

“EVOLUCIÓN CLÍNICA EN NIÑOS CON SHOCK SÉPTICO REFRACTARIO TRATADOS CON DOPAMINA O ADRENALINA. ESTUDIO OBSERVACIONAL EN UN SERVICIO DE URGENCIAS”

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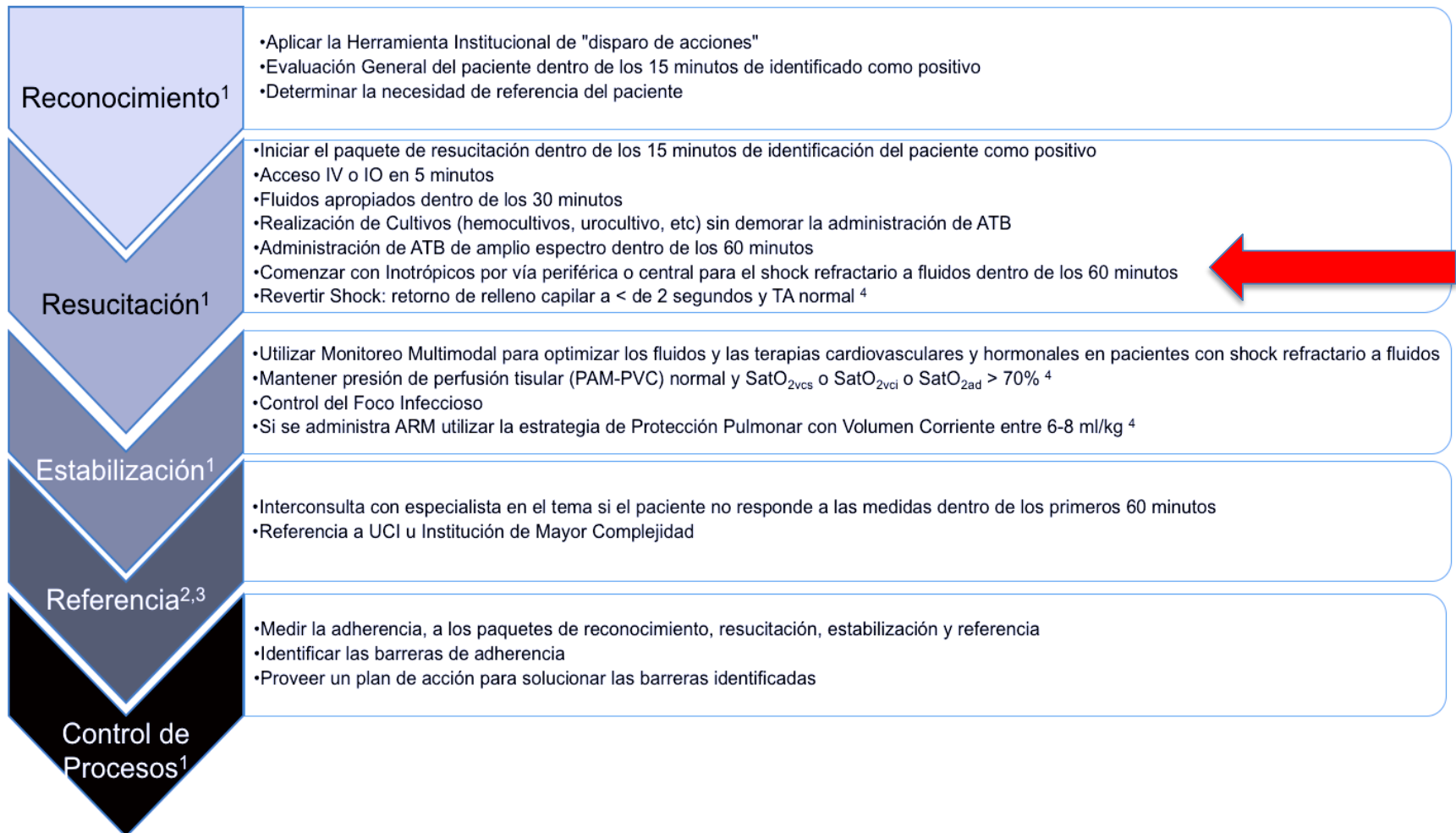


No tengo ningún conflicto de interés en relación
a esta presentación...





¿QUÉ RECOMIENDAN LAS GUÍAS ACTUALES?



¿QUÉ NOS DICE LA EVIDENCIA?

Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock

Andréa M. C. Ventura, MD¹; Huei Hsin Shieh, MD¹; Albert Bouso, MD¹; Patrícia F. Góes, MD²; Iracema de Cássia F. O. Fernandes, MD²; Daniela C. de Souza, MD²; Rodrigo Locatelli Pedro Paulo, MD²; Fabiana Chagas, RN¹; Alfredo E. Gílio, MD¹

Objectives: The primary outcome was to compare the effects of dopamine or epinephrine in severe sepsis on 28-day mortality; secondary outcomes were the rate of healthcare-associated infection, the need for other vasoactive drugs, and the multiple organ dysfunction score.

Design: Double-blind, prospective, randomized controlled trial from February 1, 2009, to July 31, 2013.

Setting: PICU, Hospital Universitário da Universidade de São Paulo, Brazil.

Patients: Consecutive children who are 1 month to 15 years old and met the clinical criteria for fluid-refractory septic shock. Exclusions were receiving vasoactive drug(s) prior to hospital admission, having known cardiac disease, having already participated in the trial during the same hospital stay, refusing to participate, or having do-not-resuscitate orders.

Interventions: Patients were randomly assigned to receive either dopamine (5–10 µg/kg/min) or epinephrine (0.1–0.3 µg/kg/min) through a peripheral or intravenous line. Patients not reaching predefined stabilization criteria after the maximum dose were classified as treatment failure, at which point the attending physician gradually stopped the study drug and started another catecholamine.

Measurements and Main Results: Physiologic and laboratory data were recorded. Baseline characteristics were described as proportions and mean (± se) and compared using appropriate statistical tests. Multiple regression analysis was performed, and statistical significance was defined as a *p* value of less than

0.05. Baseline characteristics and therapeutic interventions for the 120 children enrolled (63, dopamine; 57, epinephrine) were similar. There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and four (7%) in the epinephrine group (*p* = 0.033). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1–37.8; *p* = 0.037) and healthcare-associated infection (odds ratio, 67.7; 95% CI, 5.0–910.8; *p* = 0.001). The use of epinephrine was associated with a survival odds ratio of 6.49.

Conclusions: Dopamine was associated with an increased risk of death and healthcare-associated infection. Early administration of peripheral or intravenous epinephrine was associated with increased survival in this population. Limitations should be observed while interpreting these results. (*Crit Care Med* 2015; 43:2292–2302)

Key Words: children; dopamine; epinephrine; mortality; septic shock; vasoactive drug

Severe sepsis continues to be recognized as a significant healthcare problem worldwide. The prevalence of sepsis in critically ill children is expected to increase as more children survive diseases that were previously considered uniformly fatal. In children, the case-fatality rate in developed countries is around 10% (1), and it is 18% in developing nations (2). If septic shock is present, the mortality can be as high as 50% (3).

International collaborative efforts to improve the diagnosis and treatment of sepsis in children and neonates have been in place for more than a decade (4, 5). Adherence to guideline recommendations has decreased mortality in developed (survival odds ratio, 6.81; 95% CI, 1.26–36.80) (6) and developing countries (mortality odds ratio, 0.33; 95% CI, 0.13–0.85) (7). Nevertheless, some aspects of the guidelines are still a matter of debate. One of these, thanks to a paucity of research, is which first-line vasoactive drug is the best choice for children with fluid-refractory septic shock. Because myocardial dysfunction is well documented in adults (8) and children with severe

- Mayor riesgo de mortalidad
- Mayor riesgo de infecciones asociadas al tratamiento

20% vs 7%

Ventura AMC, Shieh HH, Bouso A, et al. Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock. *Crit Care Med*. 2015;43(11):2292-2302.

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This work was performed at Hospital Universitário da Universidade de São Paulo.

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000001260

Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock

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Objective: We compared efficacy of dopamine and epinephrine as first-line vasoactive therapy in achieving resolution of shock in fluid-refractory hypotensive cold septic shock.

Design: Double-blind, pilot, randomized controlled study.

Setting: Pediatric emergency and ICU of a tertiary care teaching hospital.

Patients: Consecutive children 3 months to 12 years old, with fluid-refractory hypotensive septic shock, were enrolled between July 2013 and December 2014.

Intervention: Enrolled children were randomized to receive either dopamine (in incremental doses, 10 to 15 to 20 µg/kg/min) or epinephrine (0.1 to 0.2 to 0.3 µg/kg/min) till and points of resolution of shock were achieved. After reaching maximum doses of test drugs, open-label vasoactive was started as per discretion of treating team. Primary outcome was resolution of shock within first hour of resuscitation. The study was registered (CTRI/2014/02/004393) and was approved by institute ethics committee.

Measurements and Main Results: We enrolled 29 children in epinephrine group and 31 in dopamine group. Resolution of shock within first hour was achieved in greater proportion of children receiving epinephrine ($n = 12$; 41%) than dopamine ($n = 4$; 13%) (odds ratio, 4.8; 95% CI, 1.3–17.2; $p = 0.019$); the trend persisted even at 6 hours (48.3% vs 29%; $p = 0.184$). Children in

epinephrine group had lower Sequential Organ Function Assessment score on day 3 (8 vs 12; $p = 0.05$) and more organ failure-free days (24 vs 20 d; $p = 0.022$). No significant difference in adverse events (16.1% vs 13.8%; $p = 0.80$) and mortality (58.1% vs 48.3%; $p = 0.606$) was observed between the two groups.

Conclusion: Epinephrine is more effective than dopamine in achieving resolution of fluid-refractory hypotensive cold shock within the first hour of resuscitation and improving organ functions. (Pediatr Crit Care Med 2016; XX:00–00)

Key Words: children; dopamine; epinephrine; fluid-refractory septic shock; septic shock

Septic shock is a leading cause of mortality and morbidity among children in developed and developing countries. Mortality ranging 10–50% is observed in developed countries and up to 80% in developing countries (1–4). Guidelines and recommendations for the management of pediatric septic shock have been published since 2002 by the American College of Critical Care Medicine (ACCM)-Pediatric Advanced Life Support and were updated in 2007 (5). The Surviving Sepsis Campaign 2012 guidelines endorse dopamine as first-line vasoactive agent in fluid-refractory septic shock (6). This recommendation is based more on the knowledge of pharmacologic effects of dopamine rather than any strong clinical evidence. Dopamine has a dose-dependent agonist effects on dopaminergic and adrenergic (α and β) receptors. In the general dosing range of 5–10 µg/kg/min, dopamine is inotropic via β -adrenergic stimulation; in the dosing range ~10–15 µg/kg/min, in addition to predominant inotropic effect, dopamine has a mild vasopressor effect via α 1-adrenergic stimulation; and in the doses more than 15 µg/kg/min, it is predominantly a vasopressor (via α 1-adrenergic effect) with minimal inotropic action (7).

There is no clinical trial that has demonstrated unequivocal benefit of dopamine on outcomes of pediatric septic shock in any of the above dose range. Furthermore, in adults with septic shock, dopamine has been observed to increase mortality and

Mayor efectividad en la resolución del shock en la primera hora

Mejor puntuación en Score SOFA al día 3

(12 vs 8, $p=0,05$)

Más días sin insuficiencia orgánica (20 vs 24, $p=0,022$)

Ramaswamy KN, Singh S, Jayashree M, Bansal A, Nallasamy K. Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock*. Pediatric Critical Care Medicine. 2016;17(11):502–512.

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This work was performed at Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/pccmjournal>).

Supported, in part, by the departmental fund.

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000000954

Vasopressors for hypotensive shock (Review)

Camper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H

Camper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H.
Vasopressors for hypotensive shock.
Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD003709.
DOI: 10.1002/14651858.CD003709.pub4.

www.cochranelibrary.com

Vasopressors for hypotensive shock (Review)
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WILEY

“...la dopamina aumenta el riesgo de arritmias en comparación con la noradrenalina y también podría aumentar la mortalidad...”.

Además...

- menor sensibilidad a la dopamina en < 6 m
 - acción inmunosupresora
- aumento del cortocircuito pulmonar



aja y entonces



SITGES 19-21 de abril 2018

23 REUNIÓN ANUAL
DE LA SOCIEDAD ESPAÑOLA
DE URGENCIAS DE PEDIATRÍA

DEATH OF DOPAMINE???



SITGES 19-21 de abril 2018

“EVOLUCIÓN CLÍNICA EN NIÑOS CON SHOCK SEPTICO REFRACTARIO A FLUIDOS TRATADOS CON DOPAMINA O ADRENALINA. ESTUDIO OBSERVACIONAL EN UN SERVICIO DE URGENCIAS”

Objetivo: Analizar la evolución clínica de niños con SSRF tratados con dopamina o adrenalina como agentes de primera elección en un SUP determinando:

- Necesidad y tiempo de permanencia en ARM
 - Estadía en UCIP
 - Estadía Hospitalaria
- Tiempo de requerimiento de inotrópicos
 - Mortalidad

“EVOLUCIÓN CLÍNICA EN NIÑOS CON SHOCK SEPTICO REFRACTARIO A FLUIDOS TRATADOS CON DOPAMINA O ADRENALINA. ESTUDIO OBSERVACIONAL EN UN SERVICIO DE URGENCIAS”

- Diseño: estudio descriptivo y observacional efectuado en un centro único.
- Población: Pacientes ingresados al SUP con diagnóstico de shock séptico refractario que recibieron adrenalina o dopamina como droga de primera opción.
- Se excluyeron: miocardiopatía primaria o secundaria, cuidados paliativos, indicación de más de un inotrópico en forma simultánea.

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- Se definió como **shock refractario a fluidos** a todos los pacientes que cumplieron durante el tratamiento inicial uno o más de los siguientes criterios:

infusión ≥ 60 ml/kg de fluidos

y/o

aparición de signos clínicos de sobrecarga de volumen: aparición de rales pulmonares y/o tos, hepatomegalia y tercer ruido cardiaco

y/o

presencia de muy mal estado general: hipotensión, desasosiego, depresión del sensorio y aspecto cianótico.

- Todos los pacientes fueron tratados siguiendo los protocolos de atención del ACCM vigentes.

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- Se revisaron las historias clínicas de todos los niños ingresados al SUP con diagnóstico de shock séptico y que requirieron soporte inotrópico luego de la administración de fluidos durante el periodo comprendido entre julio de 2009 y noviembre de 2017.
- Test paramétricos y no paramétricos.
- Software: RedCap y Spss V21.

RESULTADOS

150 pacientes con shock séptico
refractario a volumen

8 excluidos por recibir 2 inotrópicos
simultáneamente desde el inicio

24 recibieron otro inotrópico

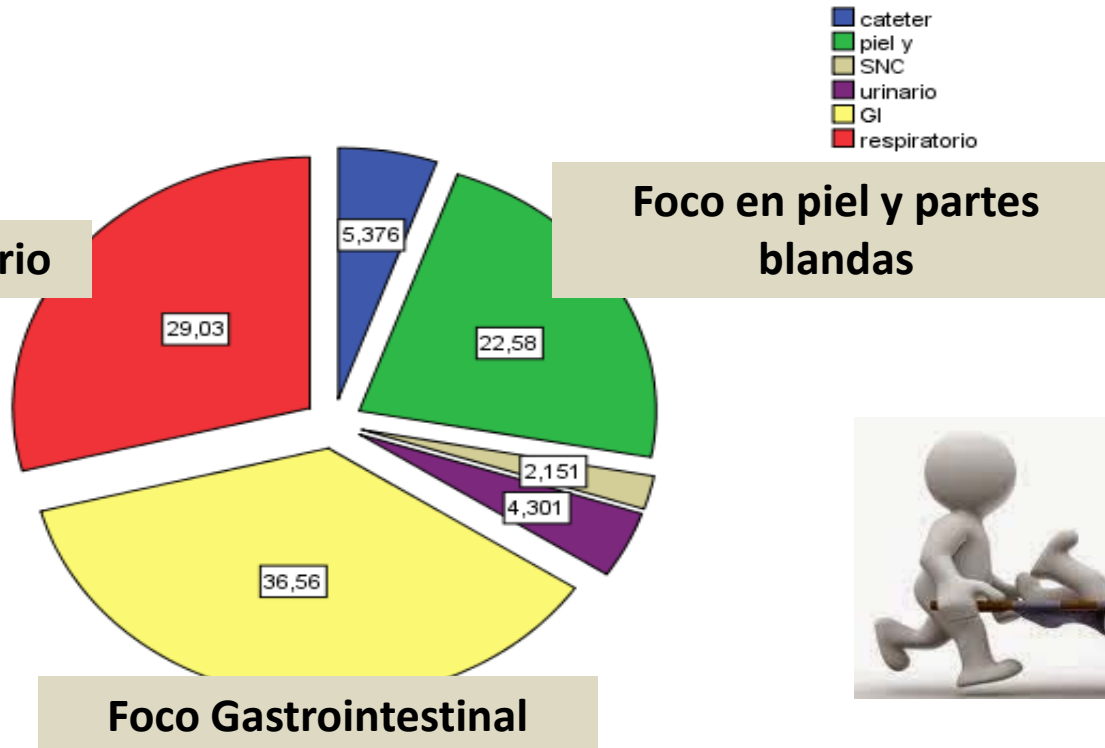
118 pacientes



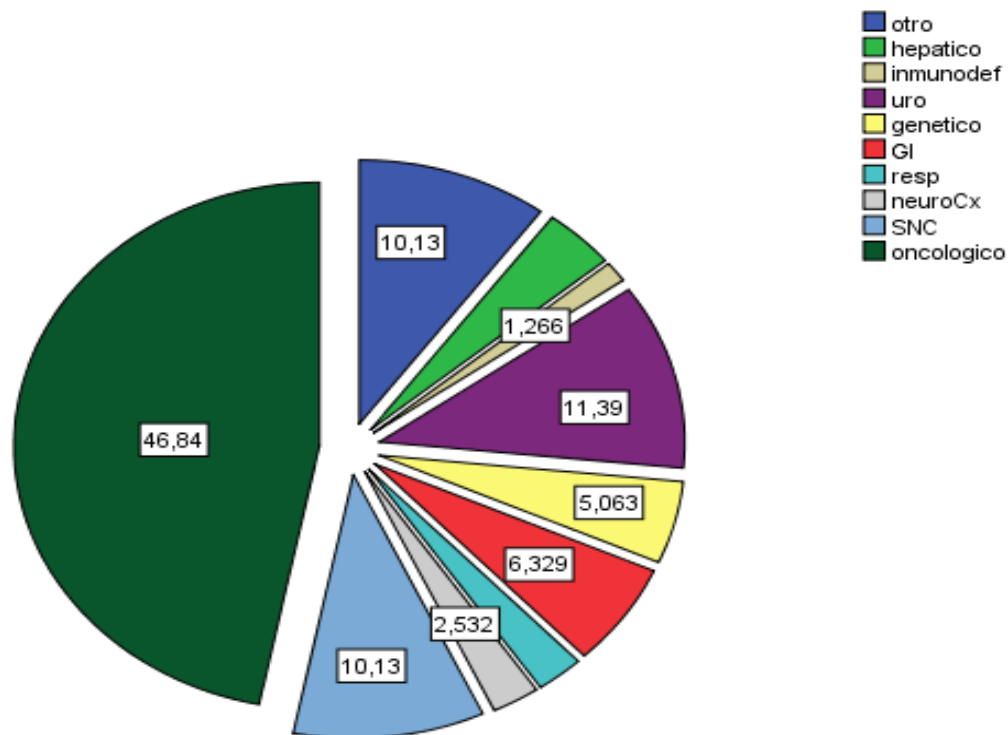
Mediana de edad (años): 5,76 (0,13 a 22,4)

SITGES 19-21 de abril 2018

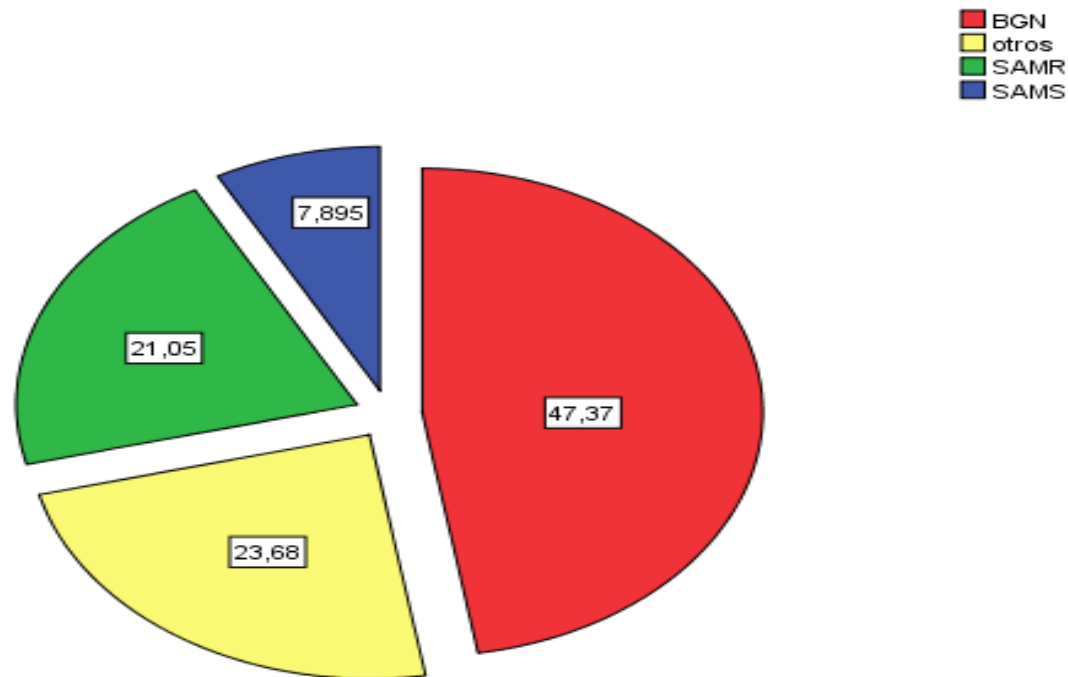
79% presencia de foco infeccioso evidente



70% con condición crónica (47% enfermedad oncológica)



33% (39) presentó hemocultivos positivos (bacilos gram negativos 48%)



RESULTADOS

		Grupo Adrenalina n = 49	Grupo Dopamina n= 69
Sexo masculino (%)		31 (63)	39 (57)
Edad (meses) ^{a,b}		63 (4-192)	81 (2-270)
Enfermedad de base (%)	Si	27 (55)	52 (75)
	oncológico	7 (14)	30 (43)
Con inmunodeficiencia (%)		13 (27)	37 (54)
ATB en 60 min (%)		36 (73)	68 (99)
Con foco de infección (%)		39 (80)	54 (78)
Foco (%)	Digestivo	18 (37)	16 (23)
	Respiratorio	6 (12)	21 (30)
	Piel y partes blandas	11 (22)	10 (15)
	Urinario	2 (4)	2 (3)
	Asociado a Catéter	1 (2)	4 (6)
	SNC	1 (2)	1 (1)
Motivo de indicación del inotrópico (%)		(n=47)	(n=66)
	Refractario a volumen (60ml/kg)	38 (81)	34 (52)
	Sobrecarga	0	6 (9)
	Muy mal estado general	9 (19)	26 (39)
Intubación en Servicio Urgencias (%)		10 (20)	7 (10)
Rescate de germen (%)	HMC +	11 (22)	28 (41)
	Uro +	5 (10)	5 (7)
	ASNF	3 (6)	11 (16)
	Cultivo de partes blandas	7 (14)	2 (3)

^a Expresada en mediana

^b Rango

RESULTADOS

	Grupo Adrenalina n=49	Grupo Dopamina n= 69	p
ARM (%)	19 (39)	28 (41)	0.84*
Días ARM (mediana en días, RQ)	4 (1-5)	5.5 (5.5-11)	0.09**
Días de Internación (mediana en días, RQ)	11 (7-17)	13 (8-22)	0.554**
Días de Inotrópicos (mediana en días, RQ)	2 (1-3)	2 (1-3)	0.714**
Días de UCI (mediana en días, RQ)	4 (2-6)	4 (2-8)	0.748**
Muerte (%)	5 (10)	9 (13)	0.638*

•Chi2

•** Mann Withney

Limitaciones

- Retrospectivo
- Único centro
- Tamaño de la muestra
- Diferencias entre las poblaciones (más pacientes oncológicos en el grupo dopamina - edad)
- Cambios en la capacitación del equipo
- Impacto de las decisiones luego de la primera hora.



CONCLUSIÓN

No observamos diferencias en relación a necesidad y tiempo de ARM e inotrópicos, estancia hospitalaria y en UCIP y mortalidad entre ambos grupos. Son necesarios estudios adicionales.



Muchas Gracias!



COMPARACIÓN SIN PACIENTES ONCOLÓGICOS n=81

	Grupo Adrenalina n=42	Grupo Dopamina n= 39	P (* **)
ARM (%)	18 (43)	17 (44)	0.95*
Días ARM (mediana en días)	3.5 (1-7)	6 (4,5 – 10,5)	0.062**
Días de Internación (mediana en días)	10 (6-15)	14 (1-47)	0.149**
Días de Inotrópicos (mediana en días)	1,5 (1-3)	2 (1-3)	0.239**
Días de UCI (mediana en días)	4 (2-6)	4 (2-8)	0.341**
Muerte (%)	5 (12)	4 (10)	0.784*

Regresión logística

Variable dependiente: Muerte

		B	Error estándar	Wald	gl	P	Exponencial (B) OR (IC 95%)
	Edad	-,001	,005	,028	1	,867	,999 (0,989-1,009)
	Dopamina	,460	,681	,457	1	,499	1,585 (0,417-6,021)
	Enf de base	-,272	,658	,171	1	,679	,762 (0,210-2,765)
	Foco	-,493	,684	,520	1	,471	,611 (0,160-2,334)
	ATB 60'	,466	,942	,245	1	,621	1,594 (0,251-10,1)
	Constante	-1,718	,965	3,166	1	,075	,179