HYDROCORTISONE SEPSIS:

WHY AND WHEN?

Eduardo Juan Troster,MD, PhD
Cristiane Freitas Pizarro, MD

USE OF CORTICOSTEROID THERAPY IN SEPSIS/SEPTIC SHOCK IS BASED IN SEVERAL ASPECTS:

- Current epidemiology of septic shock;
- Anti-inflammatory properties of corticosteroids;
- Diagnosis of adrenal insufficiency: baseline cortisol and post corticotropin-stimulated test;
- Incidence of adrenal insufficiency and relative adrenal insufficiency;
- Relation between cathecolamine-dependent septic shock and relative adrenal insufficiency.

CURRENT EPIDEMIOLOGY OF SEPTIC SHOCK

- Septic shock remains a common condition associated with substantial morbidity, mortality and economic cost in intensive care units (ICUs) world-wide;

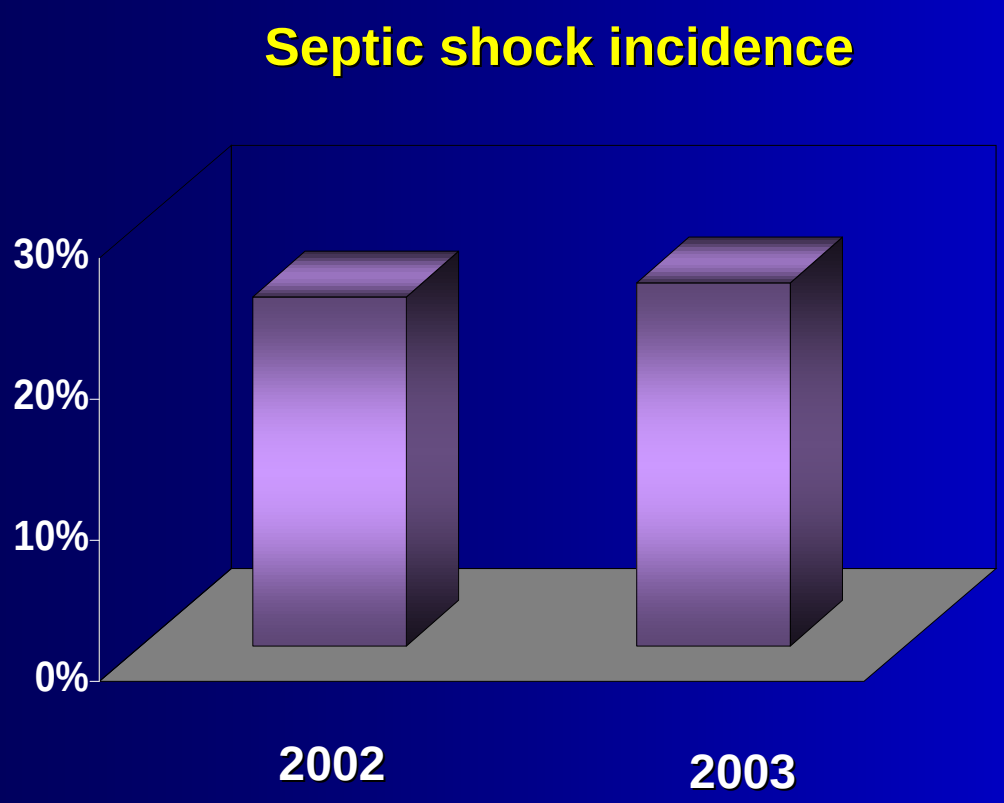
- An estimated 750,000 cases of severe sepsis occur annually in the United States and the mortality rate is about 30%; (Angus et al. - 2001);

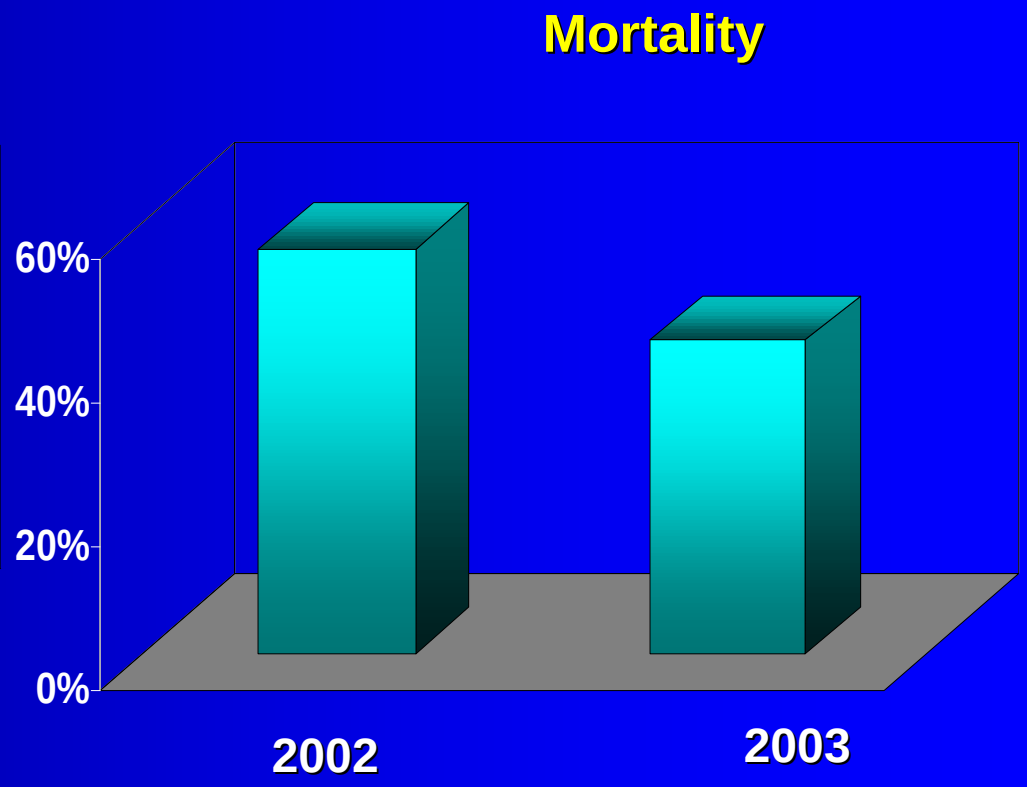
BRAZILIAN SEPSIS EPIDEMIOLOGICAL STUDY

- Data suggest that sepsis is a major public health problem, with an incidence density of about 57 per 1000 patients /day;

Silva E, et al. Crit Care Med, 2004 8:4;r251-60

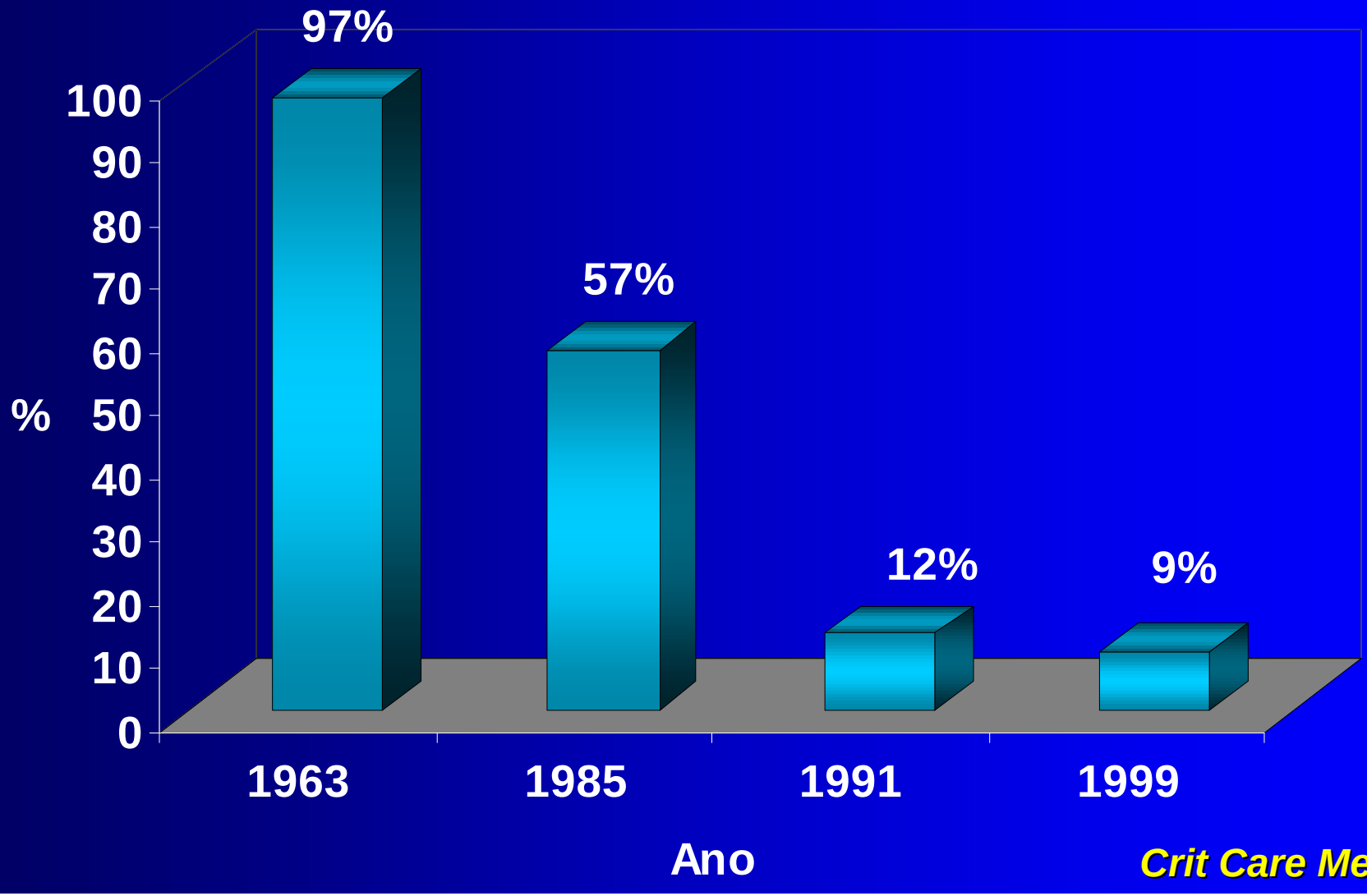
PEDIATRIC ICU OF SÃO PAULO UNIVERSITY





Sá, Kalil, Oliveira, Vaz, 2003

SEVERE SEPSIS/SEPTIC SHOCK MORTALITY IN CHILDREN - USA



Crit Care Med 2003; 19

RESUSCITATION OF PEDIATRIC SEPTIC SHOCK

Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock*

Joseph A. Carcillo, MD; Alan I. Fields, MD; Task Force Committee Members

Crit Care Med 2002 Vol. 30, No. 6

Pediatric considerations

Margaret M. Parker, MD, FCCM; Jan A. Hazelzet, MD; Joseph A. Carcillo, MD

Crit Care Med 2004 Vol. 32

RESUSCITATION OF PEDIATRIC SEPTIC SHOCK – ADAPTED PARKER MM, HAZELZET JA AND CARCILLO JA - 2004

0-5min

Recognize decreased mental status and perfusion.

Maintain airway and establish access according to PALS guidelines.

Push 20cc/Kg isotonic saline or colloid boluses up to and over 60cc/Kg.

Correct hypoglycemia and hypocalcemia.

15min

Fluid responsive shock
(Normalization of blood pressure and tissue perfusion)

Observe in ICU

FLUID REFRACTORY SHOCK

Establish central venous access, begin dopamine or dobutamine therapy and establish arterial monitoring.

Fluid refractory-dopamine/dobutamine resistant shock

Titrate epinephrine for cold shock and norepinephrine for warm shock to normal

MAP-CVP difference for age and SVCO2 saturation > 70%

60min

Catecholamine –resistant shock

At risk of adrenal insufficiency?

Draw baseline cortisol level then give hydrocortisone

Not at risk?

Draw baseline cortisol level or perform ACTH stim test. Do not give hydrocortisone

Normal blood pressure
Cold shock
$SVCO_2$ Sat < 70%

→ **Add vasodilator or type III PDE inhibitor with volume loading**

Low blood pressure
Cold shock
$SVCO_2$ Sat < 70%

→ **Titrate volume resuscitation and epinephrine**

Low blood pressure
Warm shock
$SVCO_2$ Sat ≥ 70%

→ **Titrate volume and norepinephrine**

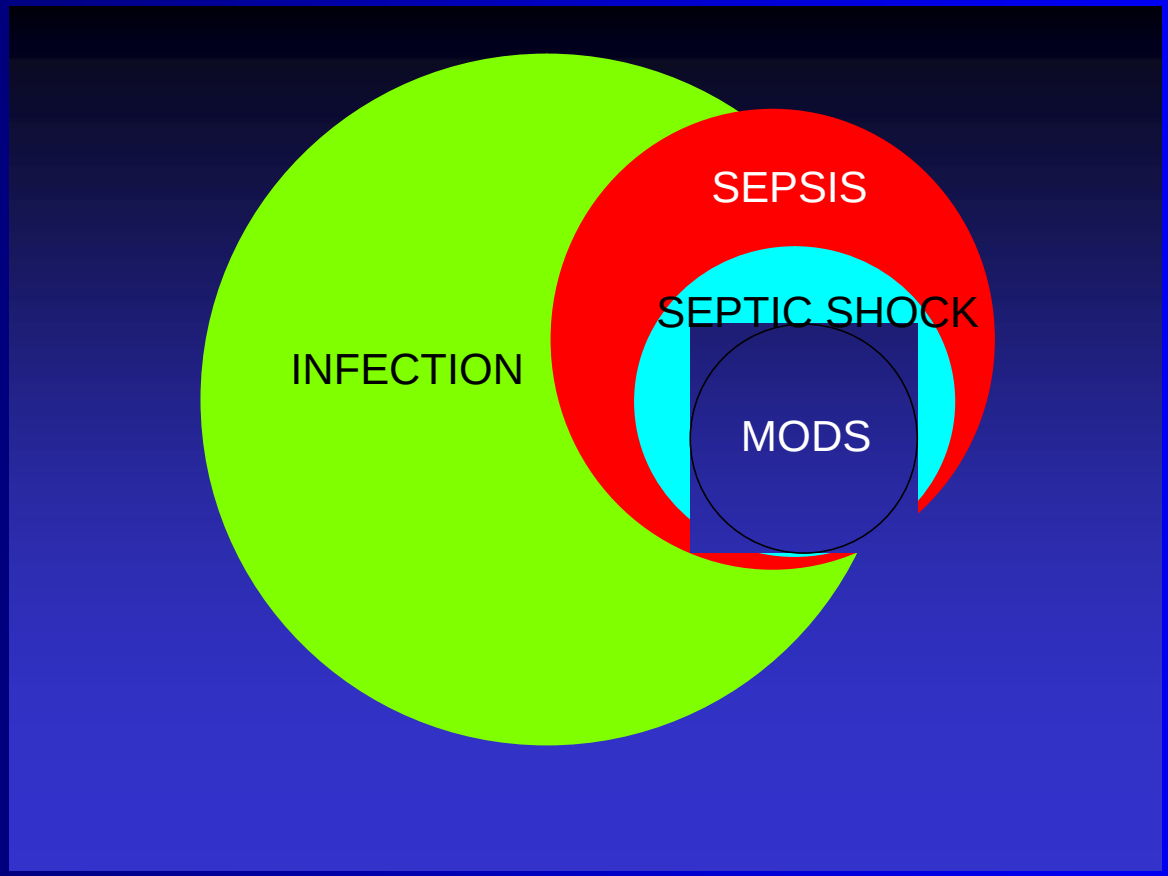
Persistent Catecholamine-resistant shock

Start cardiac output measurement and direct fluid, inotrope, vasopressor, vasodilator, and hormonal therapies to attain normal MAP-CVP and CI > 3.3 and < 6.0L/min/m^2.

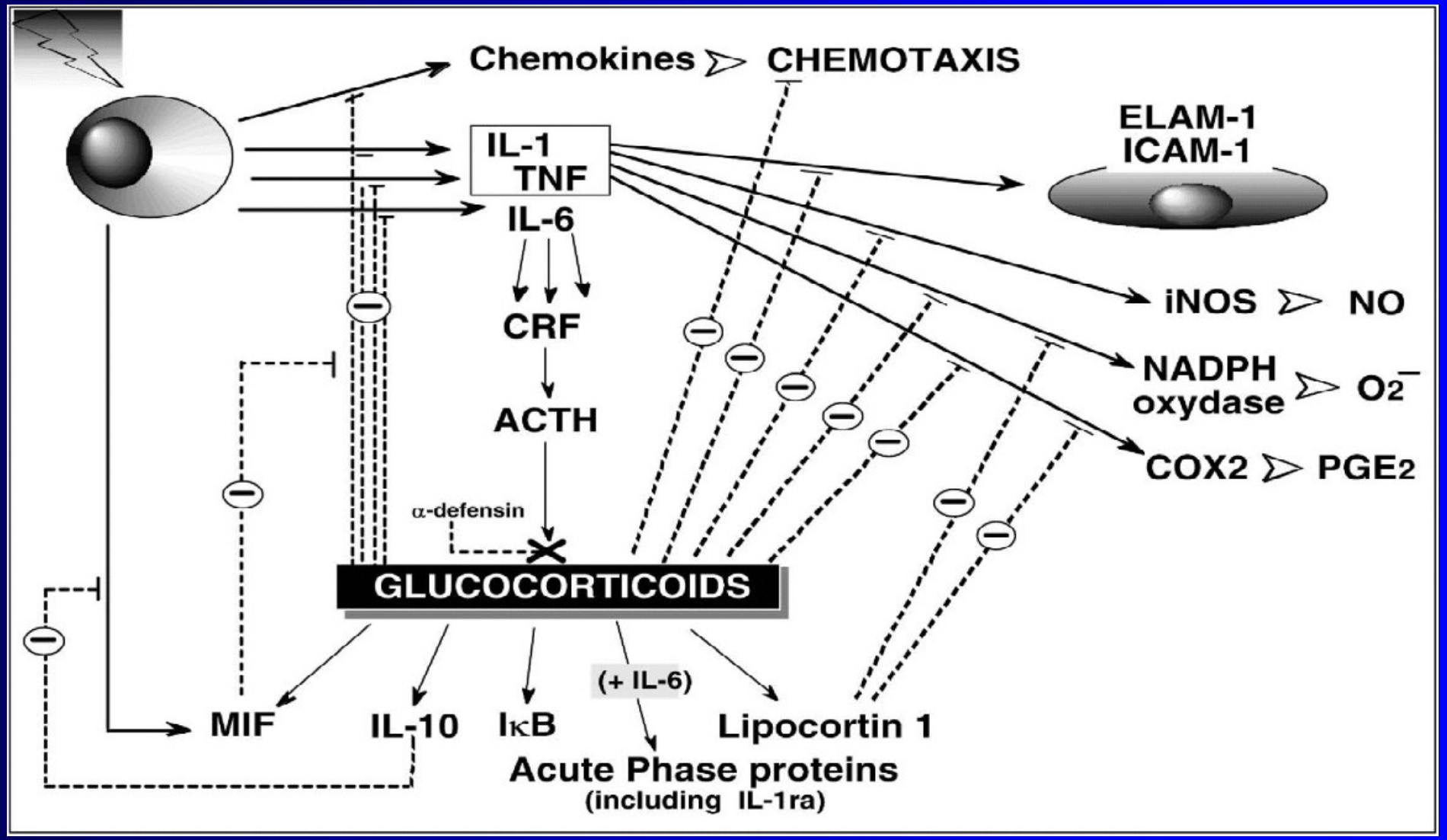
Refractory shock

Consider ECMO

ANTI-INFLAMMATORY PROPERTIES OF CORTICOSTEROIDS



SCHEMATIC SUMMARY OF GLUCOCORTICOID PROPERTIES



SHOCK, 20(3): 197-207, 2003

What are the criteria to be used in diagnoses of adrenal insufficiency and relative adrenal insufficiency in critically ill patients?

DIFFERENT CRITERIA UTILIZED TO DEFINE ADRENAL INSUFFICIENCY ACCORDING TO SEVERAL AUTHORS

Author (Yr)	Cortisol Level (μg/dl)
Rothwell *et al*. (1991)	Increment cortisol < 9 after ACTH stimulated test
Soni *et al*. (1995)	Cortisol < 18 after ACTH stimulated test
Hatherill *et al*. (1999)	Increment cortisol < 7,5 after ACTH stimulated test
Menon e Clarson (2002)	Baseline Cortisol < 7 and/or cortisol < 18 after ACTH stimulated test
Loisa *et al*. (2002)	Baseline cortisol < 25 and increment ≤ 9
Marik e Zaloga (2003)	Baseline cortisol< 25
Pizarro *et al*. (2005)	Increment cortisol ≤ 9 after ACTH stimulated test

What are the appropriate plasma cortisol concentrations in patients with sepsis and septic shock?

- The value of baseline cortisol and post corticotropin stimulated test in critically ill patients remains a controversial issue;
- “Normal” or “high normal” plasma cortisol concentrations may represent relative adrenal insufficiency or unresponsiveness in sepsis and septic shock and an insufficient response to stress;
- The rapid corticotropin stimulation test has been suggested to be useful in evaluating adrenocortical function and as a predictor of mortality in sepsis;

INCIDENCE OF ADRENAL INSUFFICIENCY ACCORDING TO VARIOUS PUBLISHED DEFINITIONS

Author (Yr)	Cortisol Level (μg/dl)	According bibliography references
Rothwell *et al*. (1991)	Increment < 9 after ACTH stimulated test	40%
Soni *et al*. (1995)	Cortisol < 18 after ACTH stimulated test	24%
Hatherill *et al*. (1999)	Increment cortisol < 7,5 after ACTH stimulated test	52%
Loisa *et al*. (2002)	Cortisol baseline < 25 and increment ≤ 9	15%
Menon e Clarson (2002)	Cortisol baseline < 7 and/or cortisol < 18 after ACTH stimulated test	31%
Marik e Zaloga (2003)	Cortisol baseline < 25	61%
Pizarro *et al*. (2005)	Increment ≤9 after ACTH stimulated test	44%

INCIDENCE OF ADRENAL INSUFFICIENCY IN CHILDREN

Summary of published studies on adrenal stimulation testing in critically ill pediatric patients

Study	Population	n	Dose of ACTH for stimulation test	Definition of adrenal insufficiency	Proportion with AI/RAI	Clinical Correlation
Hatherill 1999	Pediatric Septic shock	33	145 μg/ m^2 To max 250 μg	Poststimulation increase > 9 μg/dl	525	Increased vasopressor requirements
Menon 2003	Pediatric Critical illness	13	>10Kg: 250 μg < 10 Kg: 125 μg	Basal cortisol < 7 μg/dl or Poststimulation cortisol < 18 μg/dl	31%	Not assessed
Bone 2002	Pediatric Sepsis	42	0.5 μg/m^2	Basal cortisol < 5 μg/dl or poststimulaton cortisol < 18 μg/dl	17%	Increased vasopressor requirements
Pizarro 2005	Pediatric Setic shock	57	250μg	Basal cortisol< 20 μg/dl Poststimulation increse < 9 μg/dl	AI – 18% RAI – 26%	Unresponsive shock

Adapted by Curr Opin Pediatr 18:448-453

Absolute and relative adrenal insufficiency in children with septic shock*

Cristiane F. Pizarro, MD; Eduardo J. Troster, MD, PhD; Durval Damiani, MD, PhD; Joseph A. Carcillo, MD

Crit Care Med 2005 Vol. 33, No. 4

Editorials

One step forward: An advance in understanding adrenal insufficiency in the pediatric critically ill*

Michael Agus, MD

Pediatric Critical Care and Endocrinology

Children's Hospital Boston Harvard Medical School Boston, MA

Crit Care Med 2005 Vol. 33, No. 4

Adrenal insufficiency in the critically ill neonate and child

Monica Langer, Biren P. Modi and Michael Agus

Curr Opin Pediatr 18:448–453. 2006

INCIDENCE OF ABSOLUTE AND RELATIVE ADRENAL INSUFFICIENCY IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

Cristiane F Pizarro; Eduardo Juan Troster

Durval Damiani and Joseph A Carcillo

PICU – CHILDREN INSTITUTE – SÃO PAULO - BRAZIL

OBJECTIVES

1. To determine the incidence of absolute adrenal insufficiency and relative adrenal insufficiency in children with septic shock and severe sepsis;

2. To evaluate their effect on vasopressor requirements and mortality.

THE PATIENTS WERE CLASSIFIED IN FOUR GROUPS ACCORDING TO ADRENAL FUNCTION:

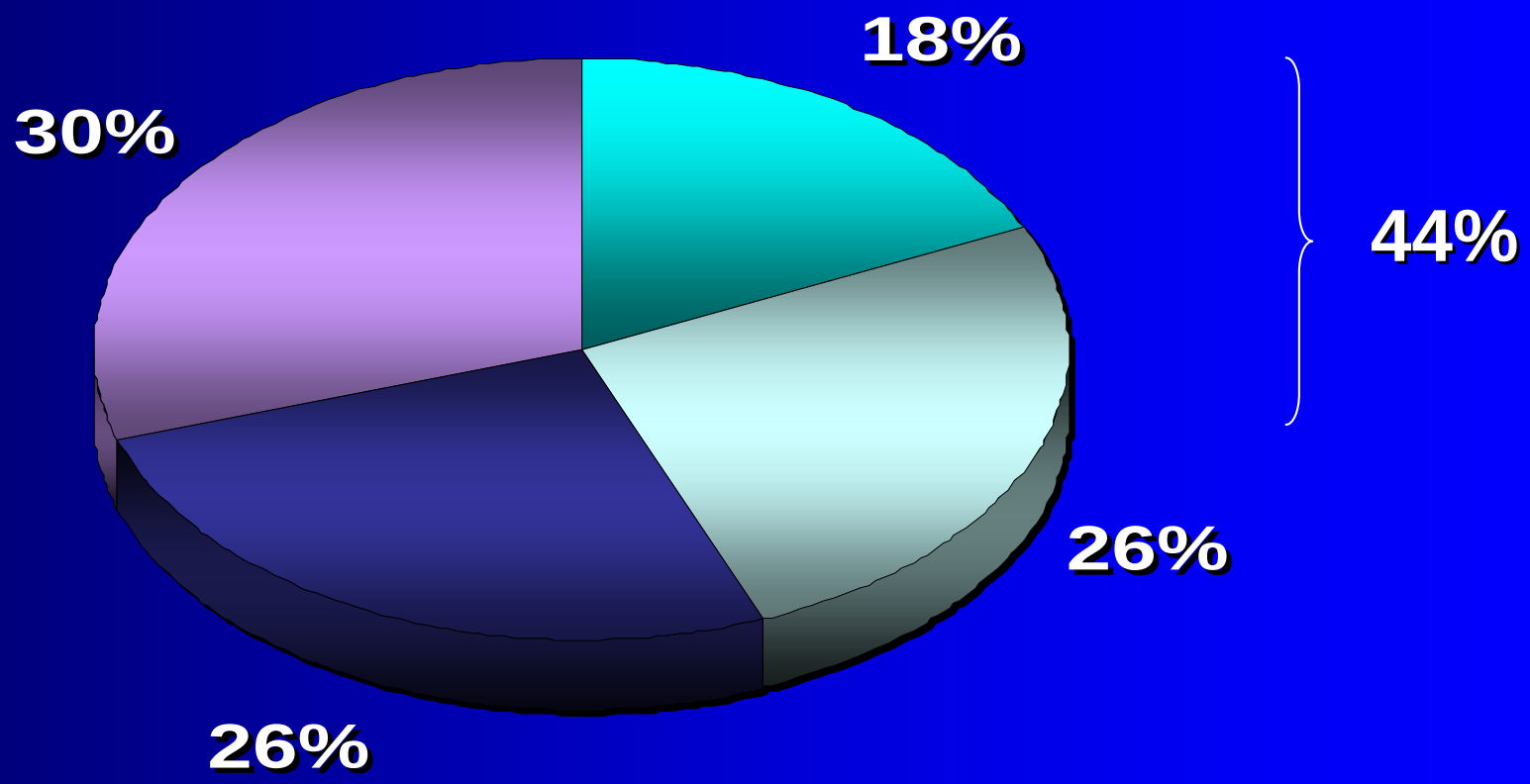
GROUP1
ABSOLUTE ADRENAL INSUFFICIENCY → **Baseline cortisol < 20µg/dl and an increment = 9µg/dl**

GROUP 2
RELATIVE ADRENAL INSUFFICIENCY → **Baseline cortisol ≥ 20µg/dl and an increment = 9µg/dl**

GROUP 3
ADEQUATE ADRENAL RESPONSE
(with elevated baseline cortisol) → **Baseline cortisol ≥ 20µg/dl and an increment > 9µg/dl**

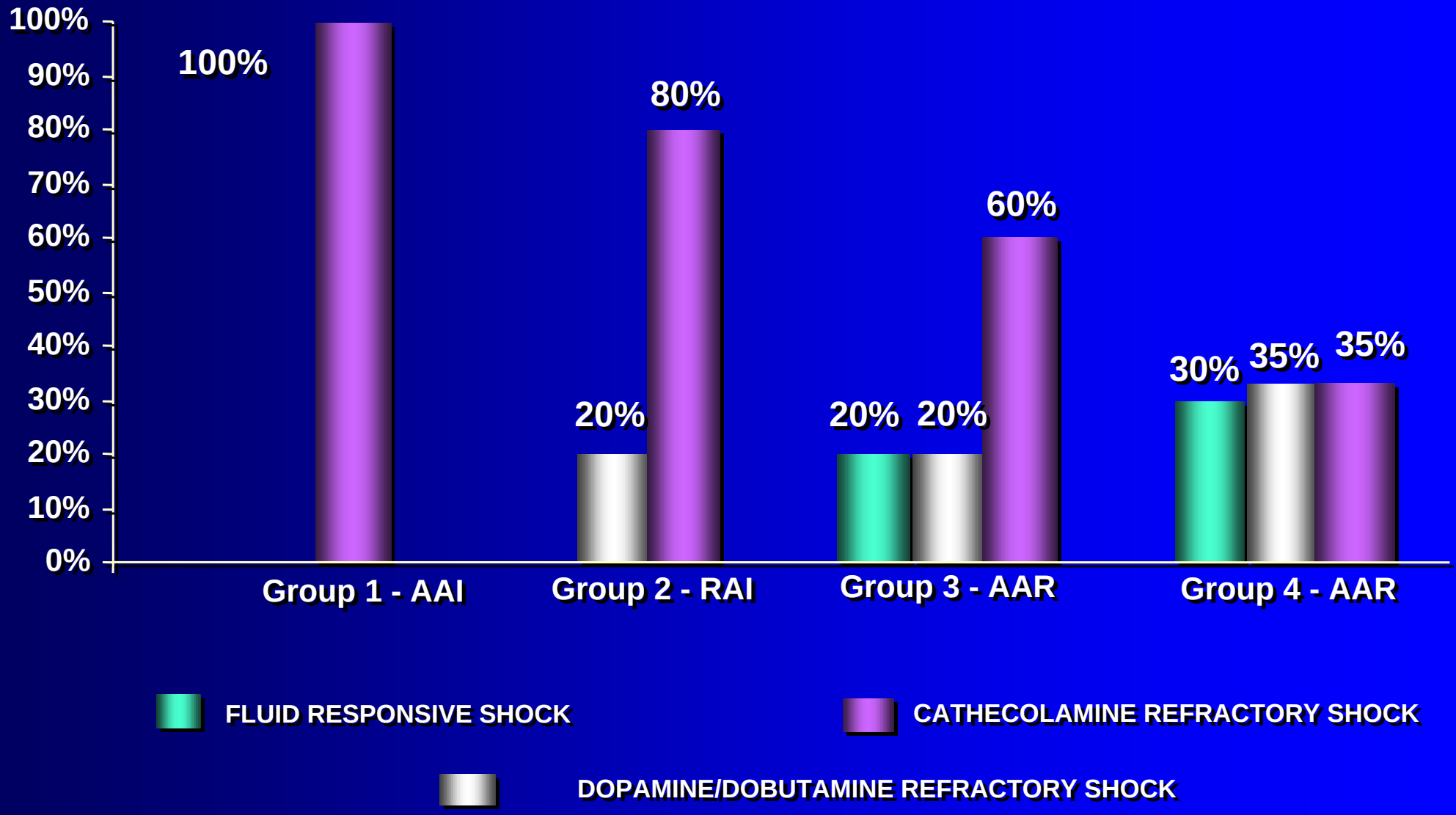
GROUP 4
ADEQUATE ADRENAL RESPONSE
(without an elevated baseline cortisol) → **Baseline cortisol < 20µg/dl and an increment > 9µg/dl**

CLASSIFICATION OF ADRENAL FUNCTION

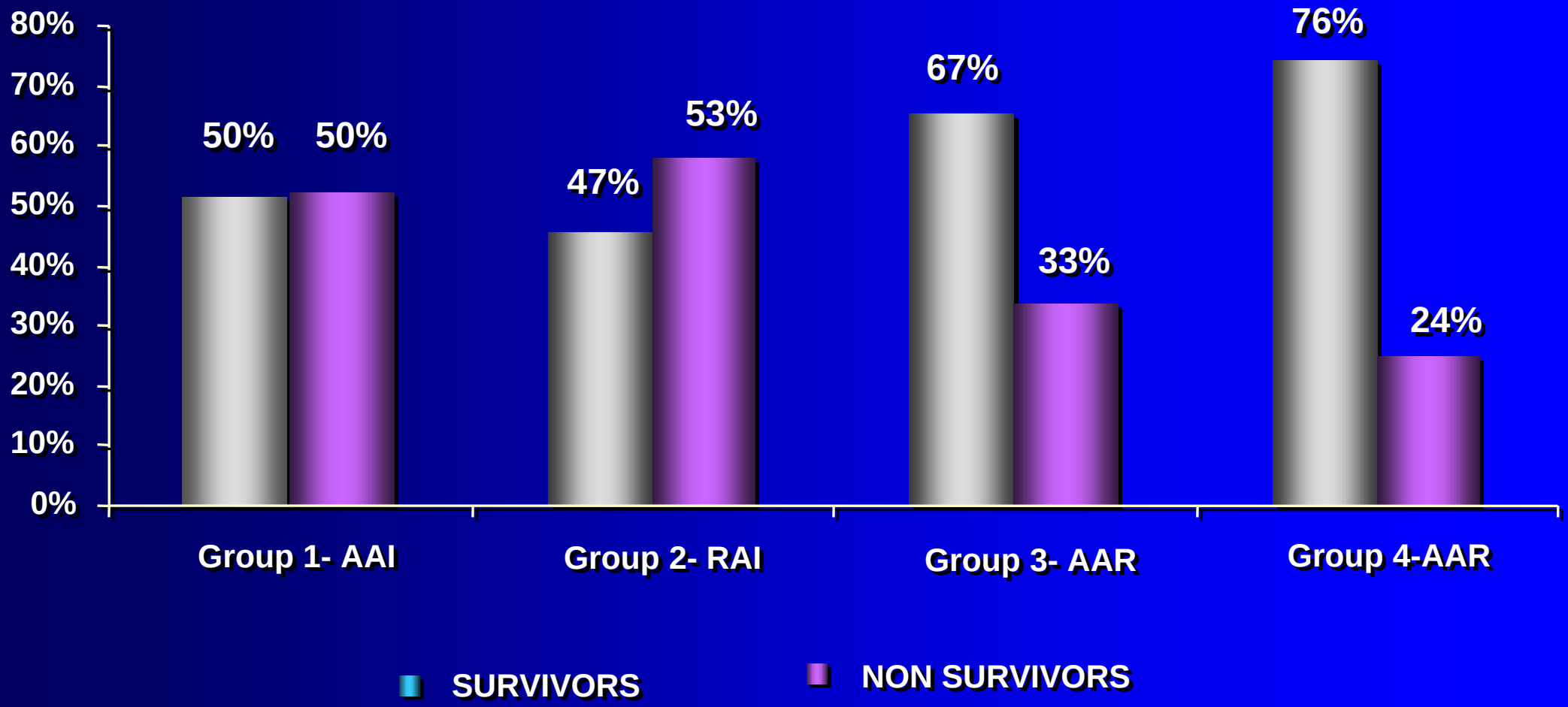


- Absolute Adrenal Insufficiency
- Adequate Adrenal Response (baseline cortisol≥ 20μg/dL)
- Relative Adrenal Insufficiency
- Adequate Adrenal Response (baseline cortisol <20μg/dL)

VASOPRESSOR AND FLUID REQUIREMENTS IN THE FOUR GROUPS



MORTALITY RATES IN THE FOUR ADRENAL FUNCTION GROUPS

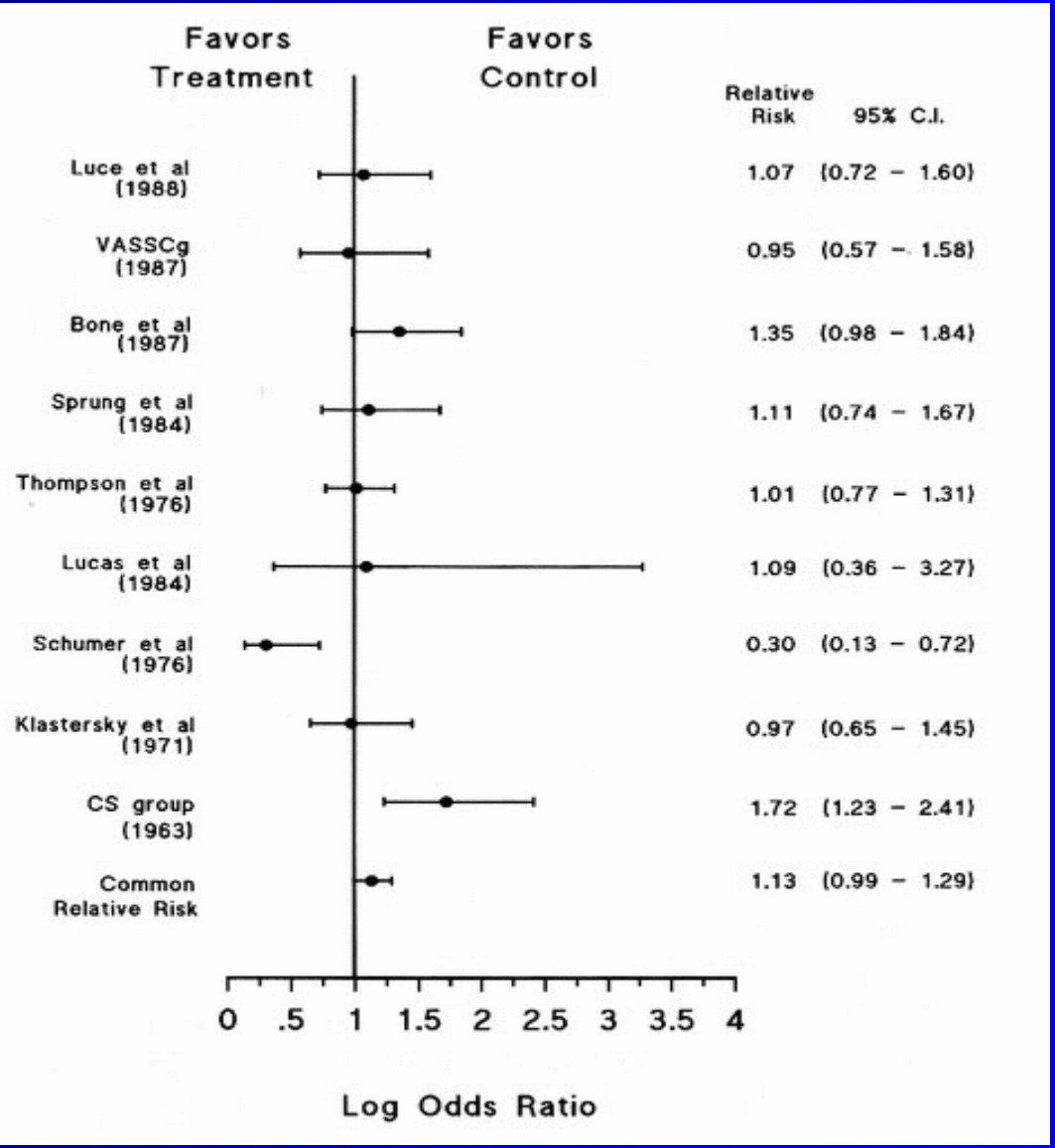


SHOULD HYDROCORTISONE BE PREFERRED TO OTHER GLUCOCORTICOIDS IN PATIENTS WITH SEPSIS / SEPTIC SHOCK? YES.

WHY ?

1. MOST OF THE EXPERIENCE WITH LOW-DOSE CORTICOSTEROID TREATMENT IN SEPTIC SHOCK HAS BEEN WITH THE USE OF HYDROCORTISONE

BEFORE EUROPEAN'S META-ANALYSIS -1995



Mortality rate ~ 11%

BEFORE EUROPEAN'S META-ANALYS

Large, RCT of High-dose
corticosteroids in septic shcok

are **not** effective,
and might even be
harmful ...

Lefering et al. Crit Care Med. 1995; 23(7):1294-302.

Cronin et al. Crit Care Med.1995; 23(8):1430-9.

Summary of study designs - 1966 - 1993

Author (Yr)	N	Drug	Dose / Duration
Cooperative Study Group (1963)	194	Hydrocortisone	300mg followed by 50mg/day (6 days)
Klastersky et al. (1971)	85	Betamethasone	1mg/kg daily (3days)
Schumer (1976)	172	Methylprednisolone Dexamethasone	30mg/kg 3mg/kg Repeated after 4hrs (x1) if necessary
Thompson et al. (1976)	60	Methylprednisolone	30mg/kg (Up to 4hrs in 24 hrs)
Sprung et al. (1984)	59	Methylprednisolone Dexamethasone	30mg/kg 6mg/kg Repeated after 4hrs (x1) if necessary
Lucas & Ledgerwood (1984)	48	Dexamethasone	2mg, 6mg/kg for 48hrs by continuous infusion
Veterans Administration (1987)	223	Methylprednisolone	30mg/kg followed by 5mg/kg (9hrs)
Bone et al. (1987)	381	Methylprednisolone	30mg/kg (24hrs)
Luce et al. (1988)	75	Methylprednisolone	30mg/kg (x4) (24hrs)

Annane et al. (2004) ⇒ meta-analysis (16 trials 1955 - 2003)

1. Short courses of high dose corticosteroids do not affect mortality from severe sepsis and septic shock;
2. Long courses of low dose corticosteroids:

a) Improve systematic haemodynamics and reduce the time on vasopressor treatment;

b) Reduce mortality at 28 days, in intensive care units, and in hospital;

c) Do not sgnificantily alter risk of gastroduodenal bleeding, superinfections or hyperglycemia.

Annane et al. BMJ. 2004, 329:480-9.

SUMMARY OF STUDY DESIGNS - 1998 - 2003

Author (Yr)	N	Drug	Dose Duration
Bollaert et al. (1998)	41	Hydrocortisone	100mg EV 8/8h 5 days, then 50mg 8/8h for 3 day and 25mg 8/8h for 3 day for responders
Briegel et al. (1999)	40	Hydrocortisone	100mg EV then 0,18mg/Kg/h until shock reversed, then 0.08mg/kg/h for 6 days, then tapered by 24mg/day
Chawla et al. (1999)	44	Hydrocortisone	100mg EV 8/8hs during 3 days
Annane et al. (2002)	299	Hydrocortisone	50mg EV 6/6hs during 7days plus fludrocortisone 50μg oral tablet 7 days
Keh et al. (2003)	40	Hydrocortisone	100mg EV 30min following 10mg/h during 3 days

2. Hydrocortisone is the synthetic equivalent to the physiologic final active cortisol;
3. Hydrocortisone has intrinsic mineralocorticoid activity, whereas methilprednisolone or dexametasone does not;
4. 20mg of hydrocortisone is equivalent to 0.05mg of fludrocortisone, and 0.05-2mg of fludrocortisone is recommended as mineralocorticoid replacement dosage after treatment of adrenal insufficiency.

WHEN

SHOULD HYDROCORTISONE BE USED

?

HYDROCORTISONE THERAPY

Carcillo JA, Task Force Committee Members - 2002

- **Should be reserved for use in children with cathecolamine resistance and suspected or proven adrenal insufficiency. Patients at risk include:**

  1. ***Purpura fulminans;***
  2. ***Children with severe septic shock;***
  3. **Children with pituitary or adrenal abnormalities;**
  4. **Children who have previously received steroid therapies for chronic illness;**

  Dose recommendation vary from ⇒ 1-2mg/kg for stress coverage to 50mg/Kg for empirical therapy of shock followed by the same dose as a 24-hr infusion.

Crit Care Med.2003;30:1365-78

USE OF GLICOCORTICOIDS

Hildebrandt et al., 2005

- There is no agreed consensus for the use of steroids in sepsis in UK practice at the moment.

  - Steroids are regularly used in 76% PICUs;
  - Only one Unit has a written protocol;
  - 84% units who use steroids gave as their main indication persistent hypotension despite the use of inotropes;
  - 79% units use hydrocortison / 21% dexamethasone;
  - 42% units perform a short synacthen test and 25%units performing syacthen tests used low-dose synacthen.

Pediatric Anesthesia.2005 15: 358-365

- **Relative adrenal insufficiency and its clinical implications have come in focus with studies demonstrating a high prevalence in septic shock patients and a significant associated morbidity;**

- **This state of "relative" adrenal insufficiency is characterized by an inadequate production of cortisol in relation to an increased demand during periods of severe stress.**

CLINICAL MANIFESTATIONS
RELATIVE ADRENAL INSUFFICIENCY

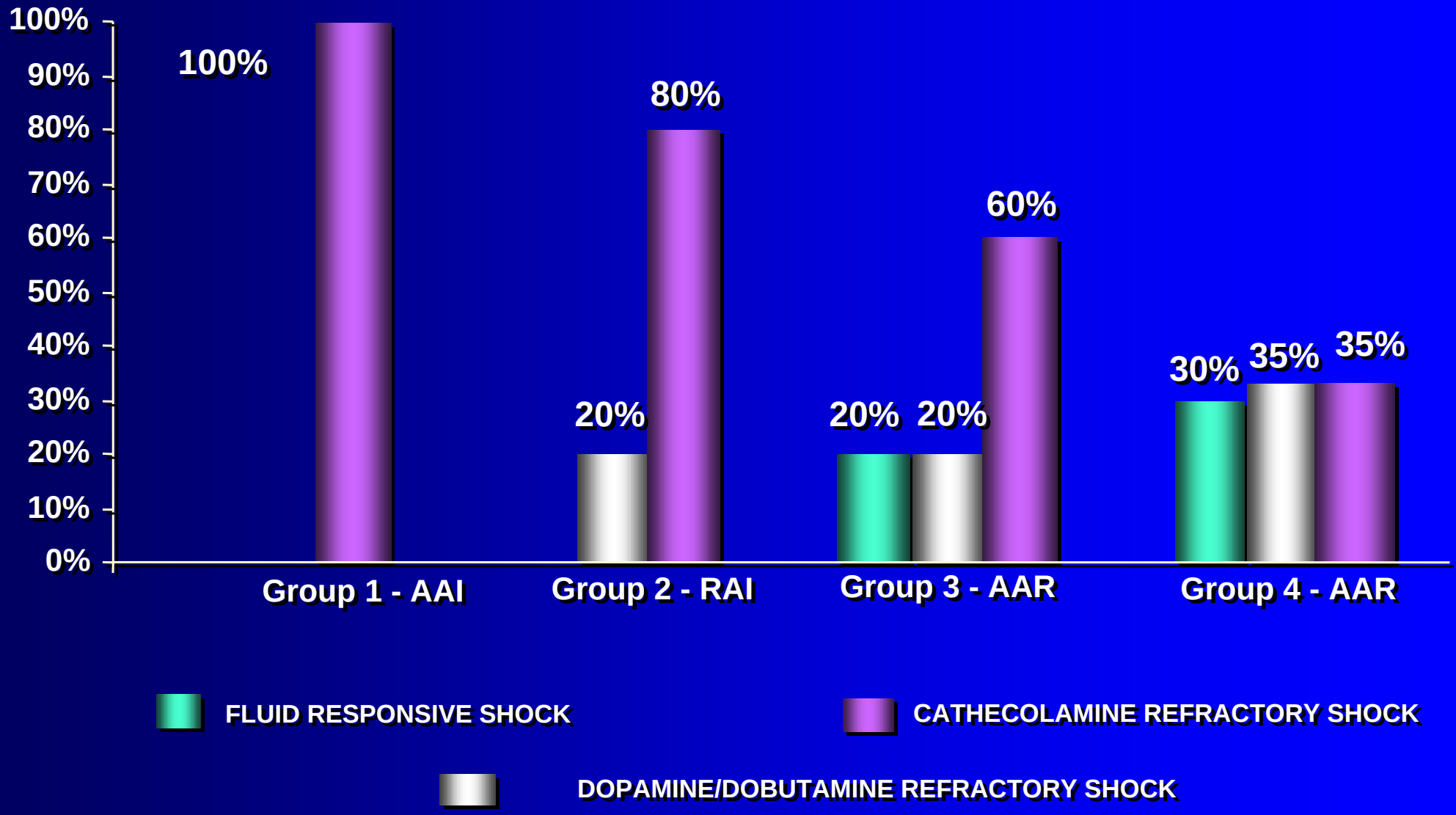
CARDIOVASCULAR INSTABILITY, WITH HYPOTENSION AND SHOCK THAT IS UNRESPONSIVE TO FLUID OR VASOPRESSOR THERAPY

RELATIVE ADRENAL INSUFFICIENCY

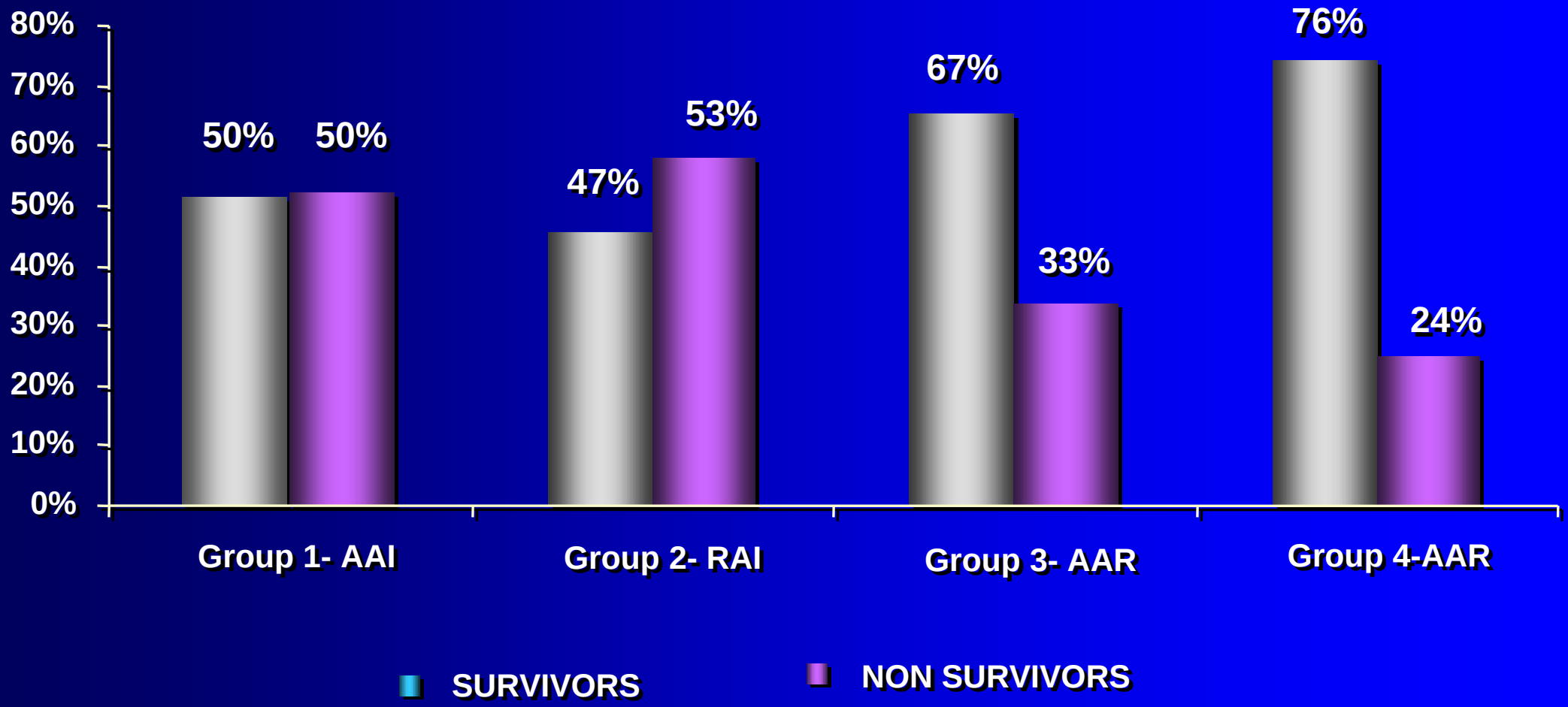
- INCREASED MORBIDITY AND MORTALITY

- ASSOCIATION BETWEEN ADRENAL INSUFFICIENCY AND A REFRACTORY SEPTC SHOCK

VASOPRESSOR AND FLUID REQUIREMENT IN THE FOUR GROUPS



MORTALITY RATES IN THE FOUR ADRENAL FUNCTION GROUPS



Relative adrenal insufficiency as a predictor of disease severity,

mortality, and beneficial effects of corticosteroid treatment in

septic shock

Margriet F. C. de Jong, MSc; Albertus Beishuizen, MD, PhD; Jan-Jaap Spijkstra, MD, PhD;

A. B. Johan Groeneveld, MD, PhD, FCCP, FCCM

Crit Care Med 2007 vol. 35, 8

CONCLUSIONS

Doubts still persist regarding the efficacy of replacement therapy with low-dose steroids in children with catecholamine-resistant septic shock, and further randomized studies are needed to determine whether treatment of such patients changes morbidity and/or mortality.