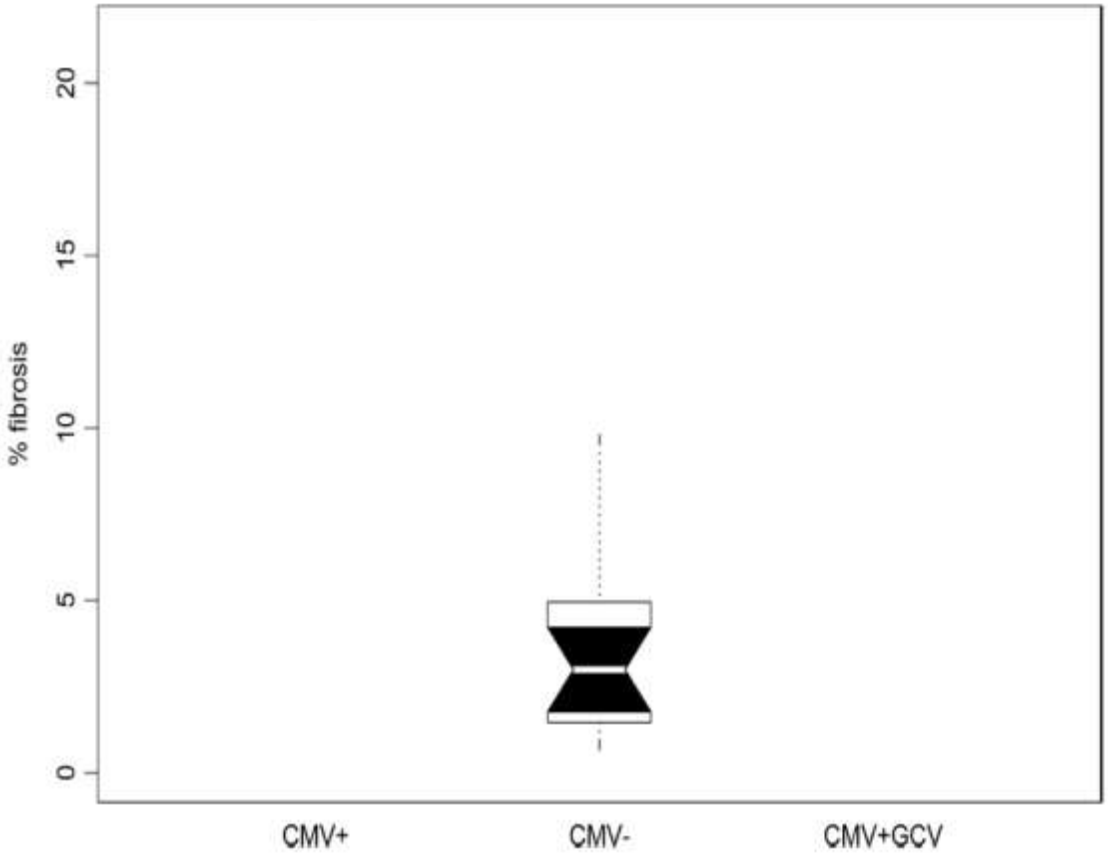
Mortality in seropositive ARDS patients presenting a reactivation

Ong et al. Intensive Care Med 2016

	Reactivation	Non-reactivation	*p* value
Death on ventilator before day 30[a]	23/74 (31)	29/197 (15)	<0.01
Death in ICU[b]	26/76 (34)	32/195 (16)	<0.01
Death by day 90[b]	35/76 (46)	55/195 (28)	<0.01
Duration of mechanical ventilation (days)	15 (10–26)	8 (6–12)	<0.01
Length of stay in ICU (days)	16 (11–28)	9 (7–14)	<0.01



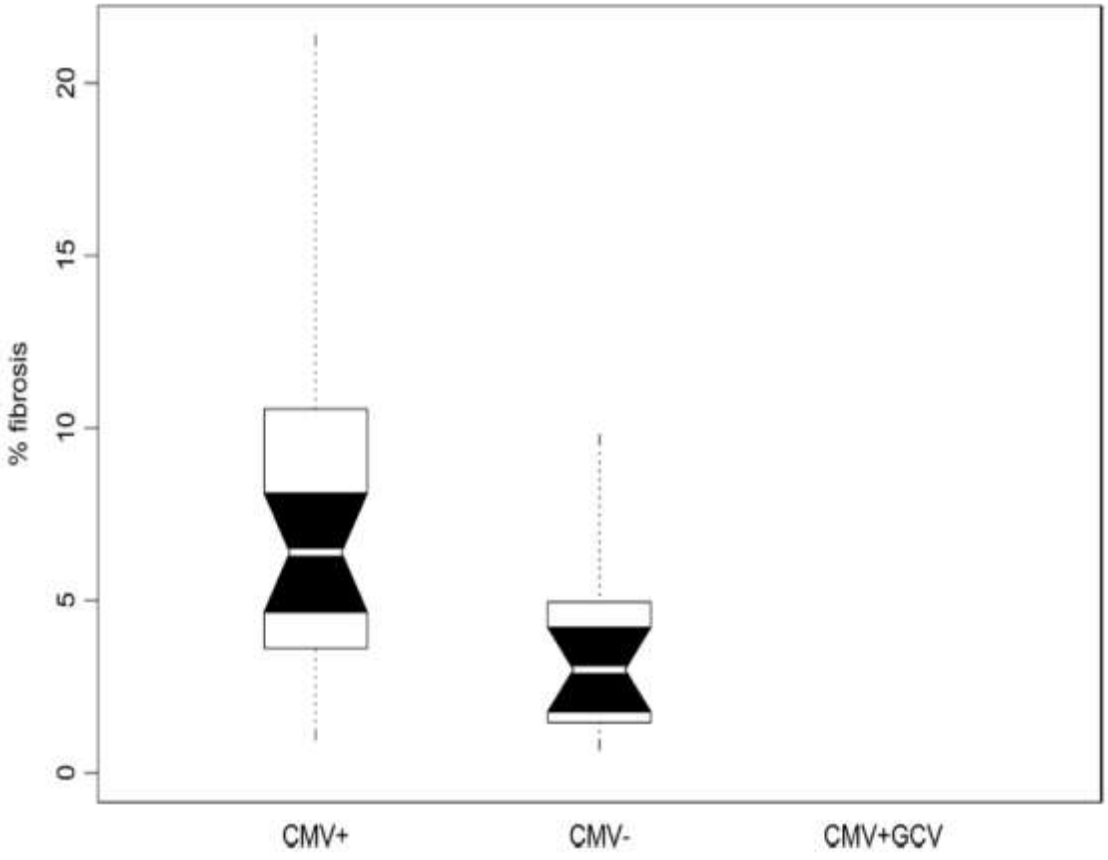
CMV and lung fibrosis



- Mice
- Peritonitis
- After 3 weeks
  - CMV -
  - Reactivation CMV
  - Reactivation CMV + Ganciclovir

Cook *et al.* Crit Care Med 2006

CMV and lung fibrosis



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Cook *et al.* Crit Care Med 2006

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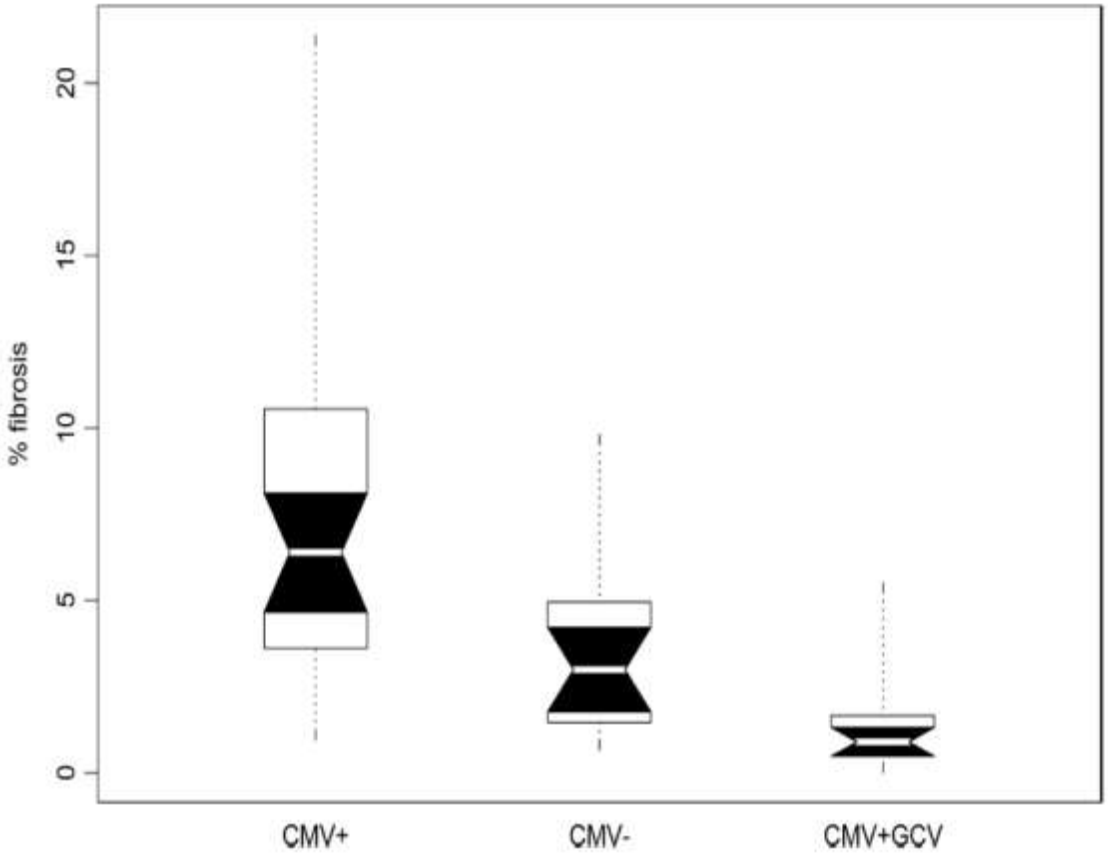


- Mice
- Peritonitis
- After 3 weeks
  - CMV -
  - Reactivation CMV
  - Reactivation CMV + Ganciclovir

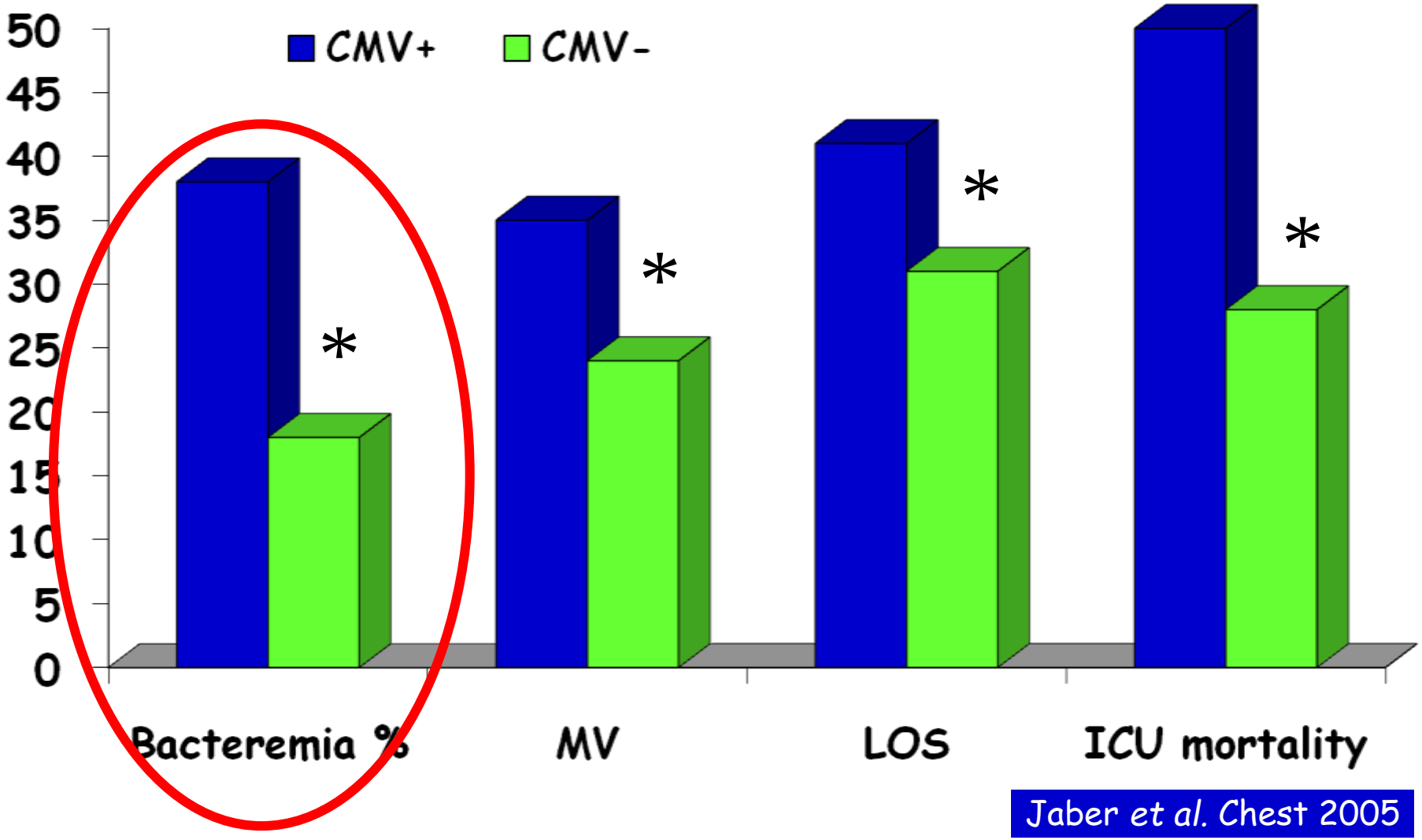
Cook *et al.* Crit Care Med 2006

CMV and bacterial infections

	CMV + (39)	CMV – (203)	
ICU death	21 (54)	76 (37)	0.08
Hospital death	23 (59)	84 (41)	0.06
VFD d28	0 (0-0)	2 (0-19)	<0.001
VFD d60	0 (0-23)	34 (0-51)	<0.001
≥ 1 VAP bact	22 (56)	47 (23)	<0.001
≥ 1 bacterial noso infection	27 (69)	68 (33)	<0.001
ARDS	17 (44)	59 (29)	0.11

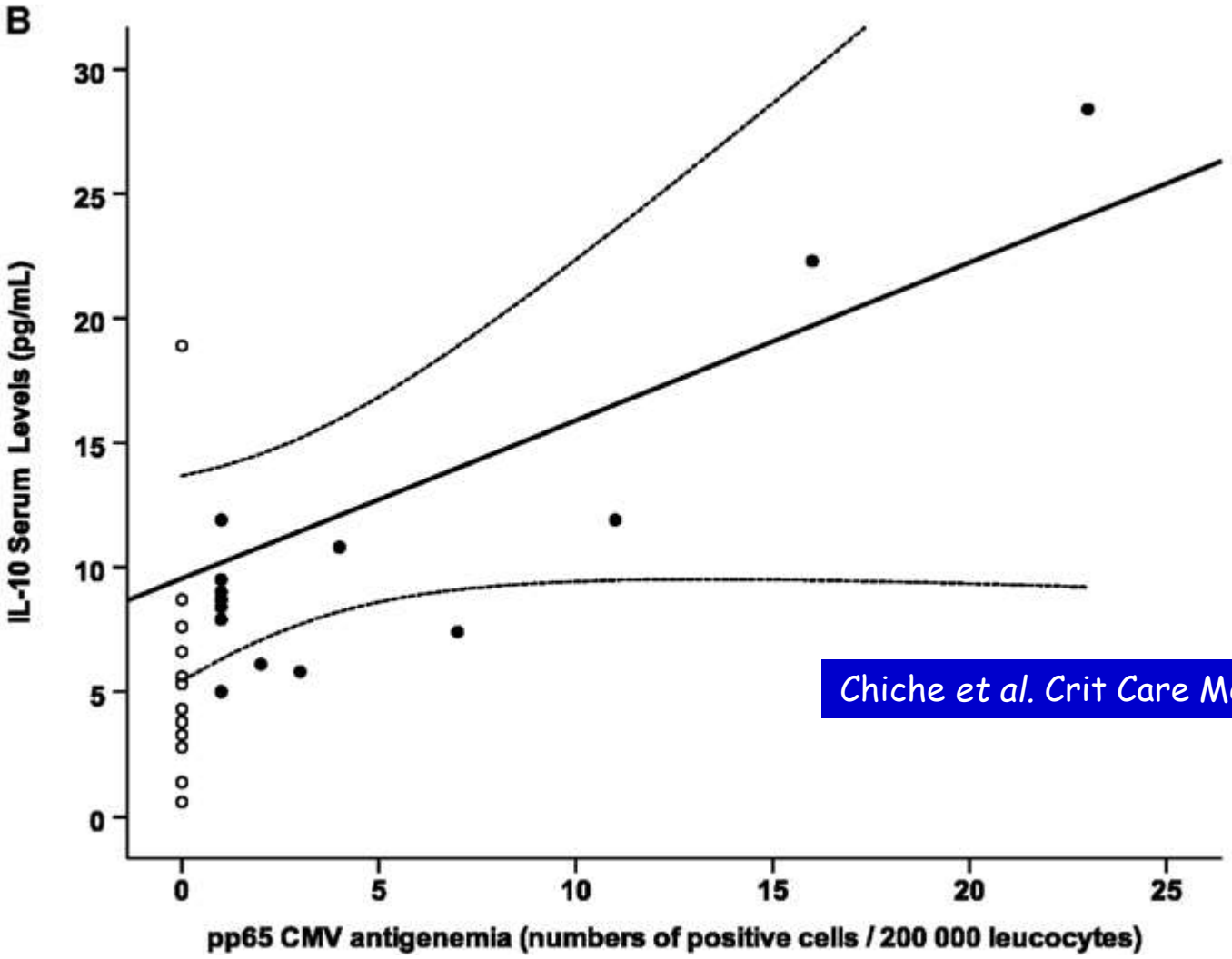
Chiche et al. CCM 2009

Morbidity – ICU mortality

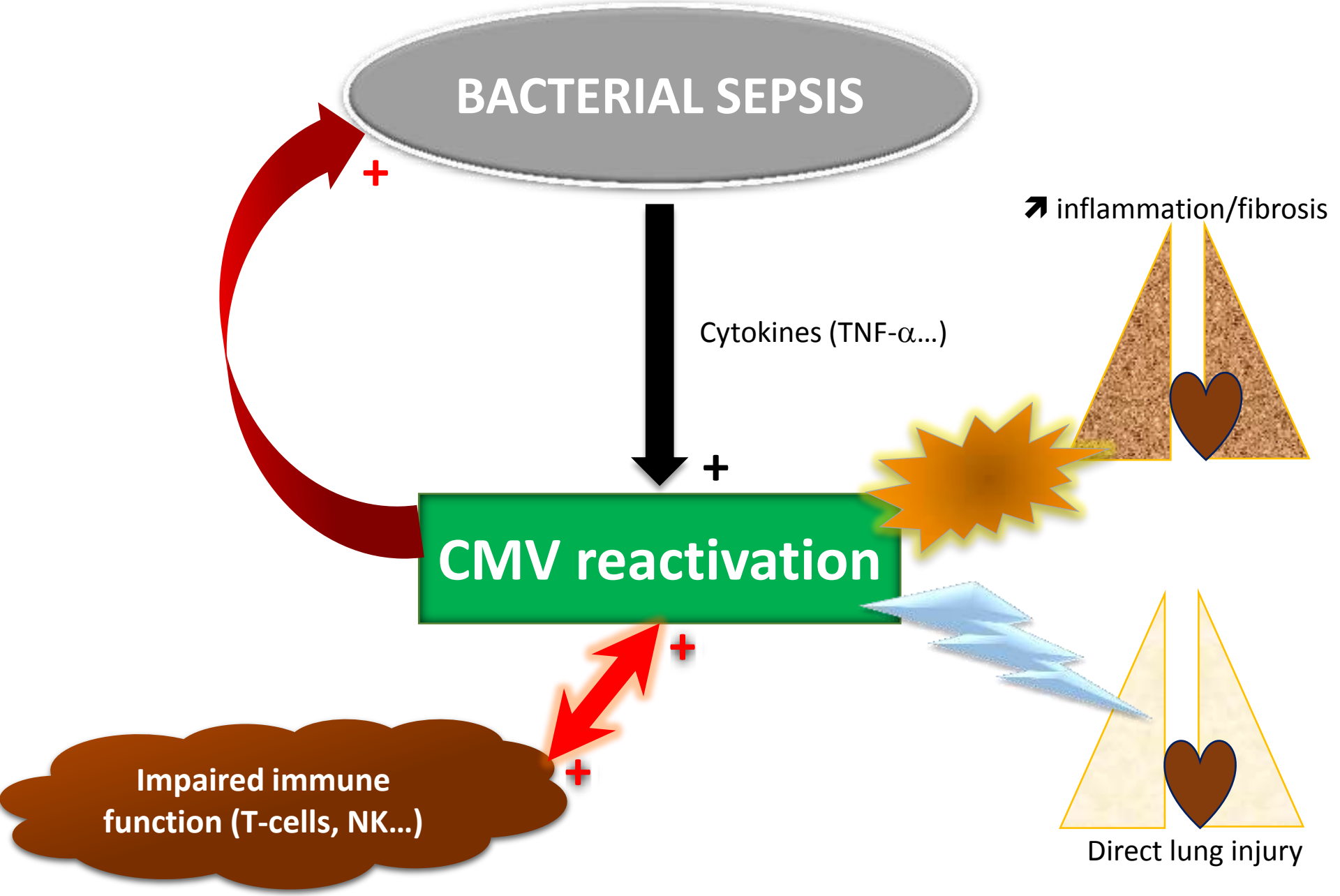


Jaber *et al.* Chest 2005

Correlation antigenemia/IL-10

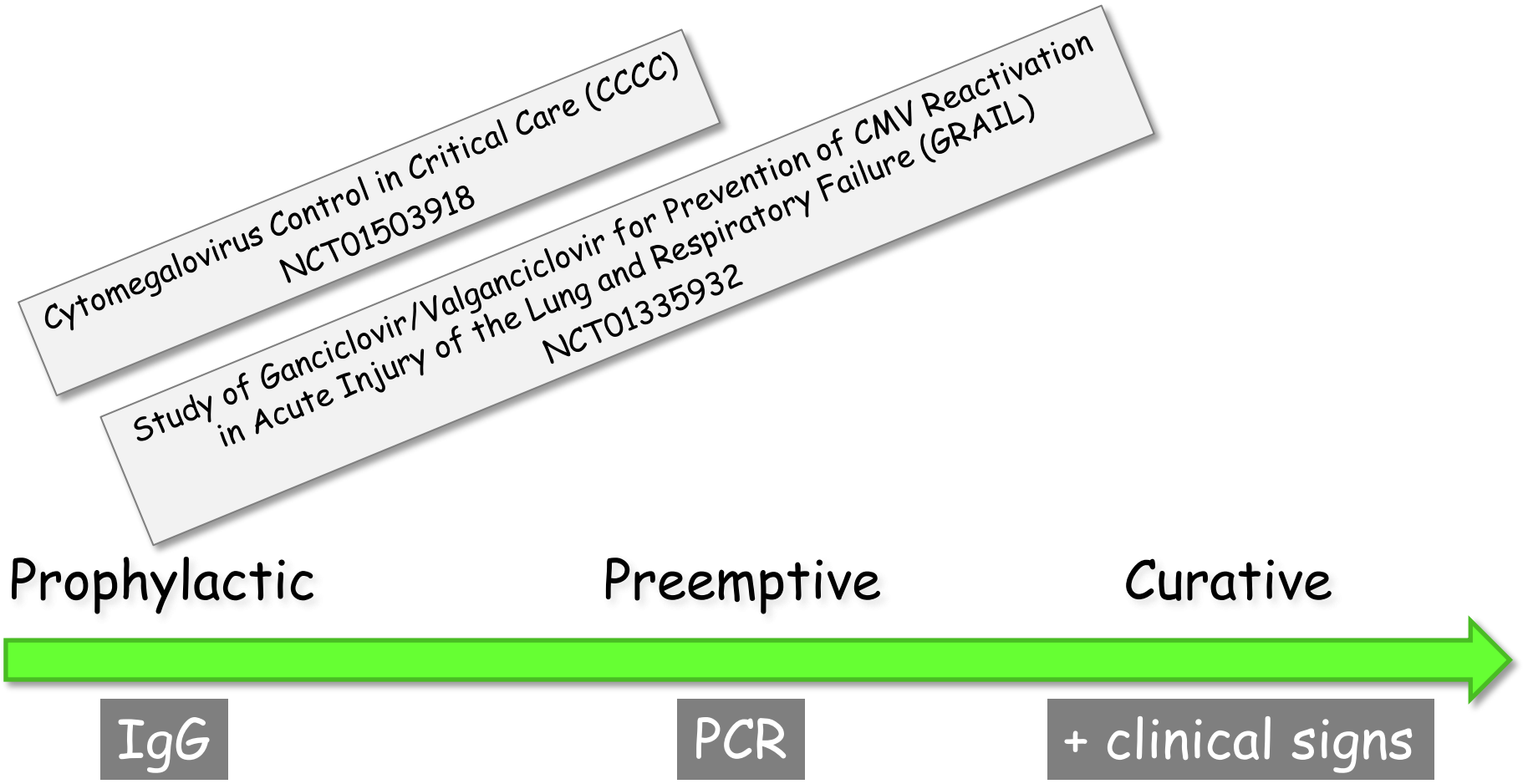


Chiche *et al.* Crit Care Med 2012



Papazian *et al.* Intensive Care Med 2015

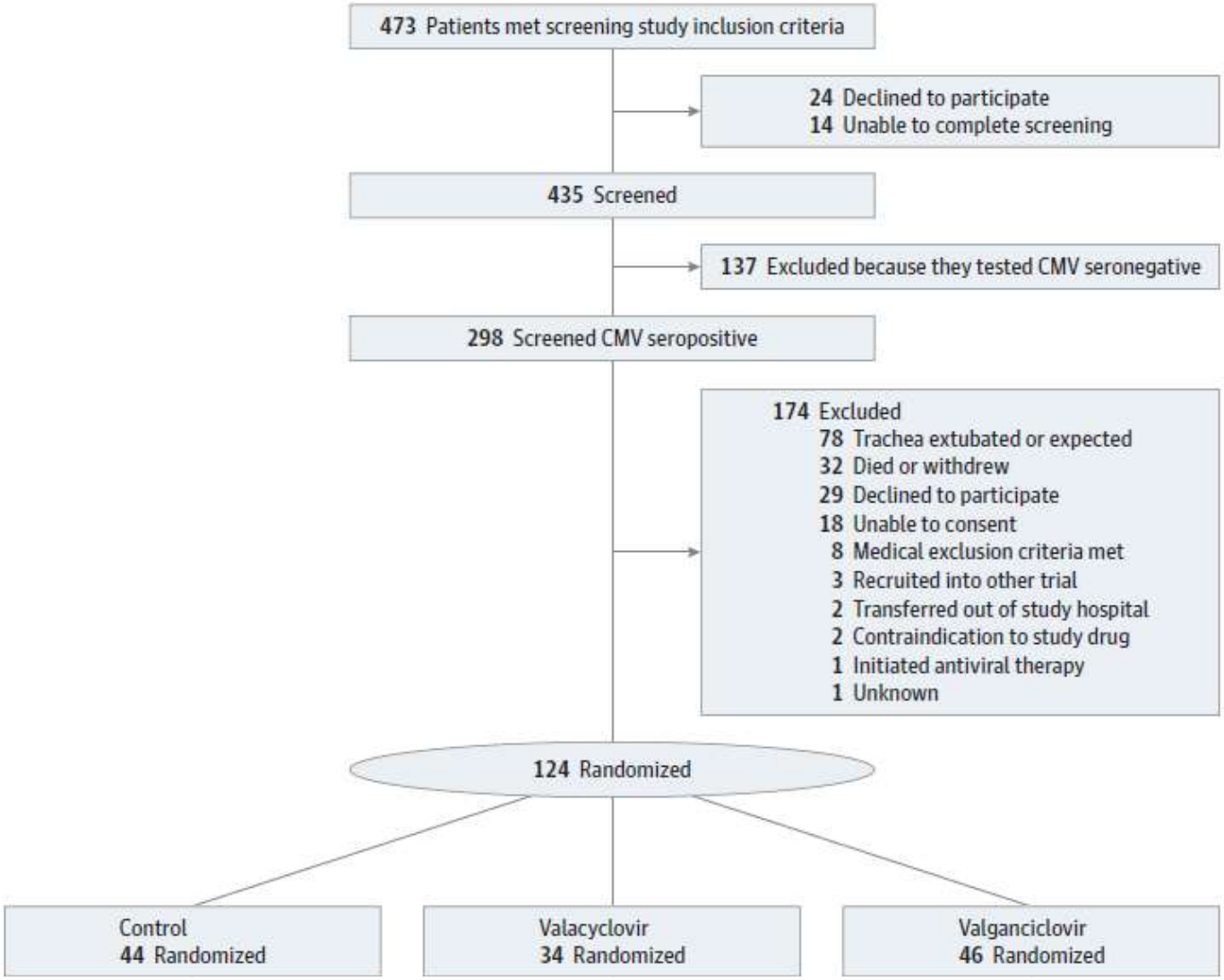
When to treat?



Reactivation prevention

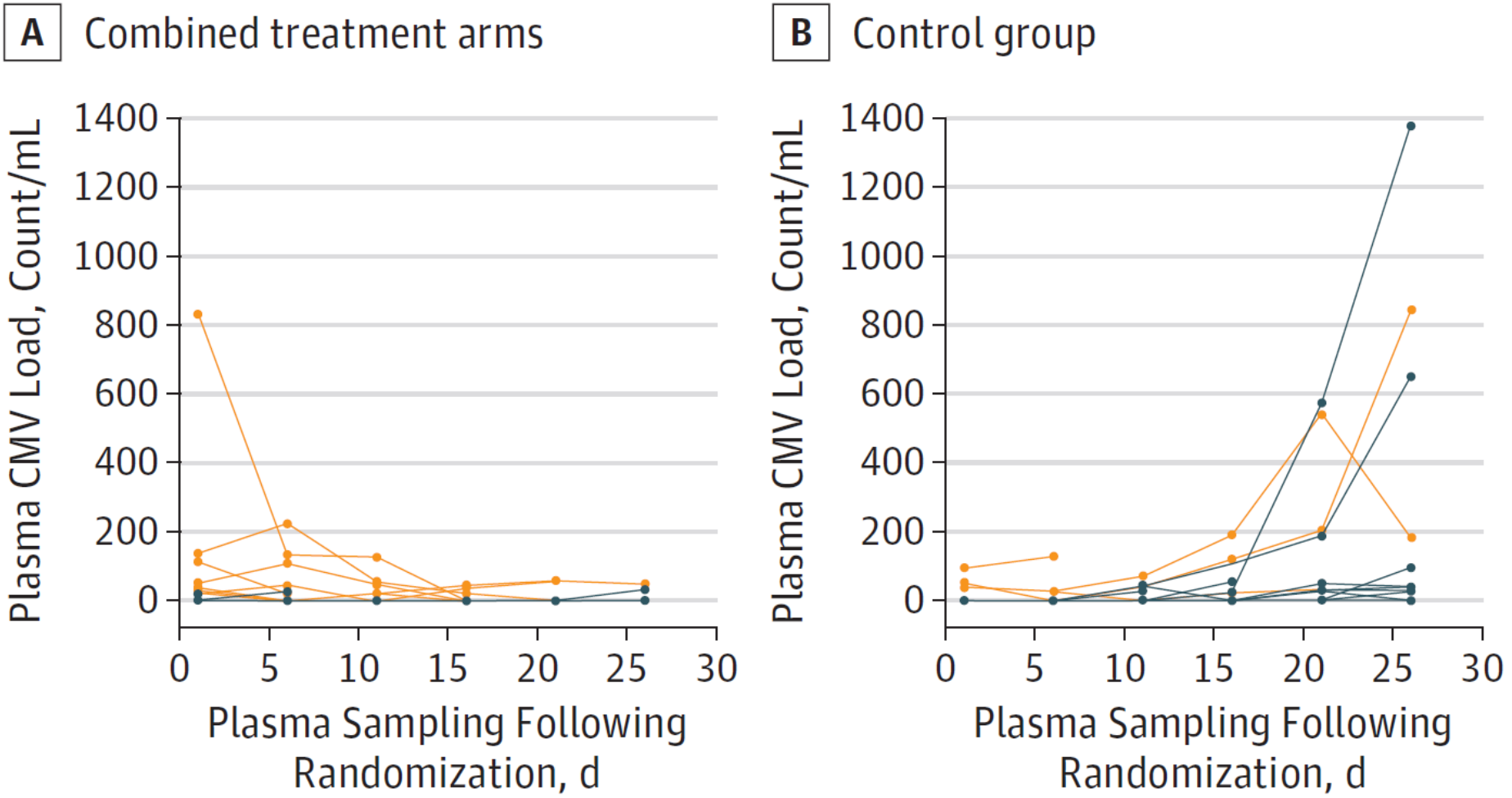
- Single-center, open label RCT, 3-armed trial of 2 anti-CMV prophylaxis treatments and standard care for patients
  - CMV IgG + and invasive MV
- Valganciclovir hydrochloride : 450mg x 1/d by the enteral route or 2.5mg/kg Ganciclovir
- Valacyclovir hydrochloride : 2g 4 x 4/d by the enteral route or Aciclovir 10 mg/kg x 3/d
- Duration : > 14 d for 28 d max

Cowley *et al.* JAMA Intern Med 2017



Cowley *et al.* JAMA Intern Med 2017

Figure 2. Cytomegalovirus (CMV) Viral Load in Blood

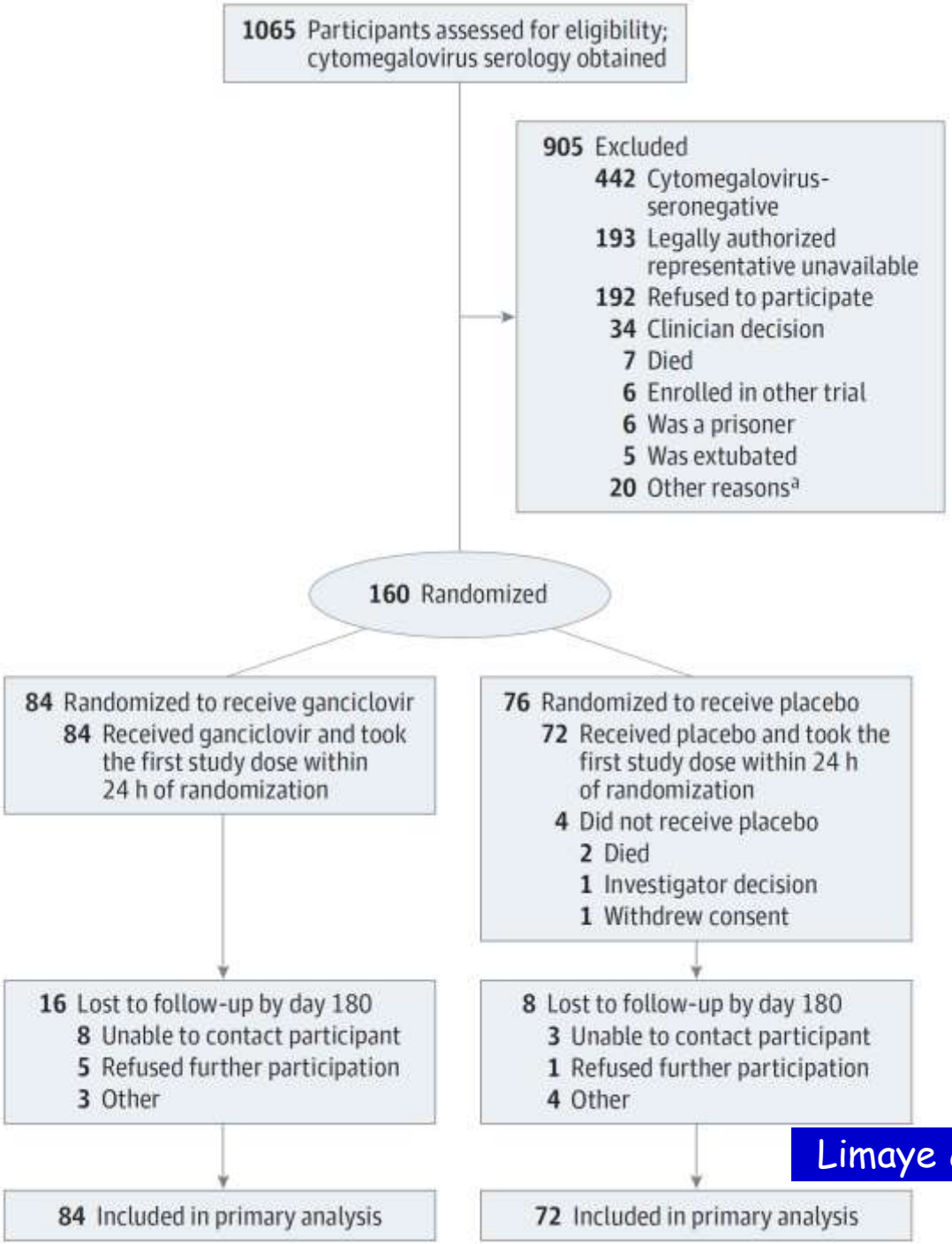


Outcome	Control (n = 44)	Valacyclovir (n = 34)	Valganciclovir (n = 46)
Secondary Clinical Measures			
Organ failure–free days (SOFA score <2), median (IQR) [range]	3.5 (0-18) [0-31]	1.5 (0-13) [0-24]	2.0 (0-11) [0-36]
Moderate organ failure–free days (SOFA score <5), median (IQR) [range]	18.0 (2-24) [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)
Safety Measures			
Requirement for G-CSF therapy, No. (%)	0	0	0
Neutropenia (<1000/μL), No. (%)	0	0	0
Platelet count (<50 × 10^3/μL), No. (%)	10 (22.7)	9 (26.5)	10 (21.7)
Platelet transfusions, No.	44	32	42
Median (IQR)	0 (0-0)	0 (0-0.5)	0.2 (0-1)
Renal insufficiency, No. (%)			
CrCl <60 mL/min	23 (52.3)	22 (64.7)	24 (52.2)
CrCl <30 mL/min or required dialysis	19 (43.2)	16 (47.1)	18 (39.1)

GRAIL study

- Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung = phase 2 clinical trial
  - To assess safety and feasibility
  - To explore potential clinical end points for future definitive phase 3 trials
  - Main outcome = Interleukin 6 (IL-6)
- Nonimmunocompromised CMV IgG–seropositive adults with respiratory failure and severe sepsis/trauma receiving invasive MV

Limaye *et al.* JAMA 2017



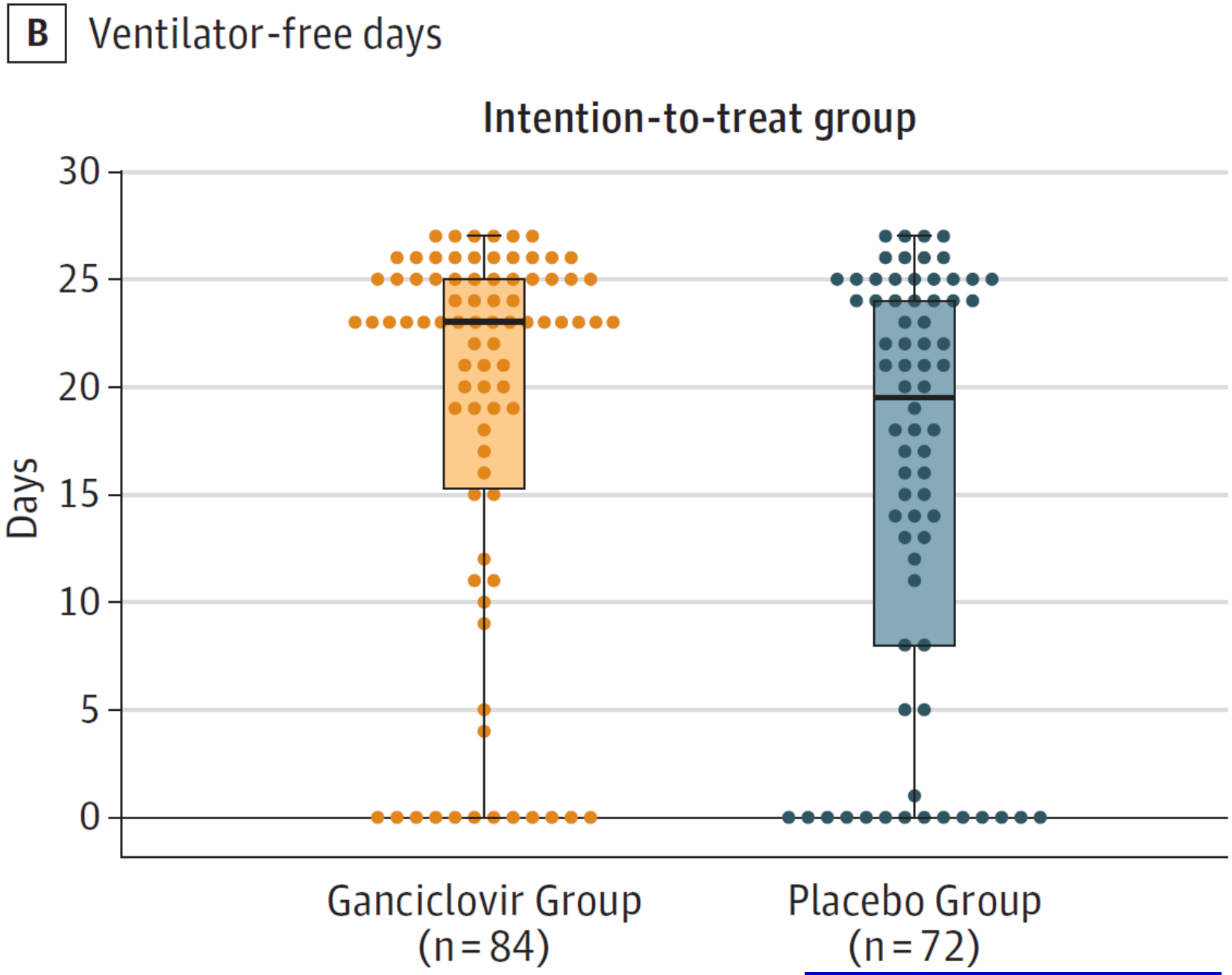
Limaye *et al.* JAMA 2017

Characteristic	Intention-to-Treat Group (n = 156)	
	Placebo Group (n = 72)	Ganciclovir Group (n = 84)
Age, median (IQR), y	58 (51-68)	57 (45-70)
Men, No. (%)	40 (56)	49 (58)
Race, No. (%)		
White	62 (86)	71 (85)
Nonwhite	10 (14)	13 (15)
Severe sepsis or septic shock, No. (%)	66 (92)	71 (85)
Trauma, No. (%)	6 (8)	13 (15)
Apache III score, mean (SD)[a]	71.12 (24.55)	77.10 (28.86)
MODS score on day 1, mean (SD)[b]	12.63 (3.33)	12.77 (3.23)
Baseline plasma IL-6 levels, mean (SD), $\log_{10}$ units	1.7 (0.8)	1.48 (0.61)
Time from ICU admission to enrollment, median (IQR), d	2 (2-4)	3 (2-4)
CMV reactivation in plasma at enrollment, No. (%)[c]	3 (4)	7 (8)
CMV reactivation in endotracheal aspirate or BAL sample at enrollment, No./Total No. (%)	12/60 (20)	14/70 (20)
Pao_2/Fio_2 ratio at enrollment, median (IQR), mm Hg	200 (149-251)	186 (141-242)

Limaye *et al.* JAMA 2017

	Intention-to-Treat Group (n = 156)			
	Placebo Group (n = 72)	Ganciclovir Group (n = 84)	Absolute Difference (95% CI)	*P* Value
Primary Outcome at Day 14				
Difference in plasma IL-6 level, mean, $\log_{10}$ units	−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				
Cumulative incidence of any plasma CMV reactivation, No. (%)	28 (39)	10 (12)	−27 (−40 to −14)	<.001
Mechanical ventilation duration, median (IQR), d[a]	6 (3 to 12)	5 (3 to 9)	−1 (−3 to −1)[b]	.16
Ventilator-free duration, median (IQR), d[a]	20 (8 to 24)	23 (16 to 25)	3 (0 to 6)	.05
ICU length of stay, median (IQR), d[a]	8 (5 to 15)	8 (4 to 14)	0 (−4 to 2)	.76
Hospital length of stay, median (IQR), d[a]	13 (8 to 23)	14 (8 to 22)	1 (−1 to 1)	.92
Secondary bacteremia or fungemia, No. (%)	11 (15)	13 (15)	0 (−10 to 10)	.97
Mortality, No. (%)	11 (15)	10 (12)	−3 (−14 to 7)	.54
Composite end point of mortality and >7 d of mechanical ventilation or >50% increase in IL-6 level, No. (%)	49 (68)	42 (50)	−18 (−33 to −3)	.02

Limaye *et al.* JAMA 2017



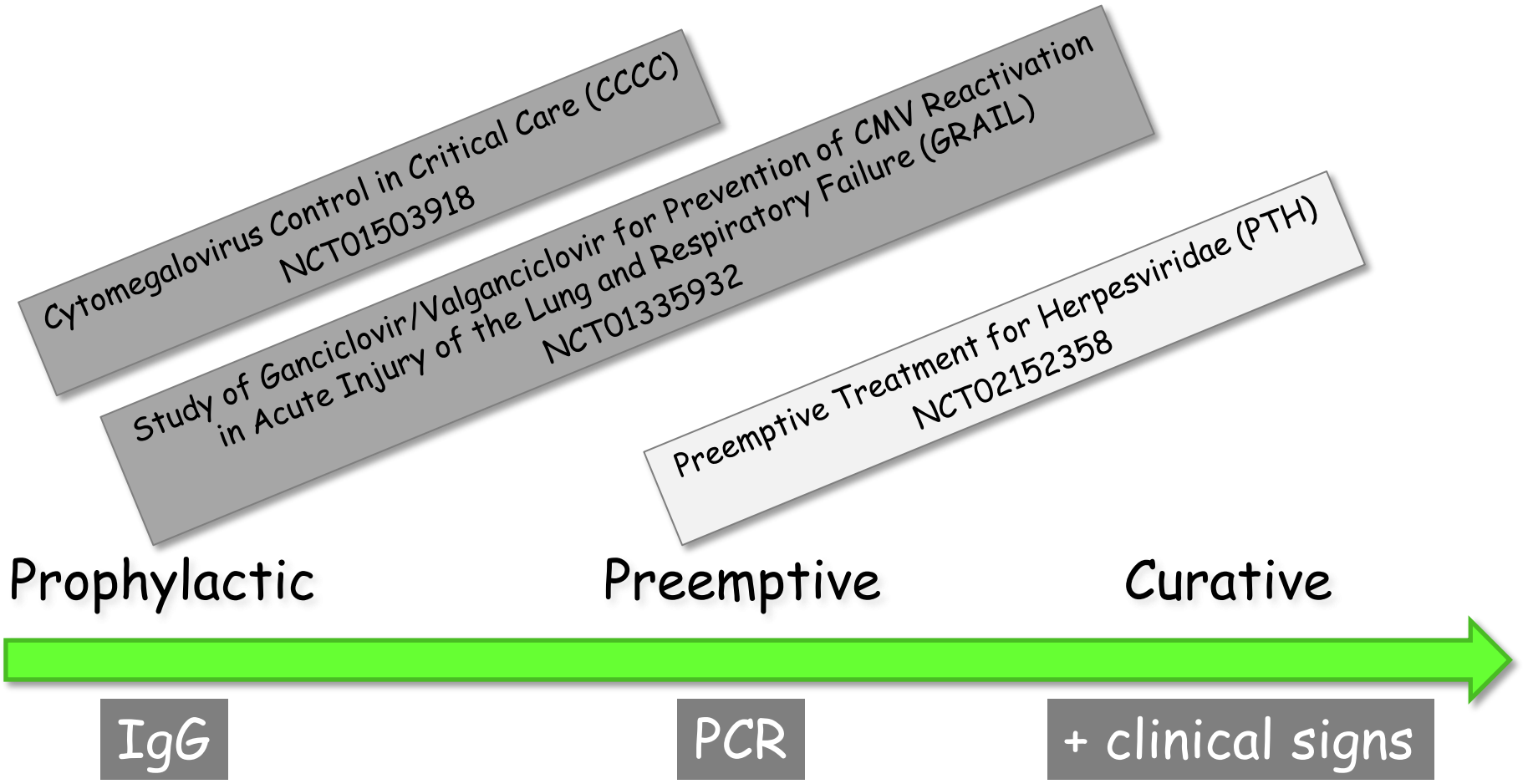
Limaye *et al.* JAMA 2017

Table 3. Safety Assessments Among Patients With Critical Illness Receiving Ganciclovir vs Placebo

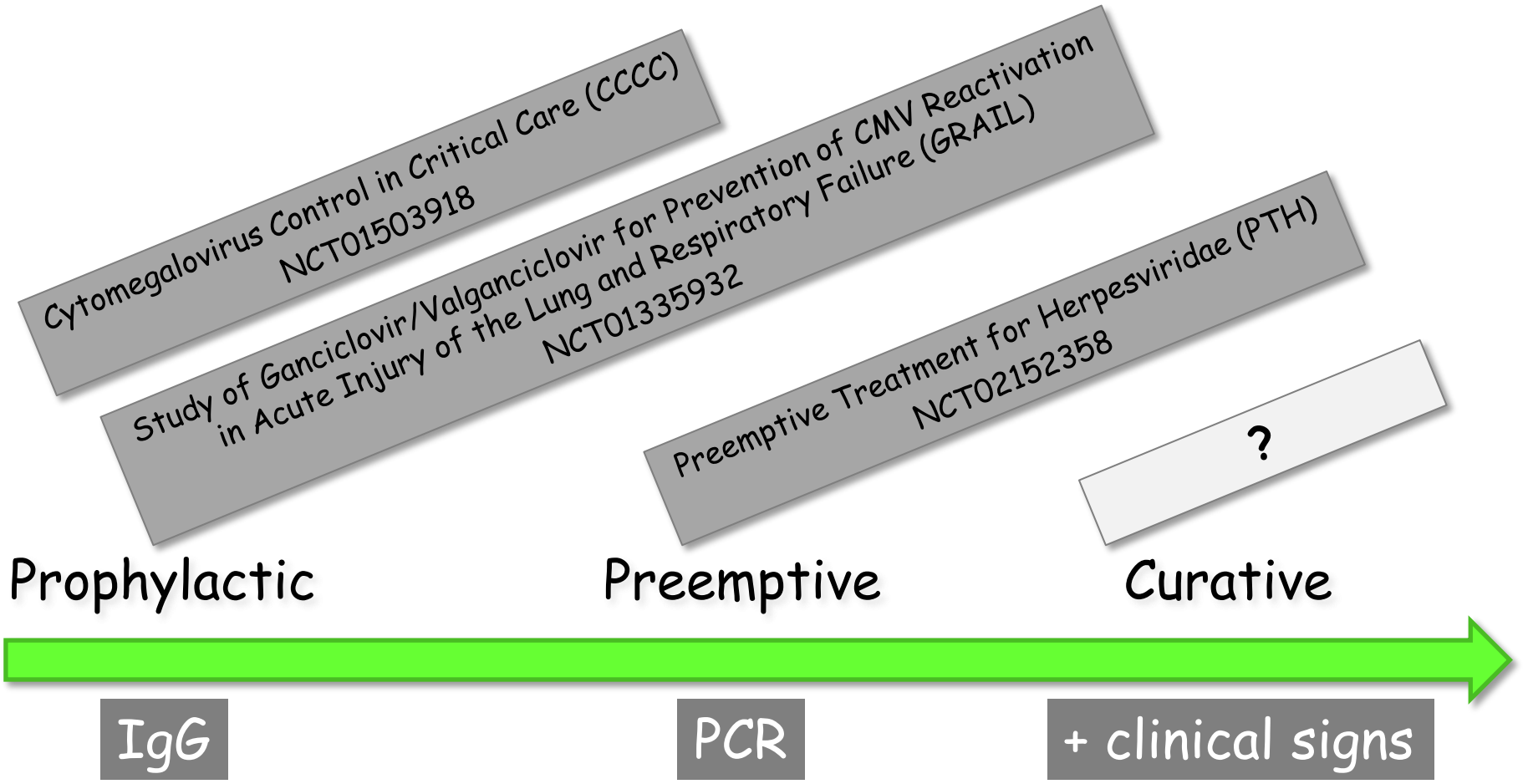
	Placebo Group, No. (%) (n = 72)	Ganciclovir Group, No. (%) (n = 84)	*P* Value
Patients with ≥1 transfusion	26 (34)	31(37)	.92
Red blood cells	26 (100)	31 (100)	.92
Platelets	7 (27)	1 (3)	.02
Transfusions per patient, median (IQR), No.	1 (1-4)	2 (1-2)	.63
Red blood cell transfusions per patient	1 (1-4)	2 (1-2)	.72
Platelet transfusions per patient	1 (1-2)	1 (1-1)	.49
New tumors at day 180	0	0	
Neutropenia at day 35[a]	0	0	
Granulocyte-colony stimulating factor use	0	0	
Renal insufficiency[b]	41 (57)	36 (43)	.08
Pregnancies	0	1 (<1)	
Patients with ≥1 adverse event[c]	13 (17)	17 (20)	.73
Patients with ≥1 adverse event of grade 3 or more[c]	10 (13)	11 (13)	.88

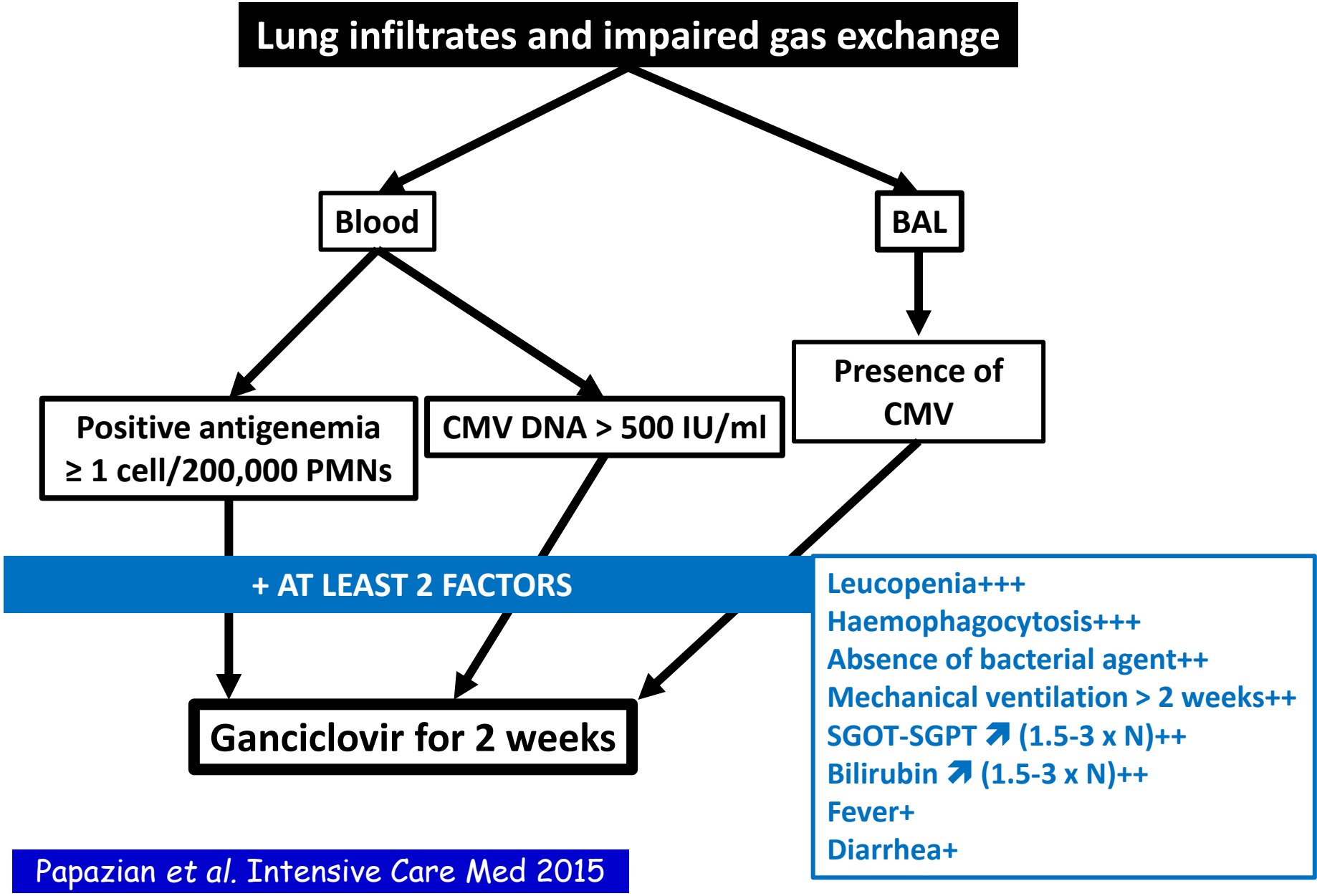
Limaye *et al.* JAMA 2017

When to treat?



When to treat?





Papazian *et al.* Intensive Care Med 2015

Conclusions

- Reactivation is frequent
- Pathogenicity?
    - Direct and/or indirect?
- Treatment when clinical signs
- Need for interventional trials
- Risk/benefit balance
- Other new (or old) viruses