

# IRA na sepse

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# IRA na sepse

- Generalidades
- Fisiopatologia
- Prevenção
- Tratamento

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- **Generalidades**
- Fisiopatologia
- Prevenção
- Tratamento

# IRA na sepse

- 35% dos pacientes em TI desenvolvem IRA (*Crit Care Med* 2007; 35:1837)
- ~ 50% dos casos de IRA em TI relacionadas à sepse (*JAMA* 2005;294:813)
- ~ 70% mortalidade (se sepse c/IRA) em contraste com 45% quando sepse sem IRA (*N Engl J Med.* 2004;351:159)

# IRA na sepse

## Fisiopatologia – Lesão inicial

- Hemodinâmica
- Celular

# Fisiopatologia da IRA na sepse

## *Vertentes hemodinâmicas*

- Simples NTA isquêmica (pela hipotensão na sepse)
- Perturbação local da hemodinâmica intrarrenal

# IRA na sepse é simples NTA isquêmica?

- Em vários modelos, redução aguda da filtração glomerular pode ser observada na ausência de hipotensão arterial. (*Kikeri et al. Am J Physiol. 1986;250:F1098 / Lugon et al. Kidney Int. 1989;36:570*)
- NTA está frequentemente ausente na histologia

# No entanto...

1: [Crit Care](#). 2008;12(2):R38. Epub 2008 Mar 6.

[Related Articles](#), [Links](#)



## **The histopathology of septic acute kidney injury: a systematic review.**

[Langenberg C](#), [Bagshaw SM](#), [May CN](#), [Bellomo R](#).

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**INTRODUCTION:** Sepsis is the most common trigger of acute kidney injury (AKI) in critically ill patients; understanding the structural changes associated with its occurrence is therefore important. Accordingly, we systematically reviewed the literature to assess current knowledge on the histopathology of septic AKI. **METHODS:** A systematic review of the MEDLINE, EMBASE and CINHALL databases and bibliographies of the retrieved articles was performed for all studies describing kidney histopathology in septic AKI. **RESULTS:** We found six studies reporting the histopathology of septic AKI for a total of only 184 patients. Among these patients, only 26 (22%) had features suggestive of acute tubular necrosis (ATN). We found four primate studies. In these, seven out of 19 (37%) cases showed features of ATN. We also found 13 rodent studies of septic AKI. In total, 23% showed evidence of ATN. In two additional studies performed in a dog model and a sheep model there was no evidence of ATN on histopathologic examination. Overall, when ATN was absent, studies reported a wide variety of kidney morphologic changes in septic AKI - ranging from normal (in most cases) to marked cortical tubular necrosis. **CONCLUSION:** There are no consistent renal histopathological changes in human or experimental septic AKI. The majority of studies reported normal histology or only mild, nonspecific changes. ATN was relatively uncommon.

# IRA na sepse – hemodinâmica local

- Hipótese 1: vasoconstricção intrarrenal
- Hipótese 2: vasodilatação intrarrenal  
(preferencial da arteríola eferente)

# Hipótese 1

- Vasoconstricção intrarenal
  - Modelos experimentais com animais anestesiados
  - Hipótese não se coaduna com o evidente estado de vasodilatação na sepse humana
  - Medidas do FPR em animais acordados e em humanos – o evento na sepse inicial é ↑ do FPR

↓ Fluxo sanguíneo renal

Table 2. Summary of several measures of whole kidney function

	GFR	ERPF	ERVR	$\dot{V}$	$U_{Na}\dot{V}$	$FE_{Na}$	$U_K\dot{V}$	$FE_K$
	<i>ml/min</i>		<i>mm Hg · min/ml</i>	<i>μl/min</i>	<i>μEq/min</i>	%	<i>μEq/min</i>	%
Group 1								
Control 1	0.96 ± 0.07	3.38 ± 0.15	31.14 ± 1.57	2.6 ± 0.2	0.45 ± 0.08	0.30 ± 0.04	1.07 ± 0.14	49.68 ± 7.83
Control 2	1.14 ± 0.05	3.65 ± 0.22	29.56 ± 1.92	3.0 ± 0.2	0.63 ± 0.12	0.35 ± 0.05	1.46 ± 0.21	60.35 ± 16.48
Group 2								
Control	0.91 ± 0.03	3.09 ± 0.14	36.31 ± 2.41	3.2 ± 0.5	0.88 ± 0.17	0.59 ± 0.11	1.22 ± 0.12	62.00 ± 9.95
LPS 0111:B4	0.39 ± 0.05 <sup>a</sup>	2.13 ± 0.29 <sup>a</sup>	63.07 ± 11.65 <sup>a</sup>	3.1 ± 0.3	0.21 ± 0.03 <sup>a</sup>	0.38 ± 0.05	0.35 ± 0.05 <sup>a</sup>	53.98 ± 6.76
Group 3								
Control	1.04 ± 0.07	3.48 ± 0.27	30.95 ± 2.43	3.5 ± 0.6	0.90 ± 0.22	0.47 ± 0.14	1.24 ± 0.18	46.36 ± 8.98
LPS 0127:B8	0.61 ± 0.04 <sup>a</sup>	3.01 ± 0.36	35.71 ± 5.16	4.7 ± 0.8	0.43 ± 0.12	0.45 ± 0.12	0.68 ± 0.09 <sup>a</sup>	35.82 ± 4.35
Group 4								
Indomethacin	1.00 ± 0.09	3.53 ± 0.38	35.67 ± 4.98	2.8 ± 0.4	0.68 ± 0.17	0.43 ± 0.09	0.98 ± 0.17	50.70 ± 10.71
Indomethacin + LPS	1.03 ± 0.16	4.26 ± 0.79	38.35 ± 5.32	4.9 ± 1.4	1.09 ± 0.45	0.49 ± 0.15	1.06 ± 0.31	43.10 ± 11.37
Group 5								
Captopril	0.94 ± 0.05	3.89 ± 0.43	38.25 ± 3.78	3.3 ± 0.4	0.89 ± 0.24	0.58 ± 0.15	1.50 ± 0.20	93.15 ± 13.73
Captopril + LPS	0.90 ± 0.14	5.02 ± 0.75	19.25 ± 1.94	4.2 ± 0.7	0.58 ± 0.22	0.35 ± 0.11	0.95 ± 0.26	68.18 ± 19.58

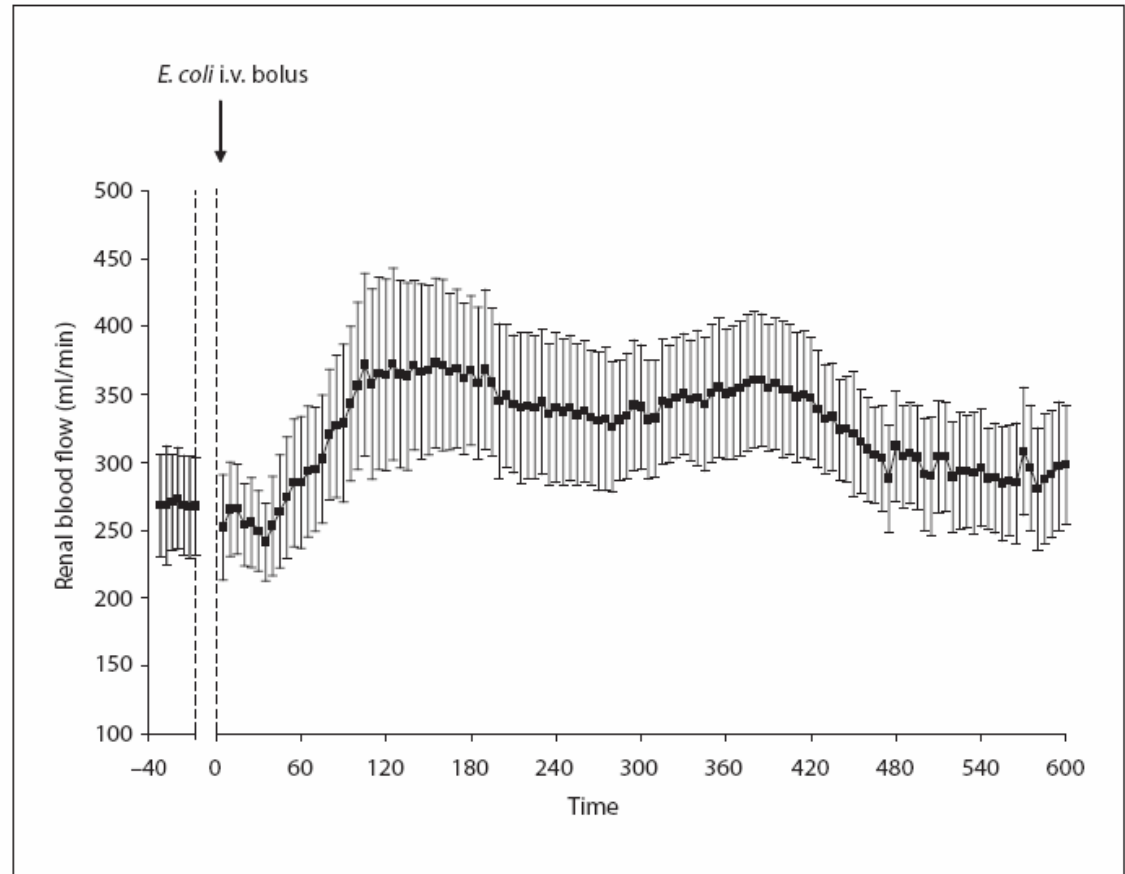
Values are expressed as the mean ± SEM. Abbreviations are: GFR, glomerular filtration rate; ERPF, effective renal plasma flow; ERVR, effective renal vascular resistance;  $\dot{V}$ , urine flow rate;  $U_{Na}\dot{V}$ , urinary excretion of sodium;  $FE_{Na}$ , fractional excretion of sodium;  $U_K\dot{V}$ , urinary excretion of potassium; and  $FE_K$ , fractional excretion of potassium.

<sup>a</sup>  $P < 0.05$  vs. values at first period

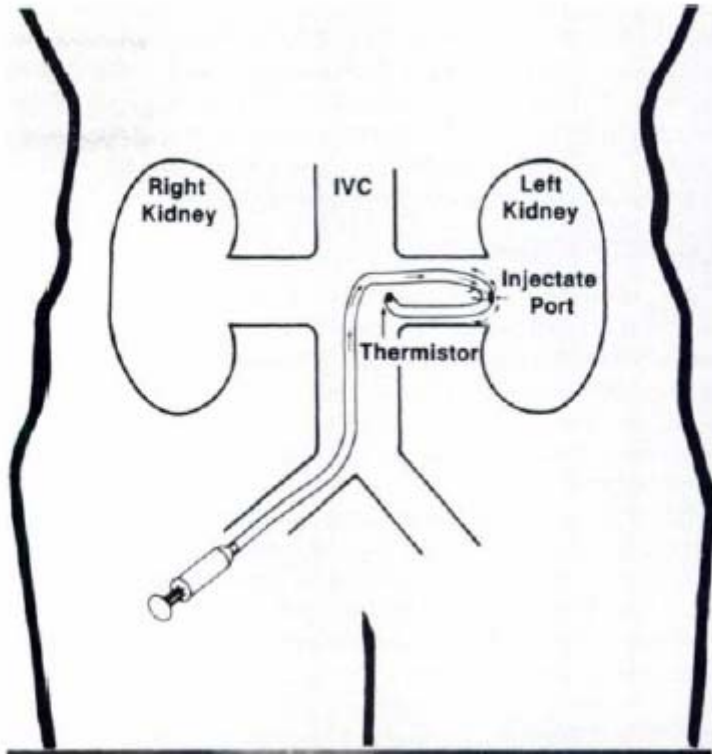
↓ Filtração glomerular

↑ Resistência vascular renal

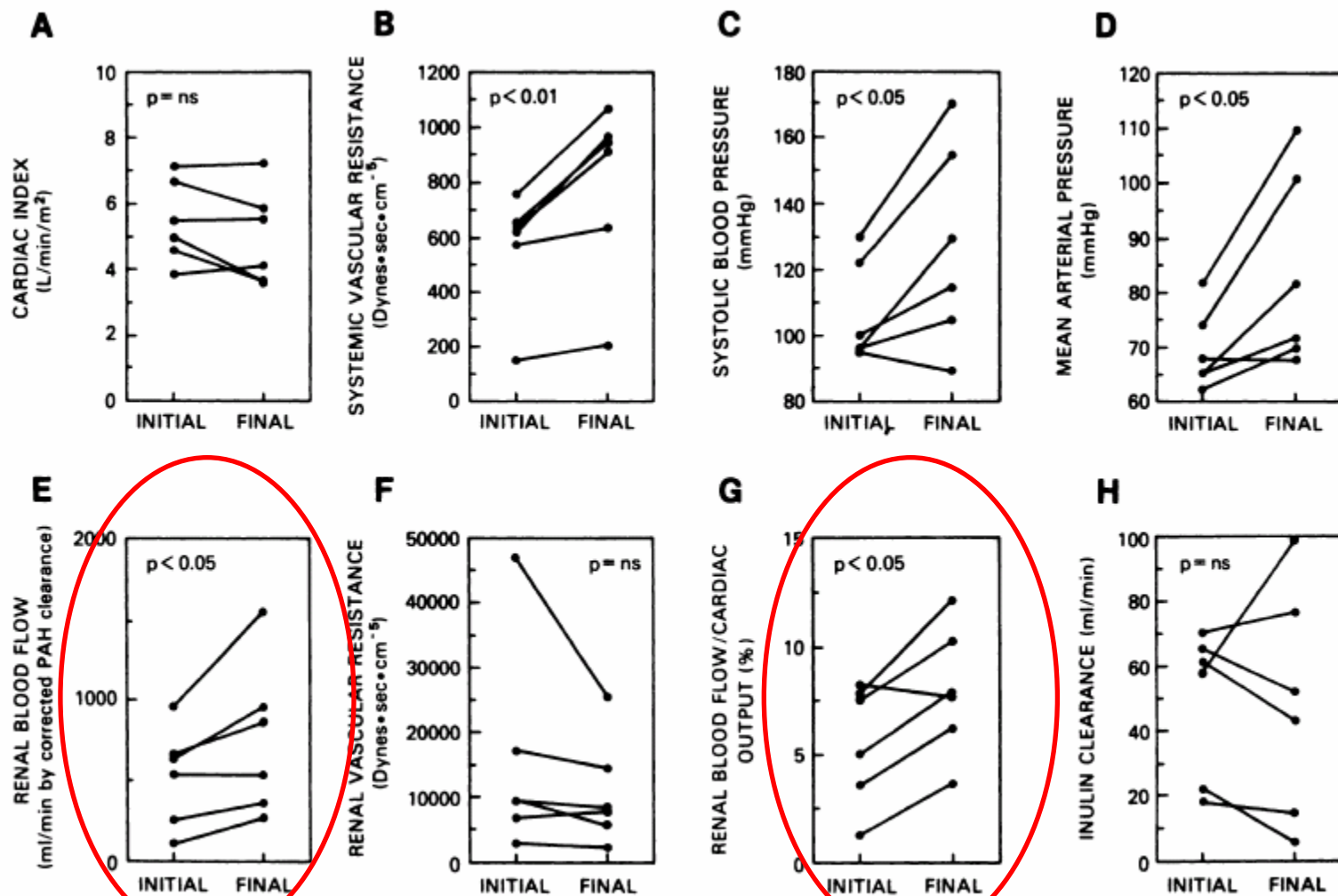
**Fig. 2.** Renal blood flow in left renal artery in sheep at baseline (before dashed vertical line) following a bolus of intravenous *E. coli* (after dashed vertical line). The x-axis represents time in minutes. The renal blood flow increased markedly after the induction of sepsis.



# Em gente



# Em gente



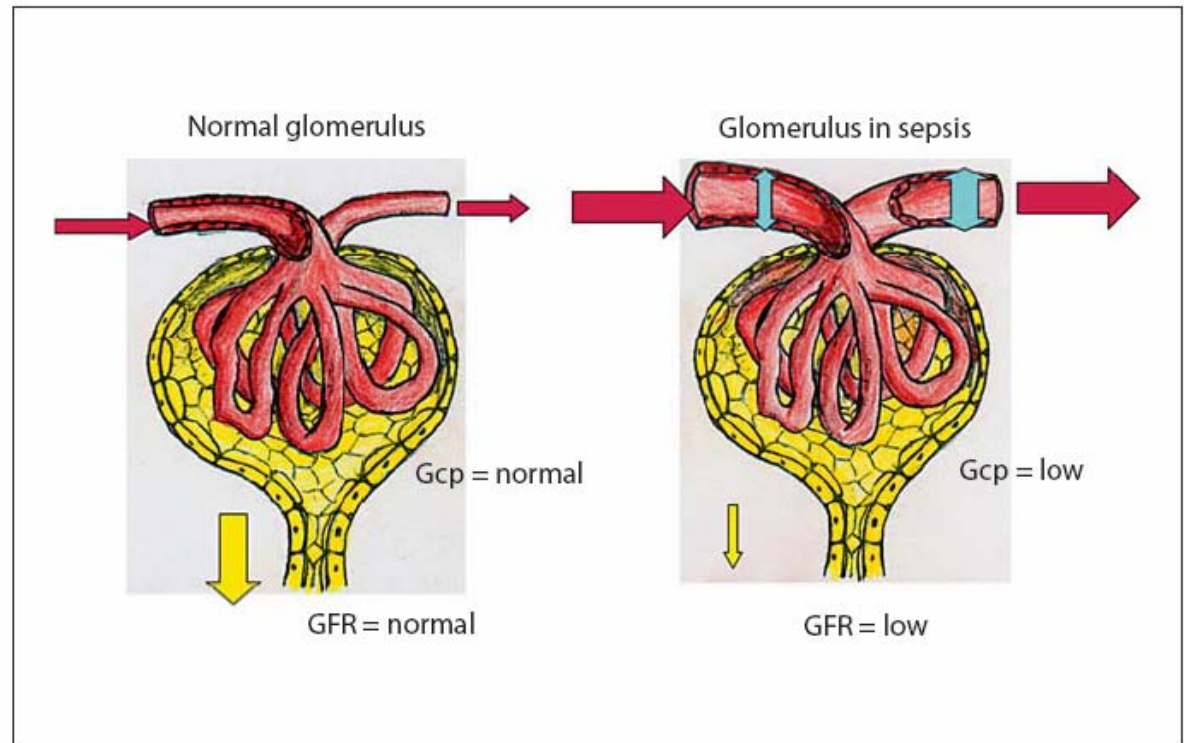
**FIGURE 4.** Individual systemic hemodynamics, renal hemodynamics and renal function tests in septic patients at the time of initial evaluation and at the time of follow-up evaluation 24 to 72 h later. **A**, CI values at initial and follow-up evaluation. **B**, SVR. **C**, Systolic blood pressure. **D**, MAP. **E**, RBF as measured by corrected  $C_{PAH}$  values. **F**, RVR. **G**, Change in the RBF/C ratio. **H**, GFR.

# IRA na sepse – Hipótese 2

## *Vasodilatação*

- Aumento do fluxo plasmático renal
- Vasodilatação preferencial da arteríola eferente

**Fig. 3.** Possible mechanisms behind the loss of GFR in hyperdynamic vasodilated sepsis despite increased renal blood. The septic glomerulus displays afferent and efferent arteriolar vasodilatation but greater efferent vasodilation as shown by the larger vertical arrow. RBF increases as shown by the larger red horizontal arrows, but GCP is low, GFR is also low and urine output falls (smaller yellow arrow).



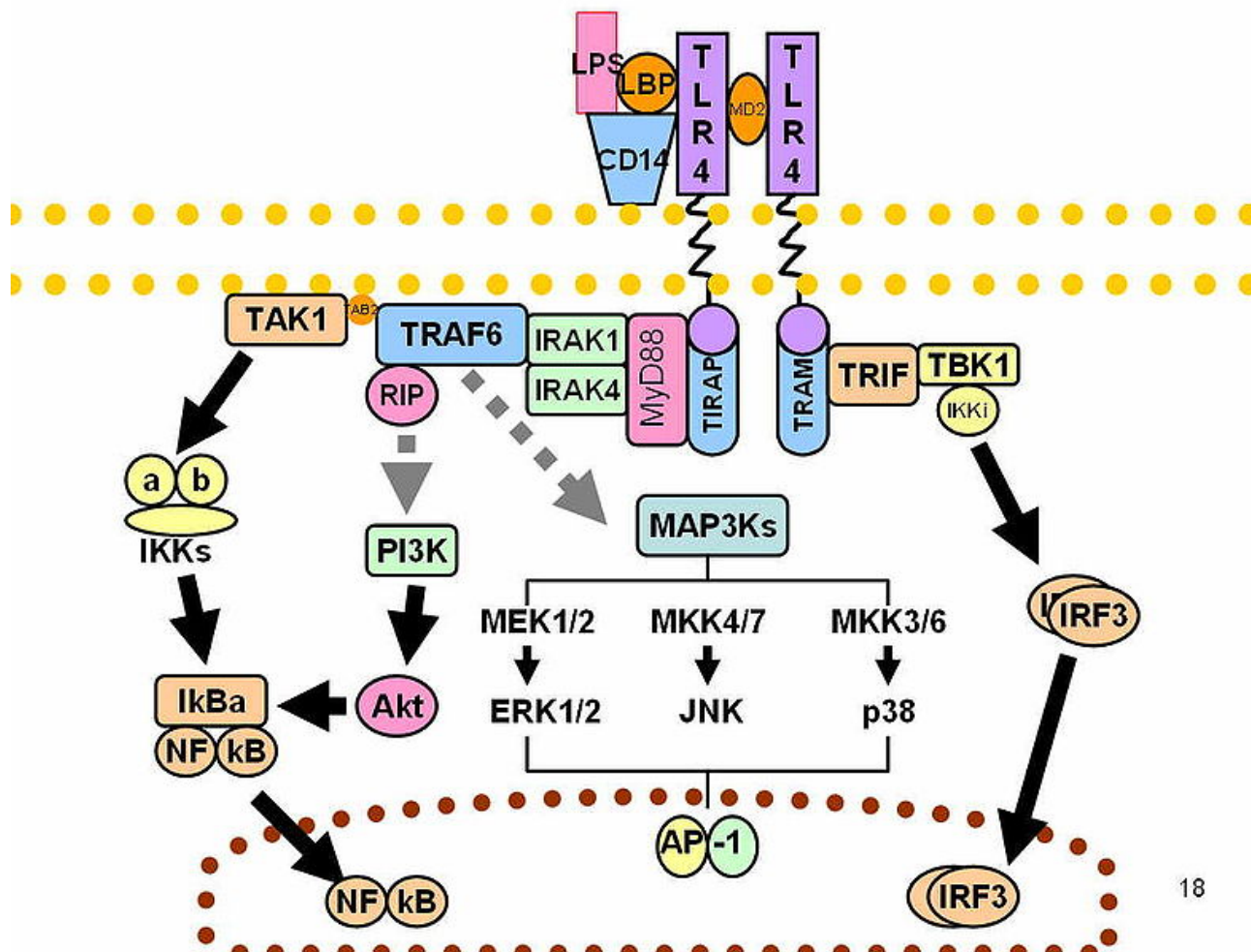
Langenberg, Nephron Exp Nephrol 2008;109:e95–e100

Lugon JR & Tancredi MLL. Abstract ISN Meeting  
1993.

# Fisiopatologia da IRA na sepse

## *Hipótese não hemodinâmica*

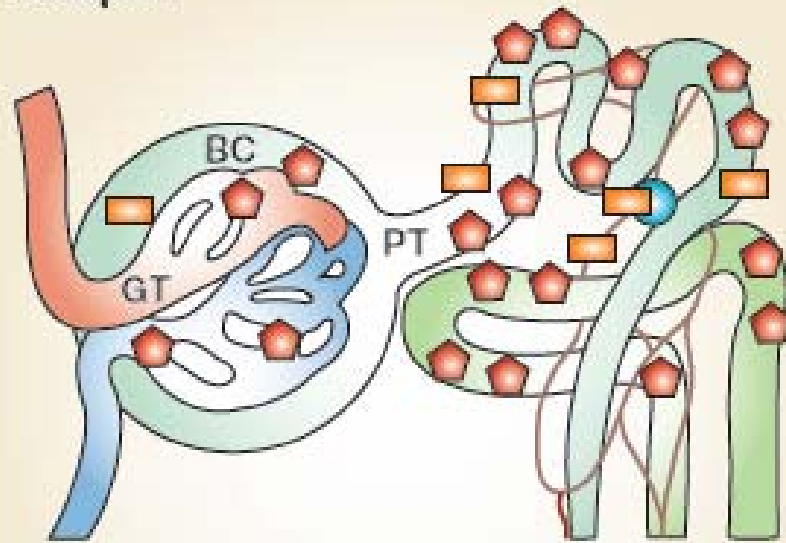
- Injúria celular renal precipitada por ligação de bactérias / produtos bacterianos com as células.



# Ligação c/ TLR4

- Papel fisiológico: ativar resposta imune inespecífica (inflamação)
- Hiperativação:
  - Hiperinflamação
  - Disfunção celular / apoptose / necrose

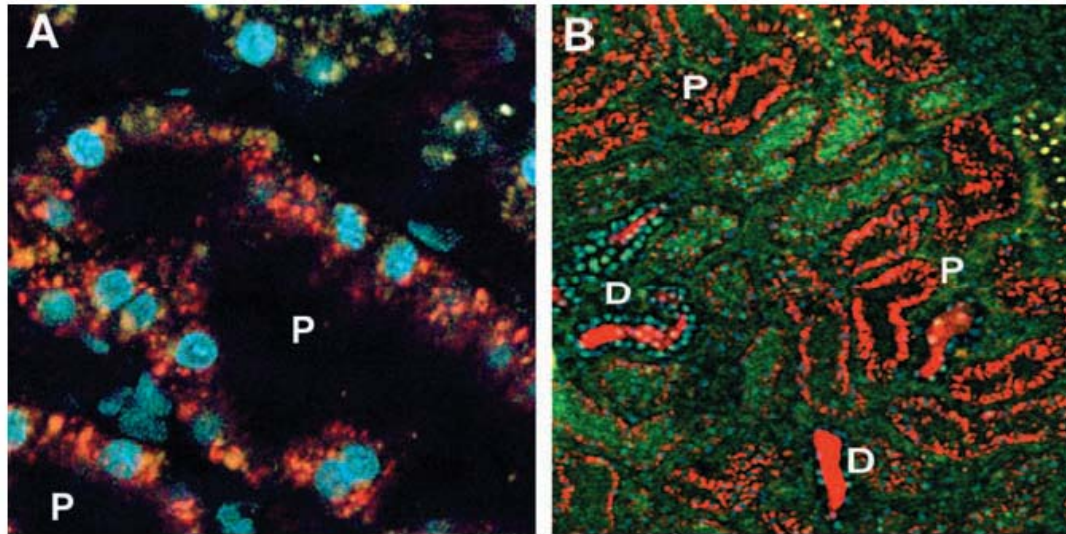
### D Sepsis



■ TLR2 on tubules,  
vasculature and infiltrating cells ●

▮ TLR4 on tubules,  
vasculature and glomeruli

# Captação de endotoxina pelo túbulo



**Figure 1 Live imaging of endotoxin uptake by rat kidney.** The images were acquired 24 h after cecal ligation and puncture (CLP) by 2-photon microscopy. Thirty minutes before imaging, *E. coli* endotoxin (100  $\mu$ g) labelled with fluorescent Alexa-568 (red colour, Molecular Probes, Eugene, Oregon, USA) was injected by tail vein. Hoechst (Molecular Probes, Eugene, Oregon, USA) was injected intravenously (500  $\mu$ g) 15 min before imaging to label all nuclei (blue colour). Green represents autofluorescence of tubules. Panel A shows two proximal tubules (P) with significant endotoxin uptake (40X objective). Panel B is a low power view (10X objective) that shows the extent of endotoxin uptake by proximal tubules. Two distal tubules (D) are seen with endotoxin concentrated in the lumen.

# Aumento de TLR-4 no rim na sepse

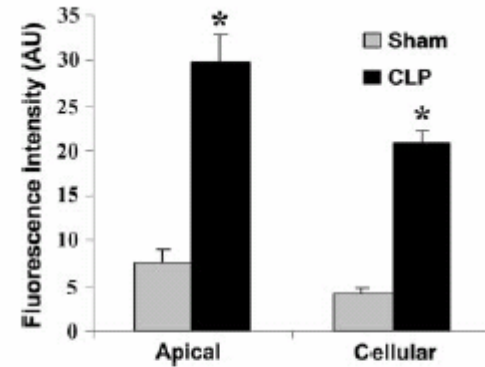
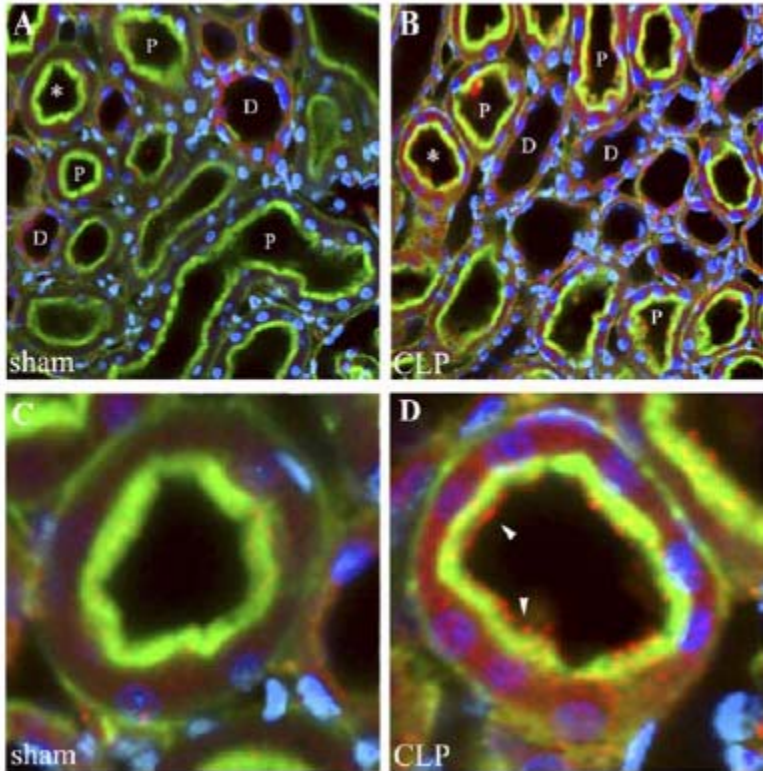


Fig. 5. Quantitation of TLR4 fluorescence in sham-operated rats and after CLP. Values represent means  $\pm$  SE. At least 6 tubules from representative fields per experimental condition were measured. Fluorescence intensity of TLR4 staining was measured separately at the apical border and the cellular compartment. \*Statistical significance with  $P < 0.01$  (unpaired  $t$ -test) when apical and cellular fluorescence was compared between sham and CLP.

# Fisiopatologia da IRA na sepse

## *Resumo*

- A IRA na sepse parece ser um modelo inicial de IRA bastante peculiar, hiperêmica (c/  $\uparrow$  FPR), com vasodilatação preferencial da AE.
- A lesão celular direta ocasionada por componentes bacterianos podem contribuir à IRA na sepse
- Hipotensão sistêmica como um evento mais tardio e mesmo nefrotoxicidade por drogas também podem contribuir à instalação de IRA na sepse

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# IRA na sepse

*É possível prevenir?*

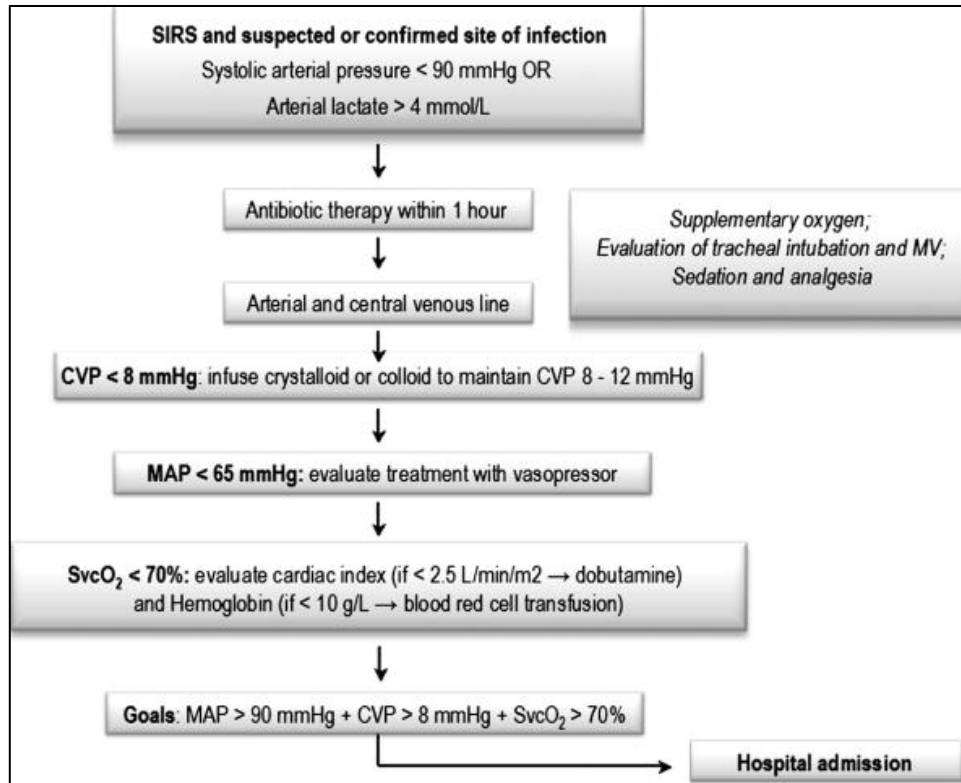
- Adequado tratamento da infecção
- Expansão de volume
- Controle glicêmico estrito
- Proteína C ativada?
- Vasoconstrictores

# Prevenção de IRA na sepse

## *Expansão volêmica vigorosa precoce*

- Alvos?
  - Normalização de pH, lactatemia, excesso de base e  $SO_2$
- Que fluido utilizar?

Fig. 2



**EARLY FLUID RESUSCITATION IN SEPSIS: EVIDENCE AND PERSPECTIVES.**

Bozza, Fernando; Carnevale, Renata; Japiassu, Andre; Castro-Faria-Neto, Hugo; Angus, Derek; Salluh, Jorge

Shock. 34(7) Suppl 1:40-43, September 2010.  
DOI: 10.1097/SHK.0b013e3181e7e668

This concept was tested both in observational studies and in a single-center RCT showing improved outcomes. However, to validate and translate this EGDT approach into standard of care, the results of ongoing multicenter trials are needed.

*Rivers et al. N Engl J Med 45:1368-1377, 2001*

Fig. 2. Algorithm for the implementation of EGDT. SIRS indicates systemic inflammatory response syndrome; MV, mechanical ventilation; CVP, central venous pressure; SvcO<sub>2</sub>, central venous oxygen saturation.

Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: A prospective sequential comparison.

[Bayer O](#), [Reinhart K](#), [Sakr Y](#), [Kabisch B](#), [Kohl M](#), [Riedemann NC](#), [Bauer M](#), [Settmacher U](#), [Hekmat K](#), [Hartog CS](#).

**DESIGN:** Prospective sequential comparison during intensive care unit stay.

**INTERVENTIONS:** Changes in standard fluid therapy, with predominantly 6% hydroxyethyl starch from January 2005 to June 2005, 4% gelatin from January 2006 to June 2006, and only crystalloids from September 2008 to June 2009.

**MEASUREMENTS AND MAIN RESULTS:** Acute kidney injury occurred in 70% of patients receiving hydroxyethyl starch (adjusted  $p = .002$ ) and in 68% of patients receiving gelatin (adjusted  $p = .025$ ) vs. 47% patients receiving crystalloids. Need for renal replacement therapy tended to be higher in the hydroxyethyl starch group (34%; adjusted  $p = .086$ ) and in the gelatin group (34%; adjusted  $p = .162$ ) in comparison to the crystalloid group (20%). Intensive care unit and hospital mortality were similar in each group (hydroxyethyl starch: 35% and 43%; gelatin: 26% and 31%; crystalloids: 30% and 37%).

**CONCLUSION:** Fluid resuscitation with only crystalloids was equally effective, resulted in a more positive fluid balance only on the first 2 days, and was associated with a lesser incidence of acute kidney injury.

# Controle glicêmico em TI

- Alvo inicial era 80-110mg/dl de glicemia obtido através de insulinização (*van den Berghe G et al. NEJM 2001; 345: 1359*)
- Mecanismo de ação desconhecido, mas houve redução da morbimortalidade e ↓ da incidência de sepse em 47%.
- Estudos subsequentes mostraram ↑ da incidência de hipoglicemia
- Alvo sugerido no presente: 140 - 180 mg/dl (*Hanazaki et al. World J Gastroenterol 15:4132, 2009*)

# Proteína C ativada na sepse

- Efeito anticoagulante
- Estudo Prowess (*Bernard et al. NEJM 344:699, 2001*)
  - Pequena redução na mortalidade em pacientes com APACHE II > 25.
  - Discreto ↑ episódios de sangramento
- Estudo ADDRESS (*Abraham et al. NEJM 353:1332, 2005*)
  - Estudo interrompido por ausência de eficácia e ↑ episódios de sangramento
- Custo p/ tratamento: 7 a 9 mil dólares
- Se indicado... uso deve ser precoce.

# Sepsis

## *Vasopressors vs. IRA*

**Objective** To compare the effects of vasopressin versus norepinephrine infusion on the outcome of kidney injury in septic shock.

**Design and setting** Post-hoc analysis of the multi-center double-blind randomized controlled trial of vasopressin versus norepinephrine in adult patients who had septic shock (VASST).

**Patients and intervention** Seven hundred seventy-eight patients were randomized to receive a blinded infusion of either low-dose vasopressin (0.01–0.03 U/min) or norepinephrine infusion (5–15 µg/min) in addition to open-label vasopressors and were included in the outcome analysis. All vasopressors were titrated and weaned to maintain a target blood pressure.

**Conclusions** Vasopressin may reduce progression to renal failure and mortality in patients at risk of kidney injury who have septic shock.

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# Há algo de particular no tratamento da IRA na sepse?

- Retirada de citocinas
- TRS precoce
- CRRT é melhor?
- Mais é melhor?

# Hemofiltração na Sepses

## Retirada de Citocinas - Problemas

- Afeta principalmente níveis plasmáticos
- TNF ativo é um trímero com PM de 54000
- Retirada por convecção é irrelevante.  
*Lonemann et al. KI 53 (S66):43s, 1998*
- Retirada por adsorção é rapidamente saturável

# Hemofiltração na Sepses

## Estudos Prospectivos Controlados

- Heering et al. Int Care Med 23:288,1997. Pacientes c/ IRA por sepse (n=18) ou de origem cardiovascular (n=15). Intervenção foi LVHF (24L/d) - Melhora hemodinâmica / retirada não significante de citocinas
- Sanchez-Izquierdo et al. Am J Kid Dis 30:483,1997. MODS s/ IRA. CCVH (n=15) ou Tratamento convencional (n=15). Eliminação de citocinas sem, entretanto, alterar níveis plasmáticos.
- Sander et al. Int Care Med 23:878,1997. SIRS independente de IRA. HF+/- . Retira IL-6 mas não TNF mas não altera seus níveis plasmáticos.

# Mediadores na Sepsis Quais Retirar?



Are the synergistic effects of high-volume haemofiltration and enhanced adsorption the missing key in sepsis modulation?\*

*Olivier Joannes-Boyau<sup>1</sup>, Patrick M. Honore<sup>2</sup>, Willem Boer<sup>3</sup> and Vincent Collin<sup>4</sup>*

*Nephrol Dial Transplant (2009) 24: 354–357*

However, at present, conclusive evidence based on well-designed, randomized controlled trials remains scarce, limiting the practical implementation of many techniques in daily practice outside the context of a study. From the few well-designed and documented studies that we have so far, it is safe to say that optimization of delivered dose in RRT has a proven positive effect. An ultrafiltration rate between 35 and 45 ml/kg/h, with adjustment for predilution and down time, can be recommended for the septic patient with AKI until other data become available. If continuous haemofiltration is not available, daily dialysis should be recommended in septic AKI.

Obrigado

Bom fim-de-semana a todos!!!!