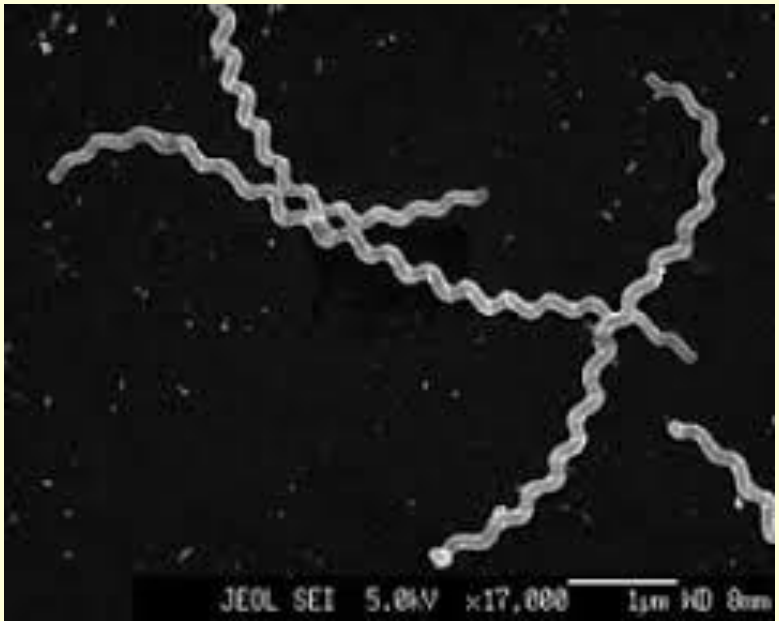
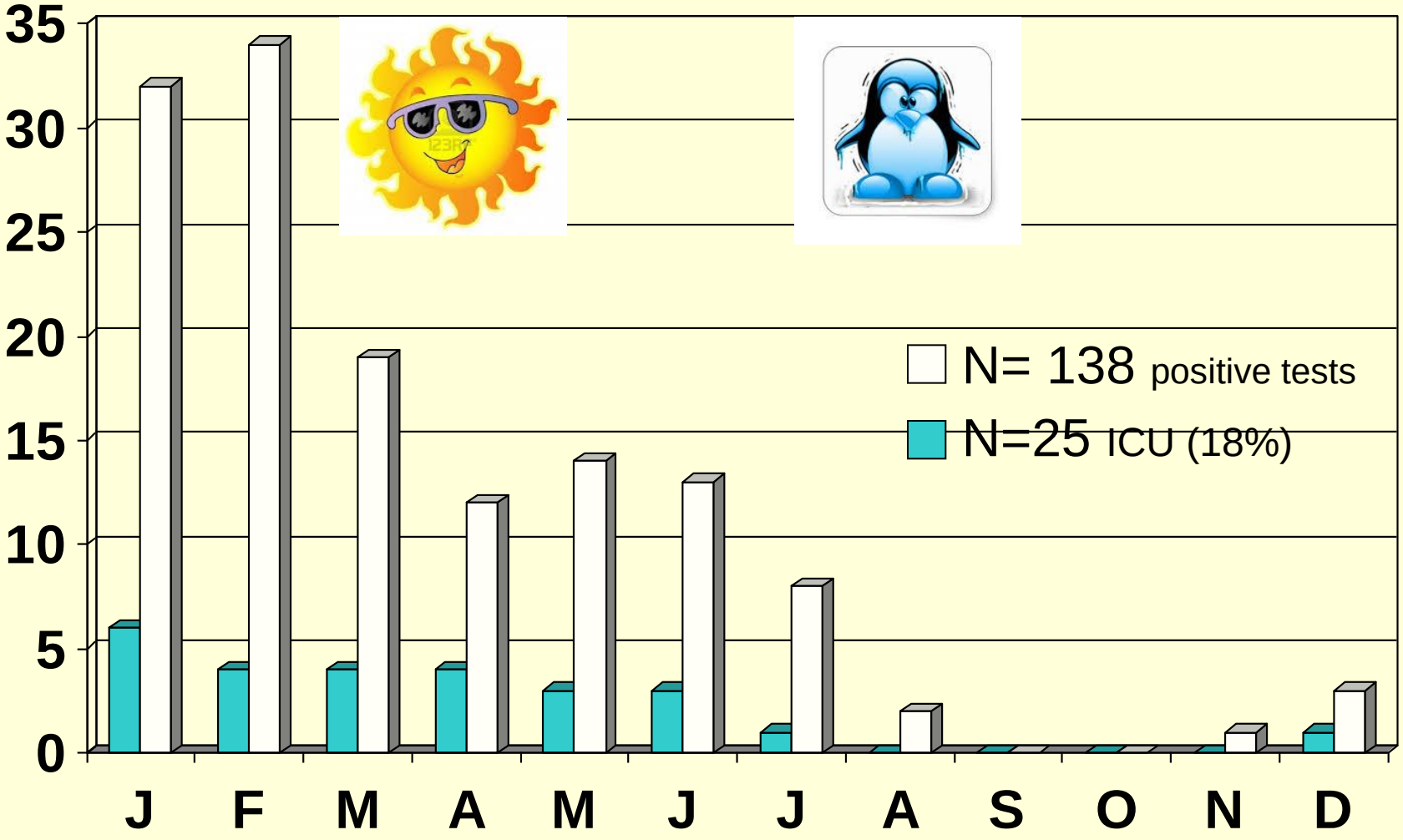
Management of severe Leptospirosis in ICU

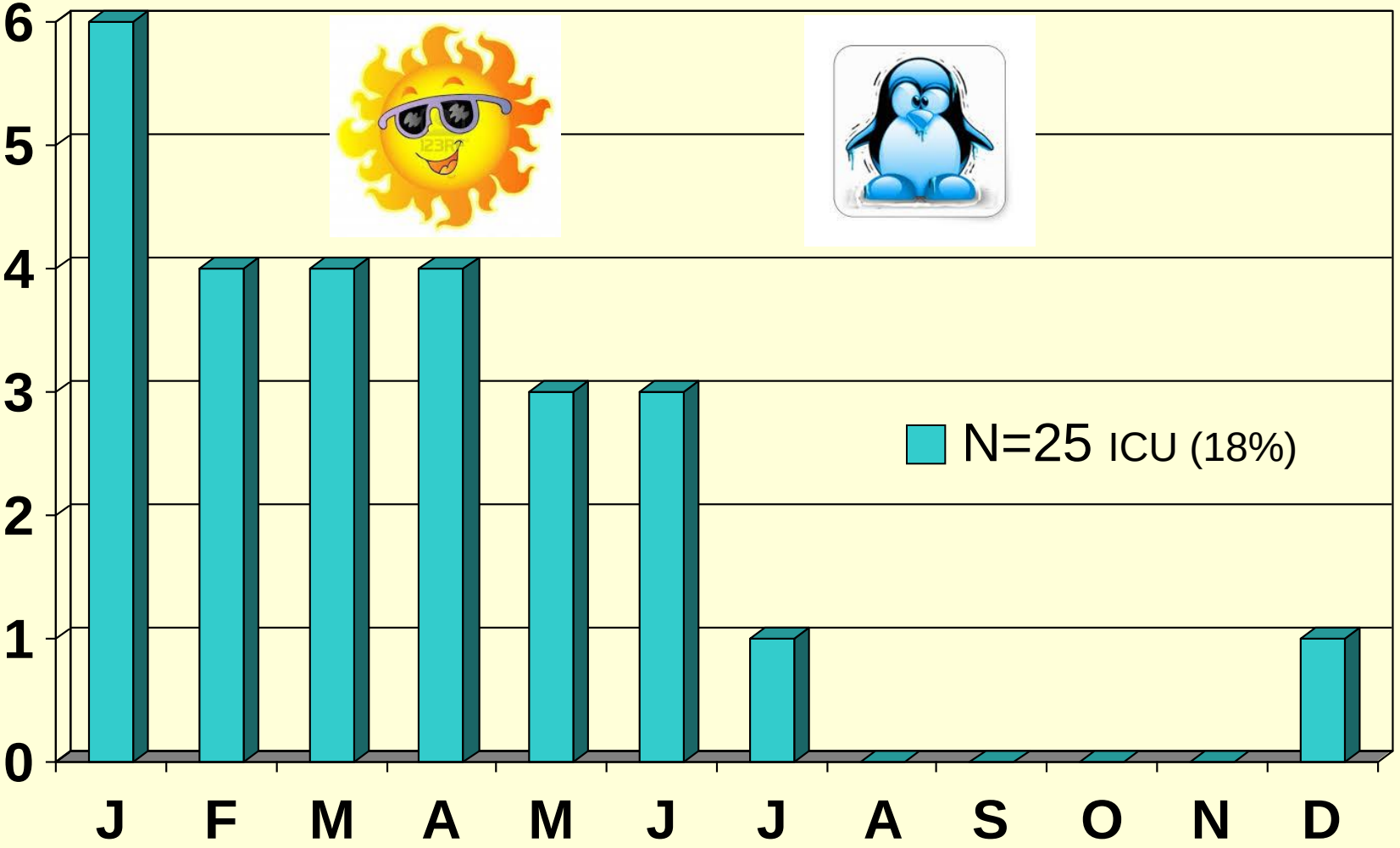


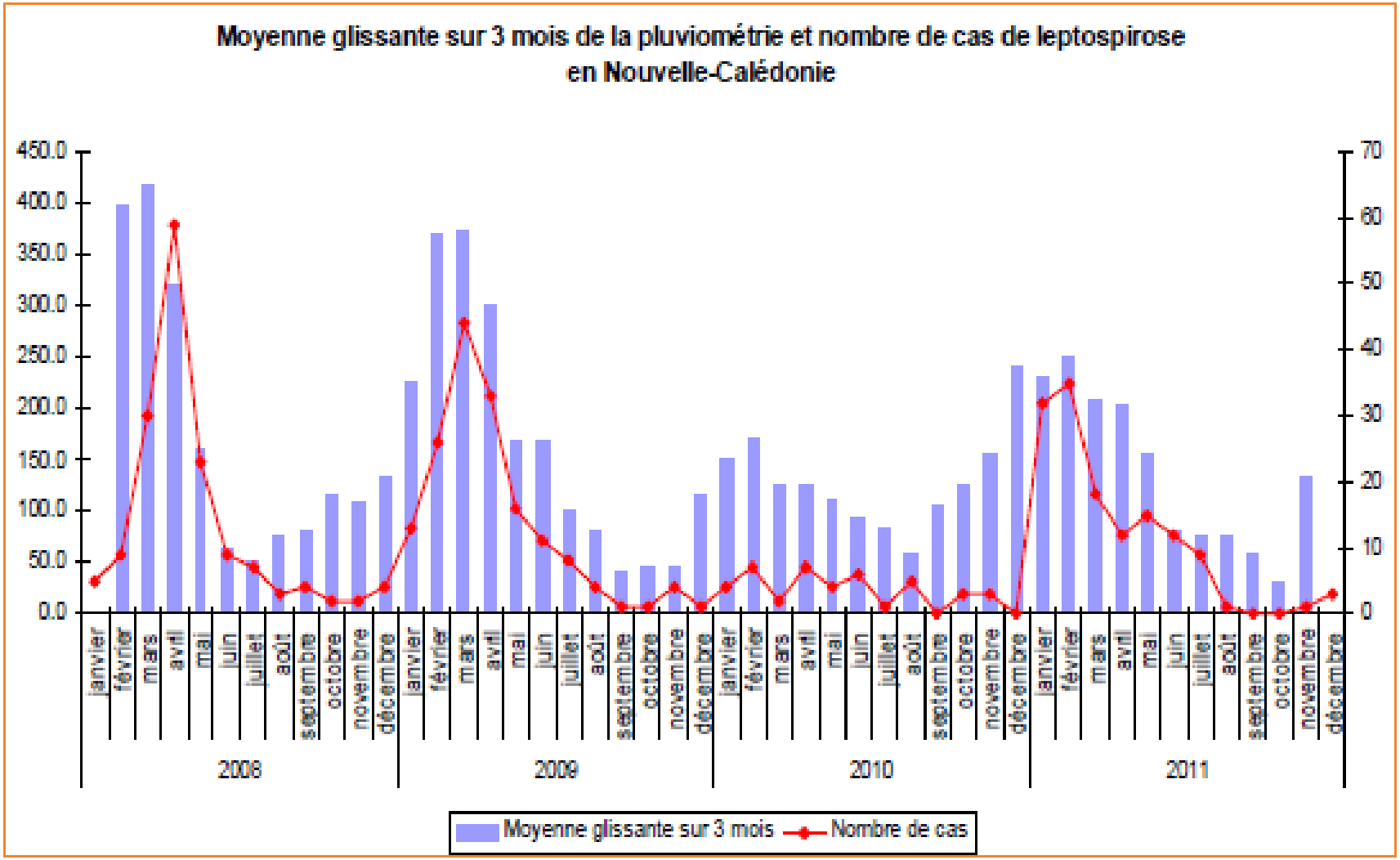
Dr Marc MIKULSKI
Nouméa, 21/11/2013

LEPTOSPIROSIS NOUMEA 2011



LEPTOSPIROSIS NOUMEA 2011





Corrélation entre nombre de cas et la moyenne mensuelle des pluies de 2007 à 2011

Organ failures

Pt. N°	Thrombopenia	Shock(VA drugs))	Renal failure	Resp. failure	Alv. Hemorrage	ARDS	MV	Dialysis	outcome
1	x	x	x	x	x		x	x	Discharged
2	x	x	x	x	x		x		Discharged
3			x	x	x				Discharged
4	x	x		x			x		Discharged
5	x	x	x	x				x	Discharged
6	x	x	x	x	x	x	x		Discharged
8	x	x	x	x	x	x	x	x	Discharged
9	x	x	x	x	x	x	x	x	Discharged
11	x	x	x						Discharged
12		x	x	x	x		x		Discharged
13	x	x	x	x			x	x	Discharged
15	x	x	x					x	Discharged
16	x	x							Discharged
17	x	x	x	x					Discharged
19	x	x	x	x				x	Discharged
20	x	x	x	x					Discharged
21	x	x	x	x	x		x		Discharged
22	x	x	x	x	x		x		Discharged
23	x	x		x	x	x	x		Discharged
24	x		x	x	x		?	x	Discharged
25	x	x	x	x			x	x	Discharged
7	x	x	x	x	x	x	x	x	Died
10	x	x	x	x	x	x	x	x	Died
14	x	x	x	x	x	x	x	x	Died
18	x	x	x	x	x	x	x	x	Died

Death: 4/25 (16%)

Risk factors

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Risk Factors and Predictors of Severe Leptospirosis in New Caledonia

Sarah Tubiana[1], Marc Mikulski[2], Jérôme Becam[3], Flore Lacassin[4], Patrick Lefèvre[5], Ann-Claire Gourinat[6], Cyrille Goarant[3], Eric D'Ortenzio[1]*

1 Unité d'Epidémiologie des Maladies Infectieuses, Institut Pasteur de Nouvelle-Calédonie, Réseau International des Instituts Pasteur, Noumea, New Caledonia, **2** Service de Réanimation, Centre Hospitalier Territorial de Noumea, Noumea, New Caledonia, **3** Laboratoire de Recherche en Bactériologie, Institut Pasteur de Nouvelle-Calédonie, Réseau International des Instituts Pasteur, Noumea, New Caledonia, **4** Service de Médecine Interne, Centre Hospitalier Territorial de Noumea, Noumea, New Caledonia, **5** Service de Médecine, Centre Hospitalier du Nord, Koumac, New Caledonia, **6** Laboratoire de Sérologie-Virologie, Institut Pasteur de Nouvelle-Calédonie, Réseau International des Instituts Pasteur, Noumea, New Caledonia

Abstract

Background: Leptospirosis is a major public health concern in New Caledonia (NC) and in other tropical countries. Severe manifestations of the disease are estimated to occur in 5–15% of all human infections worldwide and factors associated with these forms are poorly understood. Our objectives were to identify risk factors and predictors of severe forms of leptospirosis in adults.

Risk factors

- Retrospective case-control study
- 306 patients hospitalized with leptospirosis January 2008-June 2011
- 176 patients included, M=62,5%, average age of 42,2+/-17,1 years
- 71 severe leptospirosis (40%), 10 death (14,1%)
- Melanesian 88,6%, tribal or rural areas 88,5%

Risk factors

Table 4. Multivariate model of independent factors associated with severe leptospirosis (N = 156) in New Caledonia, 2008–2011.

	OR (95% CI)	P value[a]
Tabacco use	2.94 (1.45–5.96)	0.003
L. interrogans serogroup Icterohaemorrhagiae	2.79 (1.26–6.18)	0.011
Delay between onset of symptoms and initiation of antibacterial therapy >2 days	2.78 (1.31–5.91)	0.008

Abbreviations: OR, odds ratio; CI, confidence interval.
[a]Significant association was classified as P<.05.
doi:10.1371/journal.pntd.0001991.t004

Genetic factors (host – HLA-DQ6?, bacterial)
Bacterial Virulence?

Table 6. Multivariate model of independent biological factors associated with severe leptospirosis (N = 176) in New Caledonia, 2008–2011.

	OR (95% CI)
	MI procedure
Platelet count ≤50 (G/L)	6.36 (1.79–22.62)
Creatinine >200 (mM)	5.86 (1.61–21.27)
Lactate >2.5 (mM)	5.14 (1.57–16.87)
Amylase >250 (UI/L)	4.66 (1.39–15.69)
Leptospiremia >1000 (leptospires/mL)	4.31 (1.17–15.92)

Abbreviations: OR, odds ratio; CI, confidence interval; MI, multiple imputation.
doi:10.1371/journal.pntd.0001991.t006

OPEN ACCESS Freely available online

PLOS ONE

The Jarisch-Herxheimer Reaction in Leptospirosis: A Systematic Review

Gilles Guerrier[1*], **Eric D'Ortenzio**[2]

1 Département d'Anesthésie-Réanimation, Centre Hospitalier Territorial, Noumea, Nouvelle Calédonie, 2 Unité d'Epidémiologie des Maladies Infectieuses, Institut Pasteur de Nouvelle-Calédonie, Réseau International des Instituts Pasteur, Noumea, Nouvelle Calédonie

Abstract

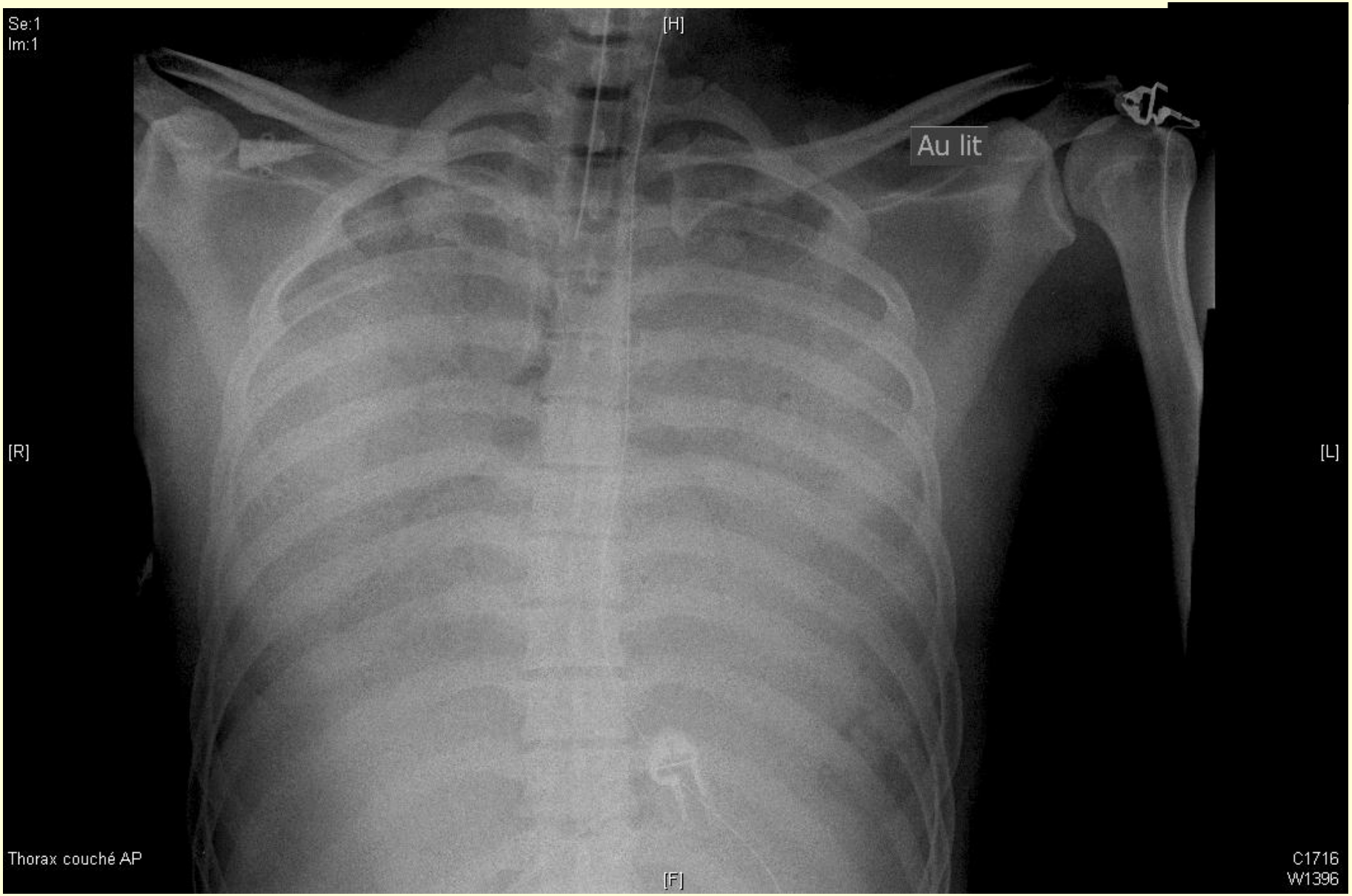
Background: Leptospirosis is an endemo-epidemic zoonotic disease associated with potentially fatal renal, cardiovascular or pulmonary failure. Recommended treatment includes antibiotics, which may induce a Jarisch-Herxheimer reaction (JHR). Since little information on the importance of this adverse event is available, we performed this review to quantify frequency and impact of JHR in leptospirosis management.

- ✓JHR vs aggravation of the leptospirosis?
- ✓No guidelines: Prevention? Management? Outcome?
- ✓JHR is not supported by any dosage of biological markers

Severe leptospirosis

- Severe Leptospirosis is a septic shock
- SIRS
- Shock with hypotension
- Multiple organe failure
- Pulmonary involvement +++, alveolar hemorrage +++

Alveolar hemorrage

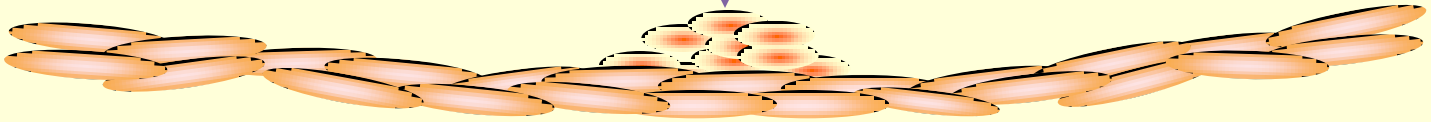


Infection

Microbial Products
(endotoxin-LPS/ exotoxin-peptidoglycans)

Inflammatory Cellular Responses
Platelets-Neutrophils-Monocyte/Macrophages

- **Platelet Activation**
- **Tissue Factor Release**
- **Cytokines TNFα, IL-1, IL-6, IL-10**
- **Nitric Oxide Free Radical Formation**
- **Complement**



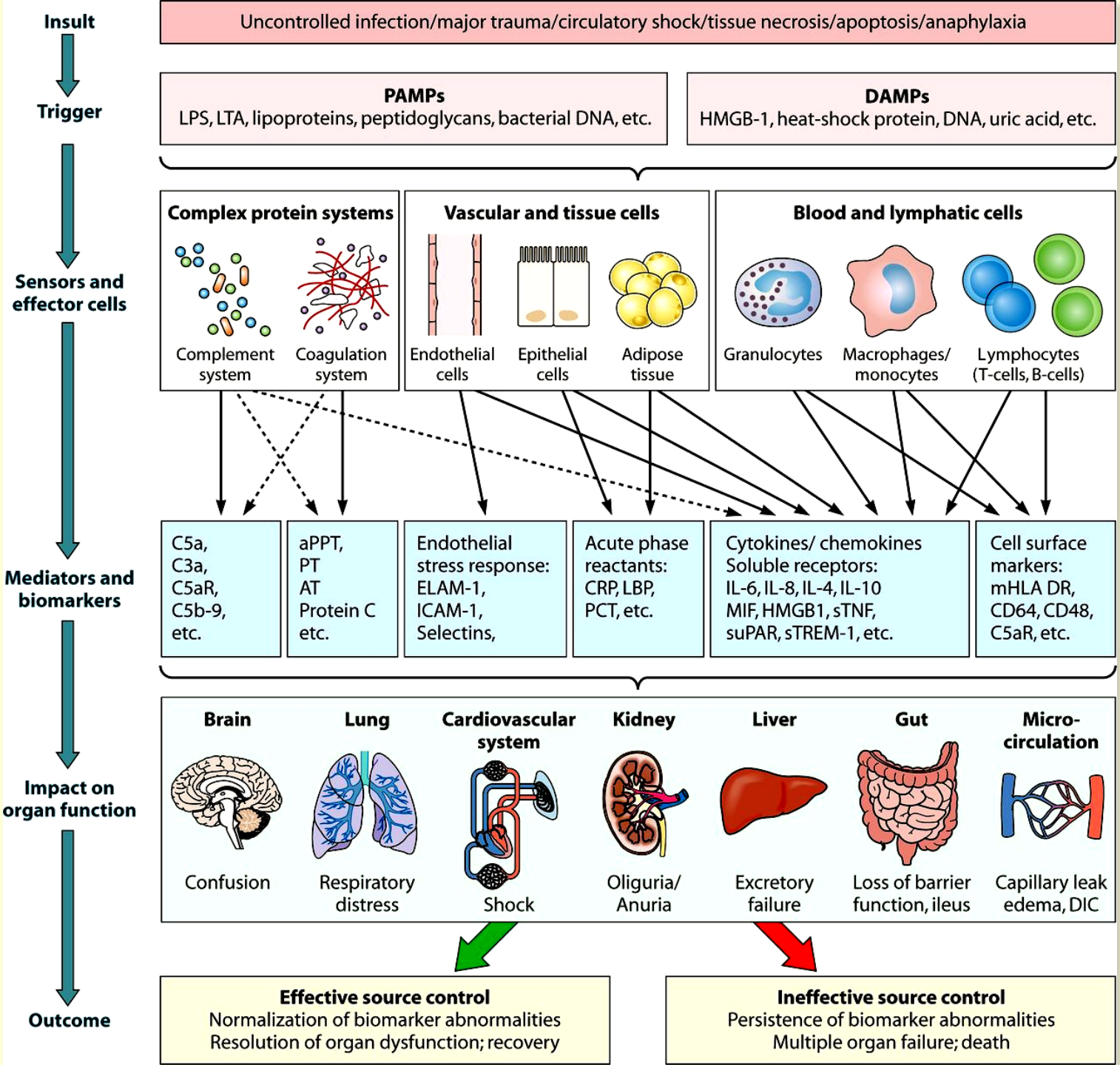
Endothelial Dysfunction

- **Capillary Leak**
- **Microvascular Thrombus**
- **Cell Adhesion**
- **Tissue Hypoxia**
- **Apoptosis**
- **Impaired Vascular tone**
- **Free Radical Damage**

Multiple Organ Dysfunction

- **Altered Mental Status**
- **PaO_2/FiO_2 ratio < 300; Tachypnea**
- **Thrombocytopenia ↑ D-dimer**
- **Hypotension Tachycardia**
- **Urine < 0.5 ml/kg/hr**
- **Metabolic Acidosis ↑ Lactate**
- **Poor Capillary Refill**

Death


Insult
Uncontrolled infection/major trauma/circulatory shock/tissue necrosis/apoptosis/anaphylaxia
Trigger
PAMPs
LPS, LTA, lipoproteins, peptidoglycans, bacterial DNA, etc.
DAMPs
HMGB-1, heat-shock protein, DNA, uric acid, etc.
Sensors and effector cells
Complex protein systems
Complement system
Coagulation system
Vascular and tissue cells
Endothelial cells
Epithelial cells
Adipose tissue
Blood and lymphatic cells
Granulocytes
Macrophages/ monocytes
Lymphocytes (T-cells, B-cells)
Mediators and biomarkers
C5a, C3a, C5aR, C5b-9, etc.
aPPT, PT AT Protein C etc.
Endothelial stress response: ELAM-1, ICAM-1, Selectins,
Acute phase reactants: CRP, LBP, PCT, etc.
Cytokines/ chemokines Soluble receptors: IL-6, IL-8, IL-4, IL-10 MIF, HMGB1, sTNF, suPAR, sTREM-1, etc.
Cell surface markers: mHLA DR, CD64, CD48, C5aR, etc.
Impact on organ function
Brain
Confusion
Lung
Respiratory distress
Cardiovascular system
Shock
Kidney
Oliguria/ Anuria
Liver
Excretory failure
Gut
Loss of barrier function, ileus
Micro-circulation
Capillary leak edema, DIC
Outcome
Effective source control
Normalization of biomarker abnormalities
Resolution of organ dysfunction; recovery
Ineffective source control
Persistence of biomarker abnormalities
Multiple organ failure; death

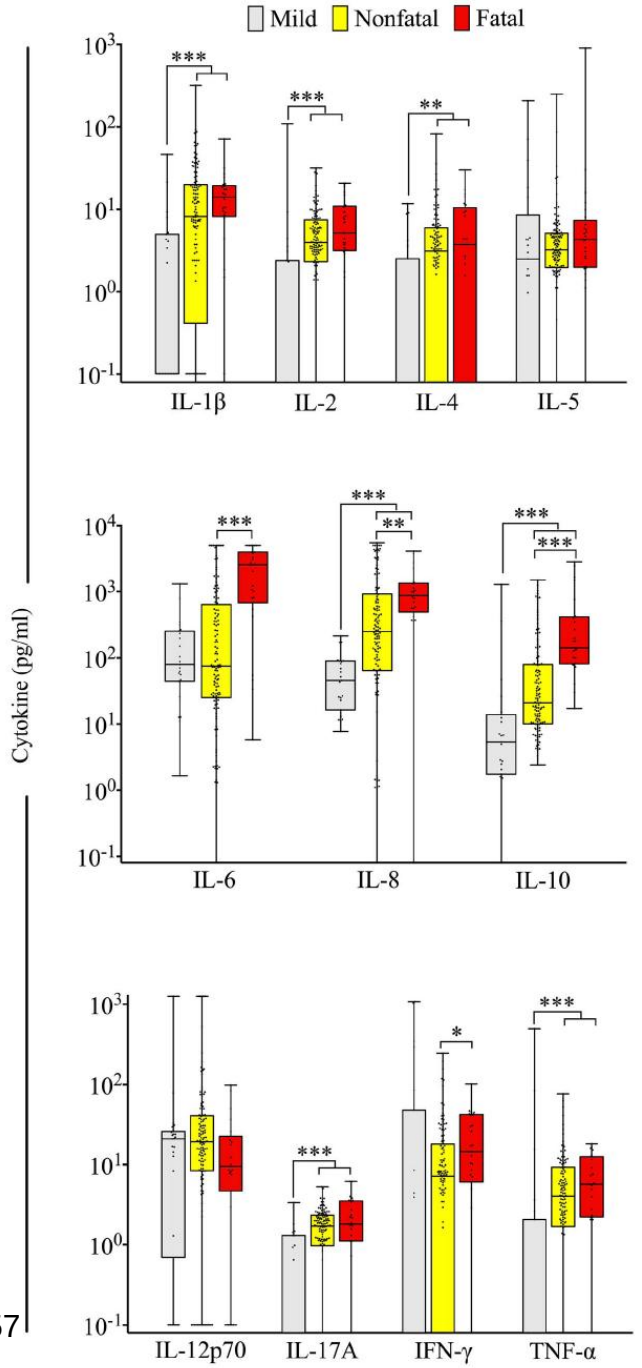
Cytokine Response Signatures in Disease Progression and Development of Severe Clinical Outcomes for Leptospirosis

Eliana A. G. Reis1, Jose´ E. Hagan

Table 2. Immunologic predictors of death among hospitalized patients.

	Odds ratio for death (95% CI)	
Factor	**Univariable model**	**Multivariable model**
Clinical variables		
Age	**1.047 (1.015–1.081)**	**1.057 (1.015–1.101)**
Male gender	0.778 (0.236–2.559)	–
Days of symptoms	0.984 (0.818–1.184)	1.274 (0.960–1.691)
Use of antibiotics	1.333 (0.506–3.515)	–
Serum cytokines		
IL-1ß	1.144 (0.878–1.492)	–
IL-2	1.509 (0.787–2.895)	–
IL-4	1.435 (0.738–2.791)	–
IL-5	1.330 (0.884–2.002)	–
IL-6	**1.781 (1.354–2.343)**	**1.726 (1.090–2.731)**
IL-8	**1.607 (1.153–2.239)**	–
IL-10	**2.088 (1.526–2.858)**	**1.895 (1.155–3.107)**
Il-12p70	0.871 (0.728–1.042)	–
Il-17A	2.505 (0.824–7.610)	–
IFN-γ	1.349 (0.845–2.153)	–
TNF-α	1.087 (0.638–1.853)	–

–, Not selected for entry into multivariable model. Bold font signifies significant association with death. Odds ratio is expressed per log increment of cytokine



Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

Sponsoring Organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maurene Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee

Crit Care Med. 2004; 32:858-73
Crit care Med 2008; 36: 1

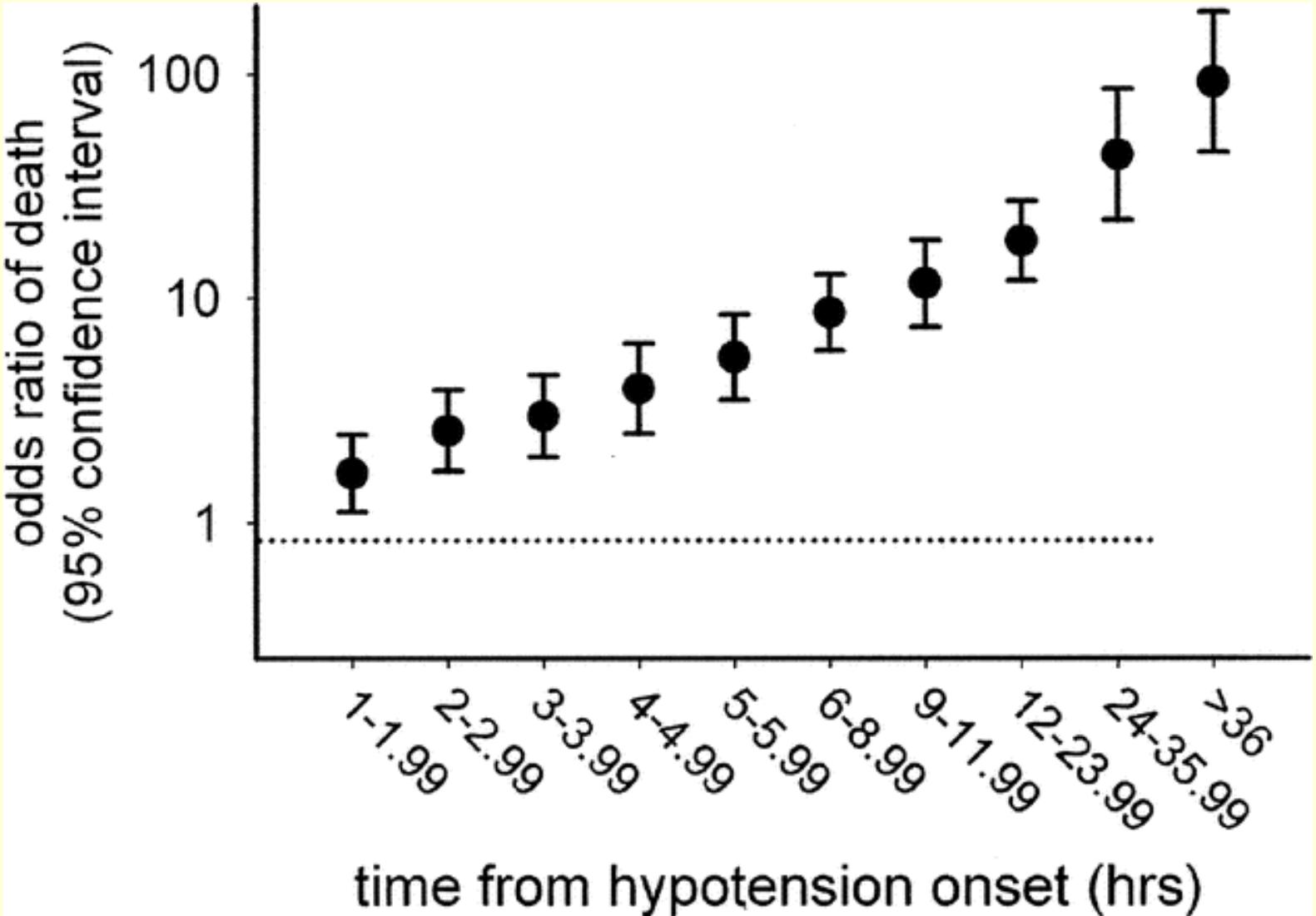
Table 2. Guidelines for the Treatment of Severe Sepsis and Septic Shock from the Surviving Sepsis Campaign.*

Element of Care	Grade†
Resuscitation	
Begin goal-directed resuscitation during first 6 hr after recognition	1C
Begin initial fluid resuscitation with crystalloid and consider the addition of albumin	1B
Consider the addition of albumin when substantial amounts of crystalloid are required to maintain adequate arterial pressure	2C
Avoid hetastarch formulations	1C
Begin initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, to achieve ≥30 ml of crystalloids per kilogram of body weight‡	1C
Continue fluid-challenge technique as long as there is hemodynamic improvement	1C
Use norepinephrine as the first-choice vasopressor to maintain a mean arterial pressure of ≥65 mm Hg	1B
Use epinephrine when an additional agent is needed to maintain adequate blood pressure	2B
Add vasopressin (at a dose of 0.03 units/min) with weaning of norepinephrine, if tolerated	UG
Avoid the use of dopamine except in carefully selected patients (e.g., patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate)	2C
Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (e.g., elevated cardiac filling pressures or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure	1C
Avoid the use of intravenous hydrocortisone if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability; if hydrocortisone is used, administer at a dose of 200 mg/day	2C
Target a hemoglobin level of 7 to 9 g/dl in patients without hypoperfusion, critical coronary artery disease or myocardial ischemia, or acute hemorrhage	1B
Infection control	
Obtain blood cultures before antibiotic therapy is administered	1C
Perform imaging studies promptly to confirm source of infection	UG
Administer broad-spectrum antibiotic therapy within 1 hr after diagnosis of either severe sepsis or septic shock	1B/1C
Reassess antibiotic therapy daily for de-escalation when appropriate	1B
Perform source control with attention to risks and benefits of the chosen method within 12 hr after diagnosis	1C
Respiratory support	
Use a low tidal volume and limitation of inspiratory-plateau-pressure strategy for ARDS	1A/1B
Apply a minimal amount of positive end-expiratory pressure in ARDS	1B
Administer higher rather than lower positive end-expiratory pressure for patients with sepsis-induced ARDS	2C
Use recruitment maneuvers in patients with severe refractory hypoxemia due to ARDS	2C
Use prone positioning in patients with sepsis-induced ARDS and a ratio of the partial pressure of arterial oxygen (mm Hg) to the fraction of inspired oxygen of <100, in facilities that have experience with such practice	2C
Elevate the head of the bed in patients undergoing mechanical ventilation, unless contraindicated	1B
Use a conservative fluid strategy for established acute lung injury or ARDS with no evidence of tissue hypoperfusion	1C
Use weaning protocols	1A

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts

Crit Care Med 2006 Vol. 34, No. 6



Conclusions

- Severe Leptospirosis → ICU admission: 20-40%
- Risk factors for severity: cigarette smoking, serogroup icterohaemorragiae, antibiotherapy delay (genetic factors?)
- Severe leptospirosis is a septic shock
- Basis for reducting mortality: prompt triage of high-risk patients, aggressive treatment and monitoring, antibiotic therapy, management of ARF, respiratory insufficiency and shock