Hepatite alcoólica: ainda existe indicação de corticóide?

Liana Codes, PhD

Hospital Universitário Prof. Edgard Santos, UFBA

Unidade de Gastroenterologia e Hepatologia do Hospital Português, Salvador

Anvisa RDC 96

Declaração de potencial conflito de interesse

Nada a declarar

Caso clínico:

Hepatite alcoólica grave => ACLF Grau 2

- Paciente masc. 60 a, PO cirurgia bariátrica, depressão, ingesta alcoólica diária
- Transferido de outro hospital com encefalopatia (grau III), icterícia , ascite e hidrotórax
- Hb 12.2 / HCM 34 / Leuco 16870 / Cr 0.7=>1.8 Na 120 / Alb 2.4 / BT 7.0 / PH 7.49 / Lact 3.3 /RNI 2.5
- MELD-Na 25 Maddrey 66 SOFA 9 Clif C OF 12 Clif C ACLF 105
- AKI 2
- ACLF grau 2
- Há benefício para corticoterapia neste paciente?

Hospital Português

Quais as perspectivas para o tratamento da hepatite alcóolica grave?

- Corticóide: modesta redução de mortalidade em curto prazo .
- Contra-indicação em pacientes com infecção não controlada ou sangramento ativo.
- Consumo excessivo de álcool e hepatite alcoólica: fatores preciptantes de ACLF.
- Alta mortalidade de curto prazo
- Transplante hepático: opção controversa para pacientes com hepatite alcoólica
- Necessidade de desenvolvimento de novos alvos terapêuticos

Objetivos do tratamento de pacientes com hepatite alcóolica

- Recuperar função hepática

- Evitar infecções, AKI, ACLF e óbito

Controvérsia para corticoterapia

Singal et al;2013

- Preocupação quanto ao risco de infecções / sepse

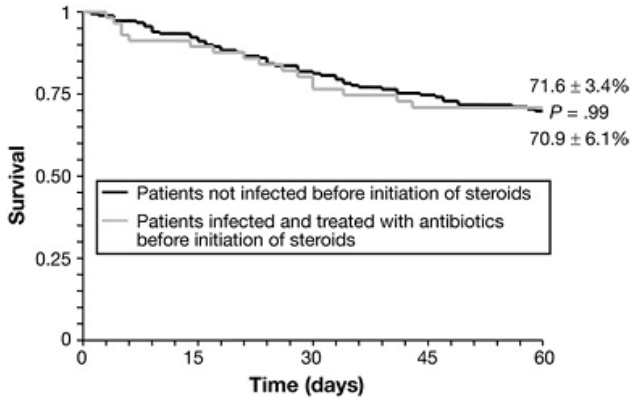
- 25 % gastroenterologistas e 45% dos hepatologistas relataram uso de corticóide no tratamento de HA grave

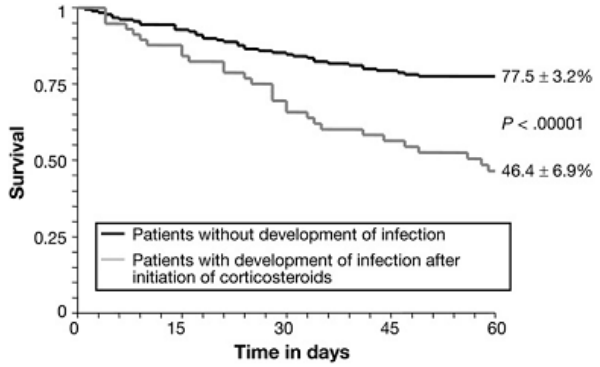
GASTROENTEROLOGY 2009;137:541–548

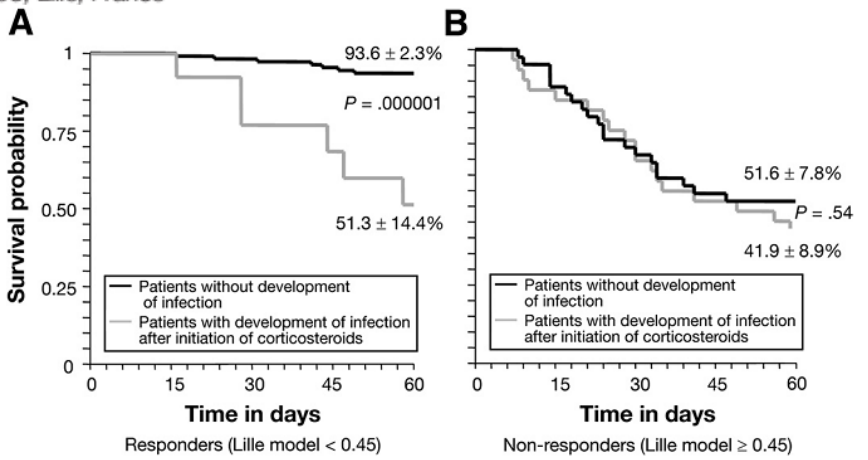
Infection in Patients With Severe Alcoholic Hepatitis Treated With Steroids: Early Response to Therapy Is the Key Factor

ALEXANDRE LOUVET,*,‡ FAUSTINE WARTEL,* HÉLÈNE CASTEL,* SÉBASTIEN DHARANCY,*,‡ ANTOINE HOLLEBECQUE,* VALÉRIE CANVA–DELCAMBRE,* PIERRE DELTENRE,* and PHILIPPE MATHURIN*,‡

Service des Maladies de l'Appareil digestif, Hôpital Huriez, Lille; and ‡Unité INSERM U795, Lille, France







- Infecção é frequente em pacientes com hepatite alcóolica - 30% “baseline”
- Corticóide pode ser utilizado após ATB
- 25-30 % infecção após admissão (“infecção incidente”) após corticóide – mortalidade
- Modelo Lille: desenvolvimento de infecção e sobrevida

Research Article

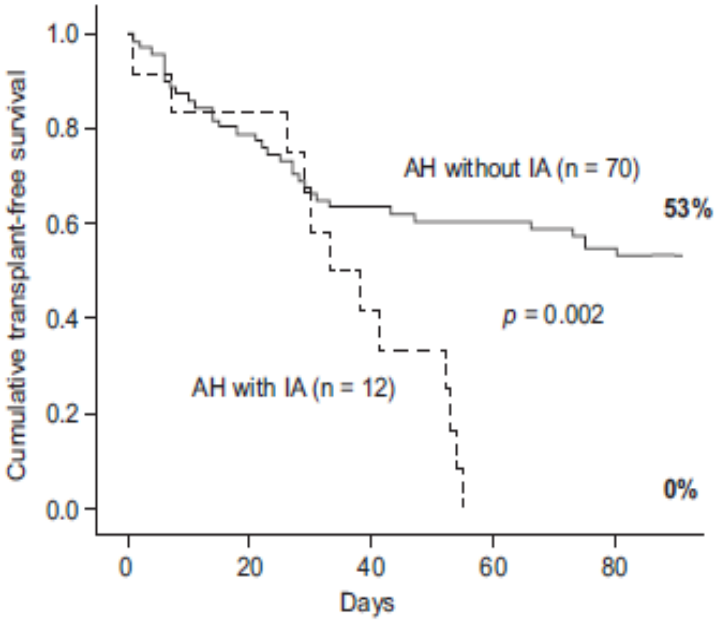
EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Invasive aspergillosis in patients with severe alcoholic hepatitis

Thierry Gustot[1,2,3,*,†], Evelyne Maillart[4,†], Massimo Bocci[1], Rudy Surin[4], Eric Trépo[1,2], Delphine Degré[1,2], Valerio Lucidi[5], Fabio Silvio Taccone[6], Marie-Luce Delforge[7], Jean-Louis Vincent[6], Vincent Donckier[5], Frédérique Jacobs[4,‡], Christophe Moreno[1,2,‡]

[1]*Department of Gastroenterology and Hepato-Pancreatology, Erasme Hospital, Brussels, Belgium;* [2]*Laboratory of Experimental Gastroenterology, Université Libre de Bruxelles, Brussels, Belgium;* [3]*INSERM, U773, Centre de Recherche Biomédicale Bichat-Beaujon CRB3, Paris, France;* [4]*Department of Infectious Diseases, Erasme Hospital, Brussels, Belgium;* [5]*Department of Digestive Surgery, Erasme Hospital, Brussels, Belgium;* [6]*Department of Intensive Care Unit, Erasme Hospital, Brussels, Belgium;* [7]*Department of Microbiology, Erasme Hospital, Brussels, Belgium*

Journal of Hepatology **2014** vol. 60 | 267–274



- 16 % dos pacientes com HA grave com aspergilose invasiva
- Fatores de risco:

  Admissão UTI

  MELD ≥ 24

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prednisolone or Pentoxifylline for Alcoholic Hepatitis

Mark R. Thursz, M.D., Paul Richardson, M.D., Michael Allison, Ph.D., Andrew Austin, M.D., Megan Bowers, M.Sc., Christopher P. Day, M.D., Ph.D., Nichola Downs, P.G. Cert., Dermot Gleeson, M.D., Alastair MacGilchrist, M.D., Allister Grant, Ph.D., Steven Hood, M.D., Steven Masson, M.A., Anne McCune, M.D., Jane Mellor, M.Sc., John O'Grady, M.D., David Patch, M.D., Ian Ratcliffe, M.Sc., Paul Roderick, Ph.D., Louise Stanton, M.Sc., Nikhil Vergis, M.B., B.S., Mark Wright, Ph.D., Stephen Ryder, D.M., and Ewan H. Forrest, M.D., for the STOPAH Trial*

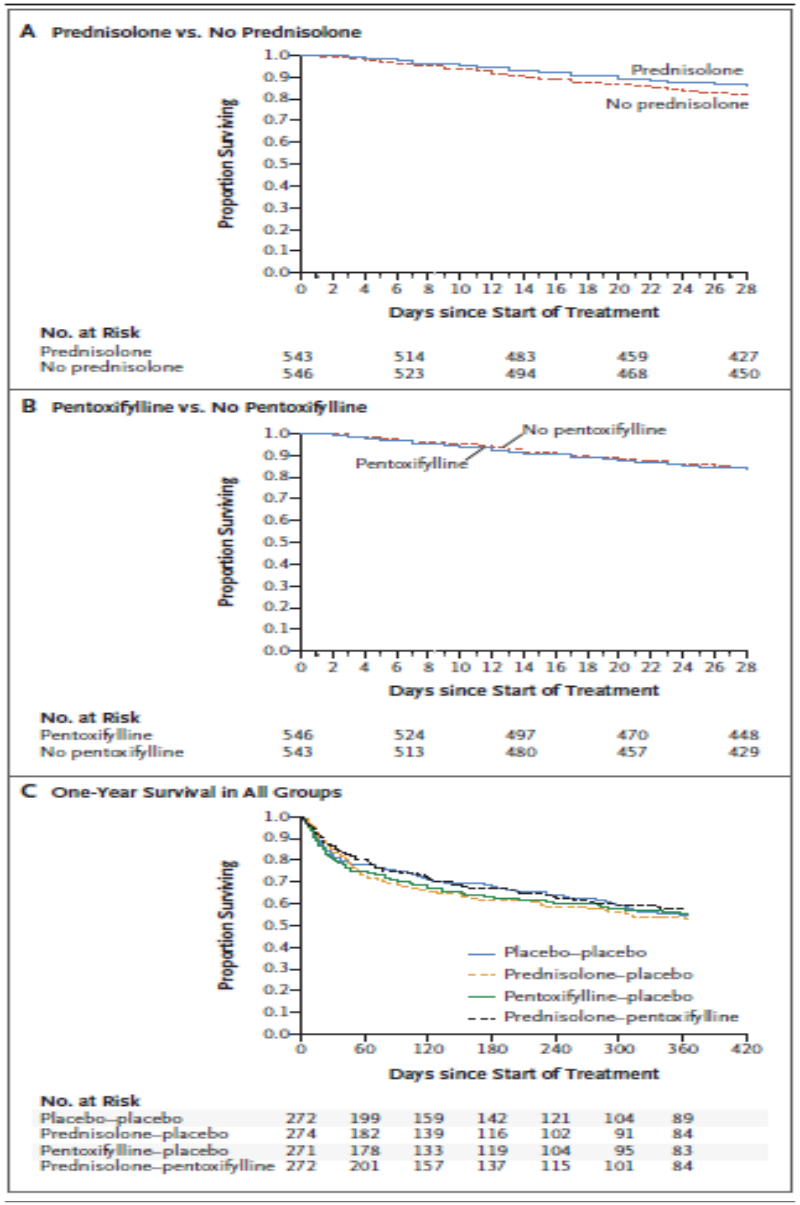
PREDNISONA:

- Redução de mortalidade 28 dias (OR 0,61,p=0.02)
- Ausência de benefício 90 dias ou 12 meses
- Maior frequência de infecções (13 vs 7%)
- Infecção pós corticóide: aumento mortalidade 90 dias
- Modelo de Lille: evitar o uso desnecesário corticóide

PENTOXIFILINA

- Nenhum benefício em monoterapia, nem em combinação com o corticóide, nem como resgate nos não respondedores

Pacientes com disfunção renal e suporte inotrópico foram excluidos do estudo

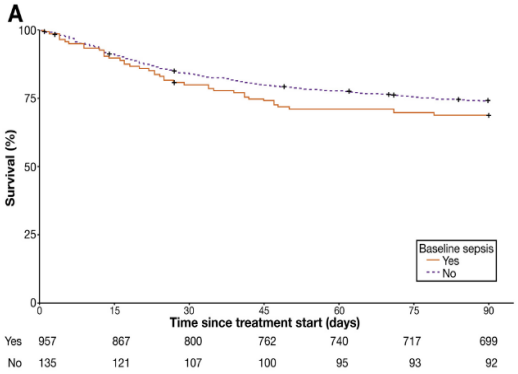


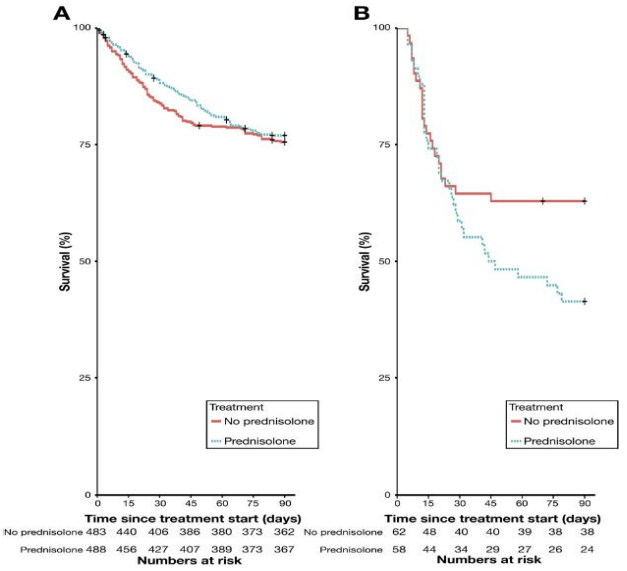
Gastroenterology 2017;152:1068–1077

CLINICAL—LIVER

In Patients With Severe Alcoholic Hepatitis, Prednisolone Increases Susceptibility to Infection and Infection-Related Mortality, and Is Associated With High Circulating Levels of Bacterial DNA

Nikhil Vergis,[1,*] Stephen R. Atkinson,[1,*] Suzanne Knapp,[1] James Maurice,[1] Michael Allison,[2] Andrew Austin,[3] Ewan H. Forrest,[4] Steven Masson,[5] Anne McCune,[6] David Patch,[7] Paul Richardson,[8] Dermot Gleeson,[9] Stephen D. Ryder,[10] Mark Wright,[11] and Mark R. Thursz[1]





- 1092 pacientes
- Infecção antes do corticóide não impacta na sobrevida
- Infecção grave nos tratados com prednisona:
  - OR 1.27, p=0.002
- Infecção após o tratamento:
  - OR 1.70;p=0.024
- Mortalidade 90 dias:
  - OR 2.46;p=0.002
- bDNA circulante: preditor de infecção nos primeiros 7 dias de prednisona (OR 4.68,p=0.001)

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Systemic Inflammatory Response and Serum Lipopolysaccharide Levels Predict Multiple Organ Failure and Death in Alcoholic Hepatitis

Javier Michelena,[1,2] José Altamirano,[1,2,3] Juan G. Abraldes,[4] Silvia Affò,[1,2] Oriol Morales-Ibanez,[1,2] Pau Sancho-Bru,[1,2] Marlene Dominguez,[5] Juan Carlos García-Pagán,[1,2,6] Javier Fernández,[1,2] Vicente Arroyo,[1,2] Pere Ginès,[1,2] Alexandre Louvet,[7,8] Philippe Mathurin,[7,8] Wajahat Z. Mehal,[9] Juan Caballería,[1,2] and Ramón Bataller[2,10]

HEPATOLOGY, September 2015

- SRIS => FMO => Mortalidade
- Procalcitonina (admissão) => Infecção
- Níveis de LPS (admissão) => Ausência de resposta ao corticóide e mortalidade

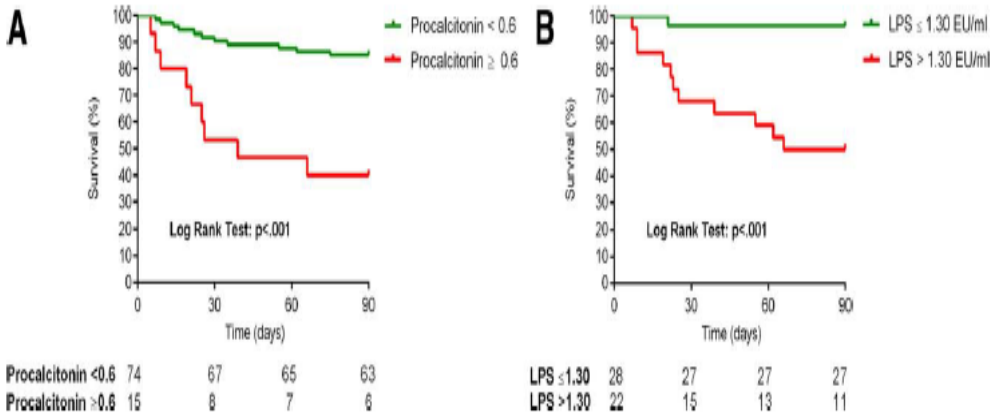


Fig. 3. Ninety-day mortality according to the levels of (A) procalcitonin and (B) LPS.

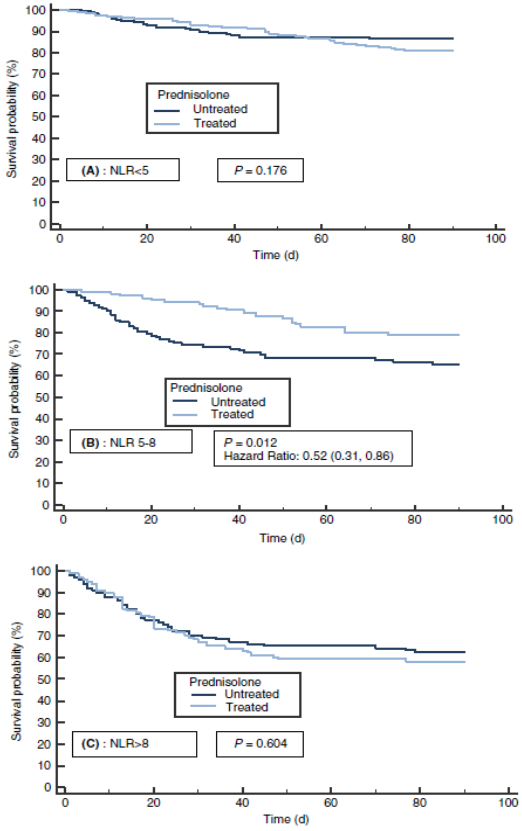
Received: 18 February 2019 | First decision: 13 March 2019 | Accepted: 14 May 2019
DOI: 10.1111/apt.15335

APT Alimentary Pharmacology & Therapeutics WILEY

Baseline neutrophil-to-lymphocyte ratio predicts response to corticosteroids and is associated with infection and renal dysfunction in alcoholic hepatitis

Ewan H. Forrest[1] | Natasha Storey[1] | Rohit Sinha[2] | Stephen R. Atkinson[3] | Nikhil Vergis[3] | Paul Richardson[4] | Steven Masson[5] | Stephen Ryder[6] | Mark R. Thursz[3] | Michael Allison[7] | Andrew Fraser[8] | Andrew Austin[9] | Anne McCune[10] Ashwin Dhanda[11] | Dev Katarey[12] | Jonathan Potts[12] | Sumita Verma[12] | Richard Parker[13] | Peter C. Hayes[2] | On behalf of the STOPAH NLR Group

		Baseline NLR	
Baseline AKI	Present n = 63	11.12 (8.64, 13.59)	P = 0.0001 (2.64, 7.62)
	Absent n = 691	5.99 (5.66, 6.31)	
Incident AKI	Present n = 67	7.53 (6.37, 8.69)	P = 0.0056 (0.46, 2.65)
	Absent n = 403	5.98 (5.58,06.38)	
Infection at Baseline	Present n = 99	7.84 (6.60, 9.08)	P = 0.021 (0.23, 2.82)
	Absent n = 690	6.32 (5.94, 6.70)	
Incident Infection Day 7	Present n = 94	7.75 (6.30, 9.20)	P = 0.035 (0.12, 3.11)
	Absent n = 695	6.14 (5.76, 6.52)	
Incident Infection Day 28	Present n = 185	7.14 (6.29, 7.99)	P = 0.025 (0.14, 2.02)
	Absent n = 604	6.06 (5.64, 6.48)	



NLR admissão: risco de infecção, AKI e resposta terapêutica ao corticóde

Journal of Hepatology 2015 vol. 62 | 759–760

EASL | JOURNAL OF HEPATOLOGY

Prognosis of treated severe alcoholic hepatitis in patients with gastrointestinal bleeding

Marika Rudler[1], Sarah Mouri[1], Frédéric Charlotte[2], Pascal Lebray[1], Romain Capocci[1], Hedi Benosman[1], Thierry Poynard[1], Dominique Thabut[1,*]

[1]AP-HP, UPMC, Department of Hepatogastroenterology, La Pitié-Salpêtrière Hospital, 47-80 boulevard de l'Hôpital, Assistance Publique-Hôpitaux de Paris, Pierre et Marie Curie University, 75013 Paris, France; [2]AP-HP, UPMC, Department of Anatomopathology, La Pitié-Salpêtrière Hospital, 47-80 boulevard de l'Hôpital, Assistance Publique-Hôpitaux de Paris, Pierre et Marie Curie University, 75013 Paris, France

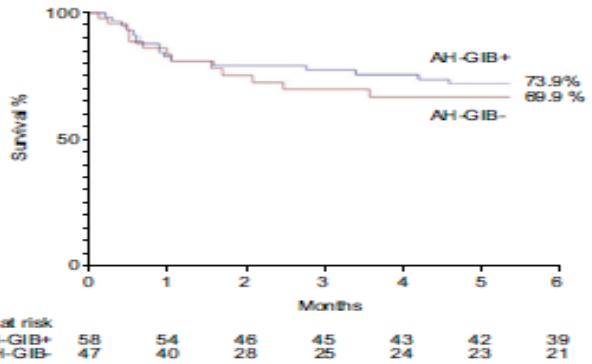


Fig. 2. Six-month survival for 58 AH-GIB+ and 47 AH-GIB– patients. (This figure appears in colour on the web.)

- Benefício da antibioticoprofilaxia no manejo da hepatite alcóolica grave

AntiBioCor Trial França – NCT 02281929 avaliando combinação de prednisona com antibioticoprofilaxia

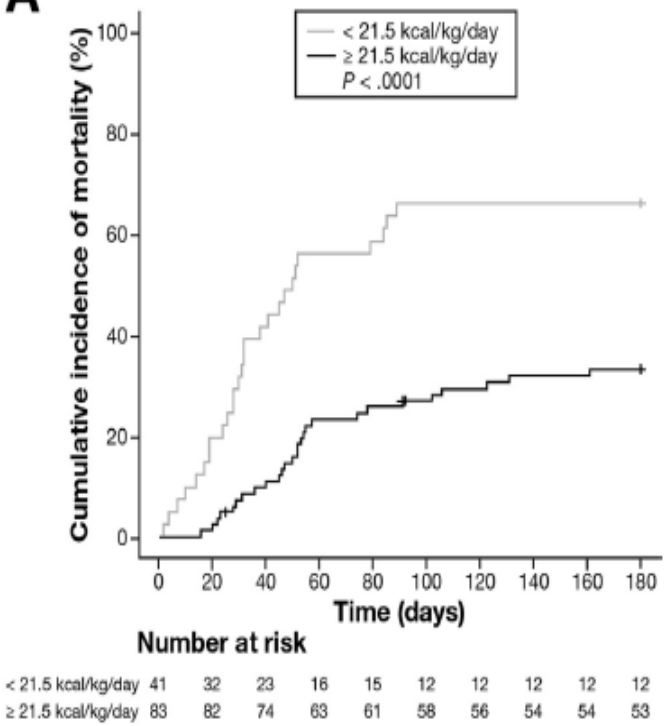
Gastroenterology 2016;150:903–910

CLINICAL—LIVER

Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids

Christophe Moreno,[1,2] Pierre Deltenre,[1,3,4] Christelle Senterre,[5] Alexandre Louvet,[6] Thierry Gustot,[1,2] Boris Bastens,[7] Axel Hittelet,[8] Marie-Astrid Piquet,[9] Wim Laleman,[10] Hans Orlent,[11] Luc Lasser,[12] Thomas Sersté,[13] Peter Starkel,[14] Xavier De Koninck,[15] Sergio Negrin Dastis,[16] Jean Delwaide,[17] Isabelle Colle,[18] Chantal de Galocsy,[19] Sven Francque,[20] Philippe Langlet,[21] Virginie Putzeys,[22] Hendrik Reynaert,[23] Delphine Degré,[1,2] and Eric Trépo[1,2]

A



Suporte nutricional oral

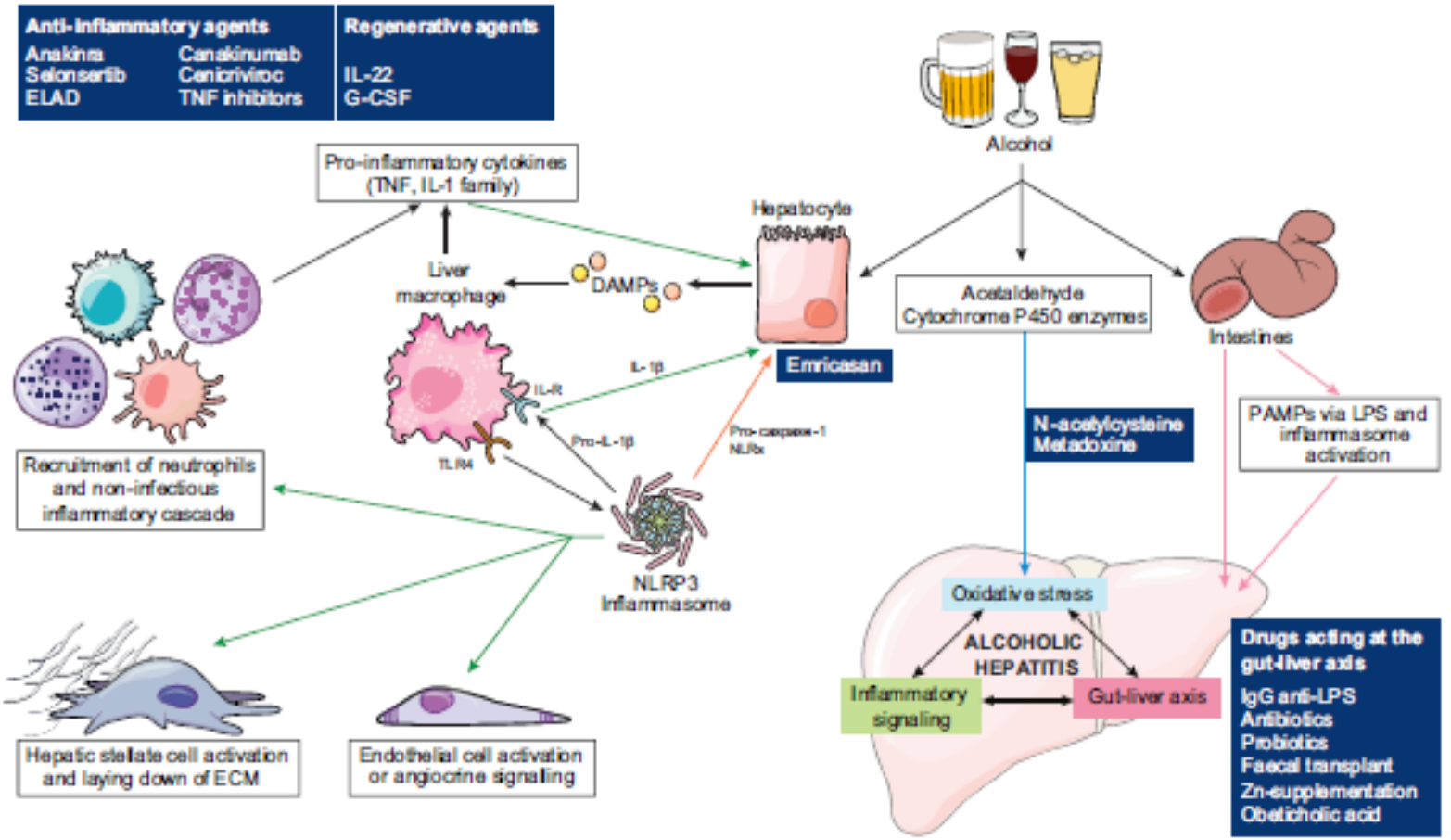
- 35-40 cal /kg/d
- 1.2-1.5 g proteina /kg/dia
- 2 g NaCl/dia
- Tiamina, B2,B12, folato, magnésio, zinco, selenium
- 4 a 5 refeições ao dia

Via enteral para casos selecionados

NPT excepcional

ACLF em pacientes com hepatite alcóolica

ACLF em pacientes com hepatite alcóolica



Journal of Hepatology **2019** vol. 70 | 305–313

JOURNAL OF HEPATOLOGY

Journal of Hepatology **2018** vol. 69 | 318–324

JOURNAL OF HEPATOLOGY

The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis

Thomas Sersté[1,2,*], Alexia Cornillie[1], Hassane Njimi[3], Marco Pavesi[4], Vicente Arroyo[4], Antonella Putignano[1], Laura Weichselbaum[1], Pierre Deltenre[1], Delphine Degré[1], Eric Trépo[1,5] Christophe Moreno[1,5], Thierry Gustot[1,4,5,6,7,*]

Coorte prospectiva HA (biópsia)

Mortalidade 28d

- Sem ACLF: 10%
- ACLF-1: 31%
- ACLF-2: 58%
- ACLF-3: 72%

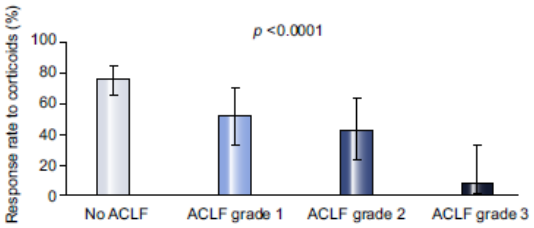


Fig. 2. Level of response to corticosteroids according to grade of ACLF. Response rates (according to Lille score) of CS treatment were compared according to ACLF grade (ANOVA). ACLF, acute-on-chronic liver failure; CS, corticosteroid.

Resposta Corticóide (Modelo de Lille)

- Sem ACLF: 77%
- ACLF-1: 52%
- ACLF-2: 42%
- ACLF-3:8%

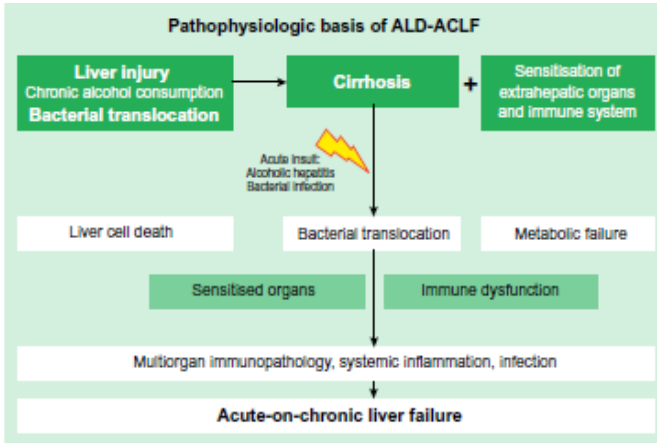
Recomendação para o corticóide em pacientes com ACLF de alto grau??
Decisão individual

Acute-on-chronic liver failure in patients with alcohol-related liver disease

Thierry Gustot[1,2,3,4,5,*], Rajiv Jalan[5,6]

JOURNAL OF HEPATOLOGY

Journal of Hepatology **2019** vol. 70 | 319–327



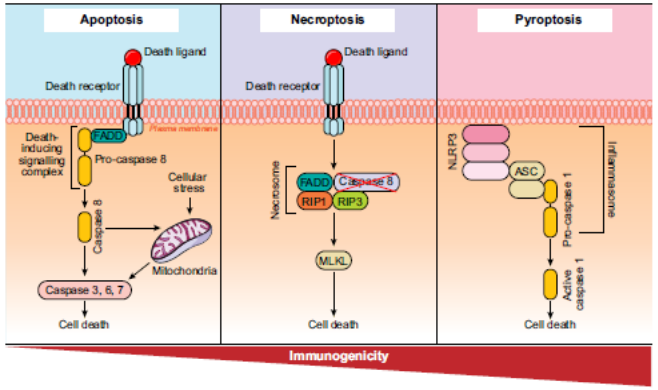


Fig. 2. Description of pathways and immunogenicity associated with 3 types of cell death (apoptosis, necroptosis and pyroptosis).

Table 1. Cellular basis of immune dysfunction in ALD-ACLF, associated mechanisms and possible therapeutic targets. (Adapted from [11])

Cell type	Main functional derangement	Mechanism	Therapeutic target
Lymphocytes[29]	Reduced T-cell IFN production in response to LPS. Increased T-cells producing IL-10.	Increased expression of PD1 and TIM-3.	Antibodies to PDI and TIM3 restored function.
Monocytes and macrophages[27,28,30,31]	Reduced LPS induced TNF production. Reduced pro-inflammatory cytokine secretion and bacterial killing. Reduced pro-inflammatory cytokine secretion in response to LPS. Reduced monocyte oxidative burst and bacterial killing. Reduced phagocytic capacity.	Reduced DR3 expression. Increased Prostaglandin E2. Increased expression of MERTK. Reduced $gp91^{phox}$ subunit of NADPH oxidase. Metabolic reprogramming and altered cellular bioenergetics.	Reduce bacterial translocation. PGE2 receptor antagonists. COX-2 inhibitors. Albumin infusion. Inhibition of MERTK, UNC569. NADPH modulators. Glutamine synthase inhibitors.
Neutrophils[26,32,33]	Increased resting burst but reduced *E. Coli* induced oxidative burst and reduced phagocytosis. Reduced bactericidal activity.	Involvement of humoral factor possibly LPS and toll-like 4 receptors. Defect of myeloperoxidase release and the AKT/p38 MAP kinase pathway.	Bacterial translocation. Removal of LPS using plasma exchange or specific filters. TLR4 antagonists. TLR7/8 agonists.

Novas perspectivas terapêuticas

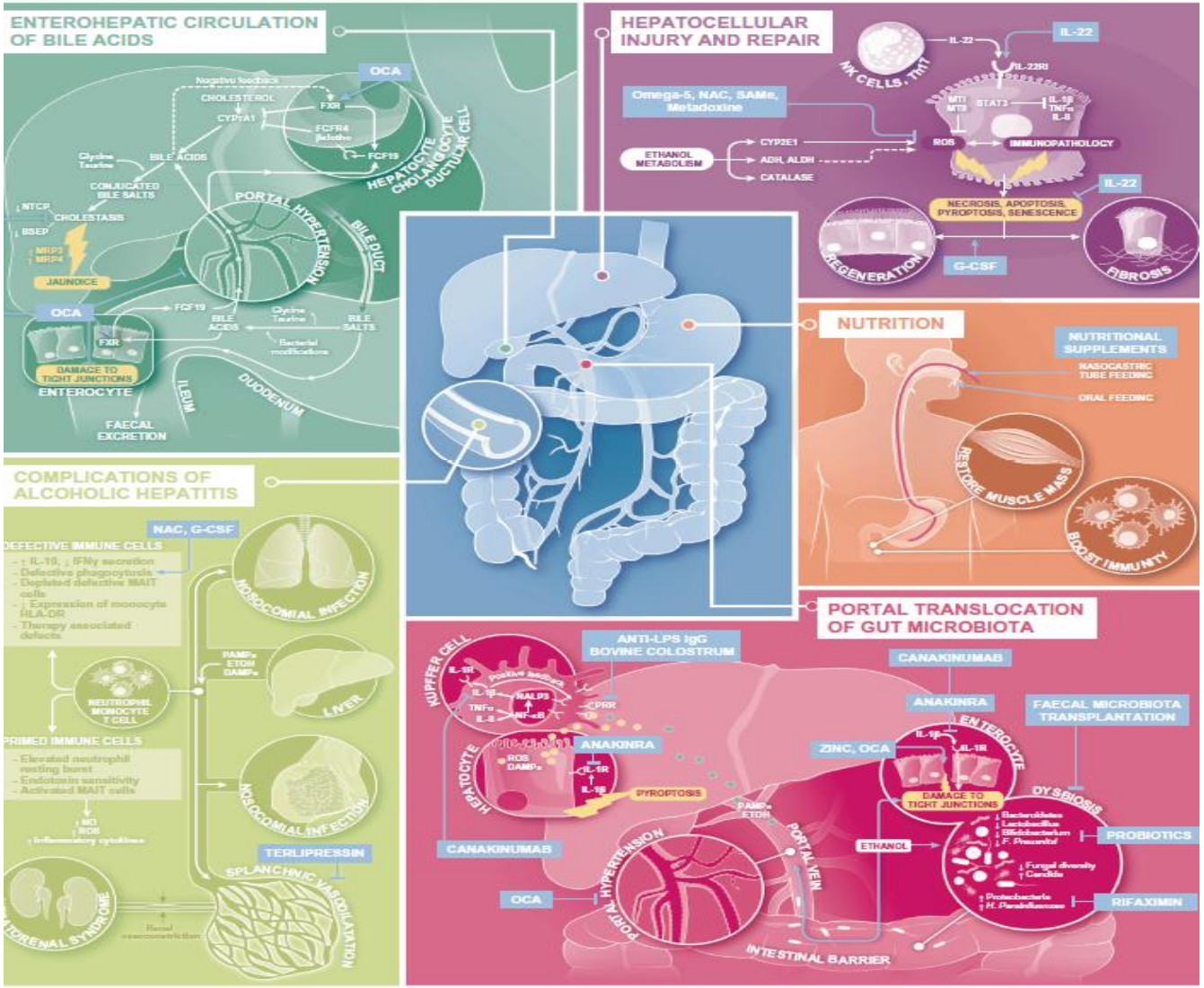
Hepatology Snapshot:

The future of therapy for alcoholic hepatitis - beyond corticosteroids

JOURNAL OF HEPATOLOGY

Nikhil Vergis*; Stephen R. Atkinson; Mark R. Thursz

Department of Hepatology, Imperial College, London
*Corresponding author e-mail: nvergis@ic.ac.uk



Keywords: alcoholic hepatitis; bile acids; hepatocyte injury; hepatocyte repair; nutrition; nosocomial infection; hepatorenal syndrome; portal translocation of gut microbiota

Received 6 November 2018; received in revised form 28 December 2018; accepted 11 January 2019.

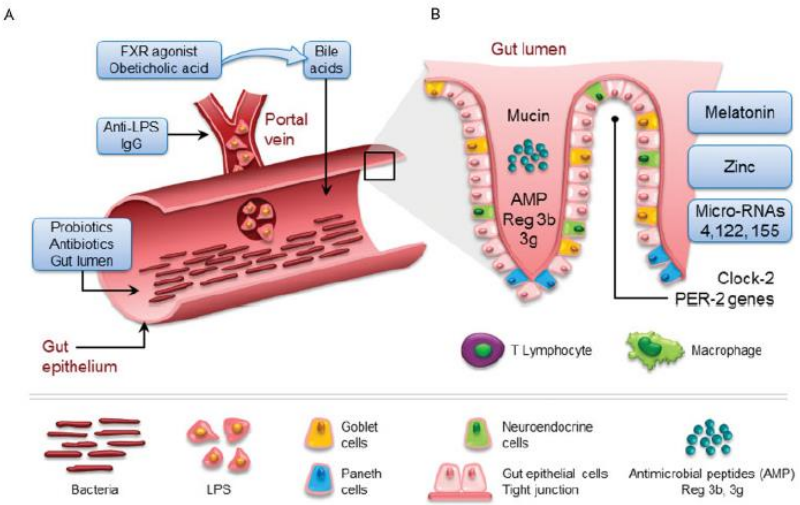
Therapeutic Strategies for the Treatment of Alcoholic Hepatitis

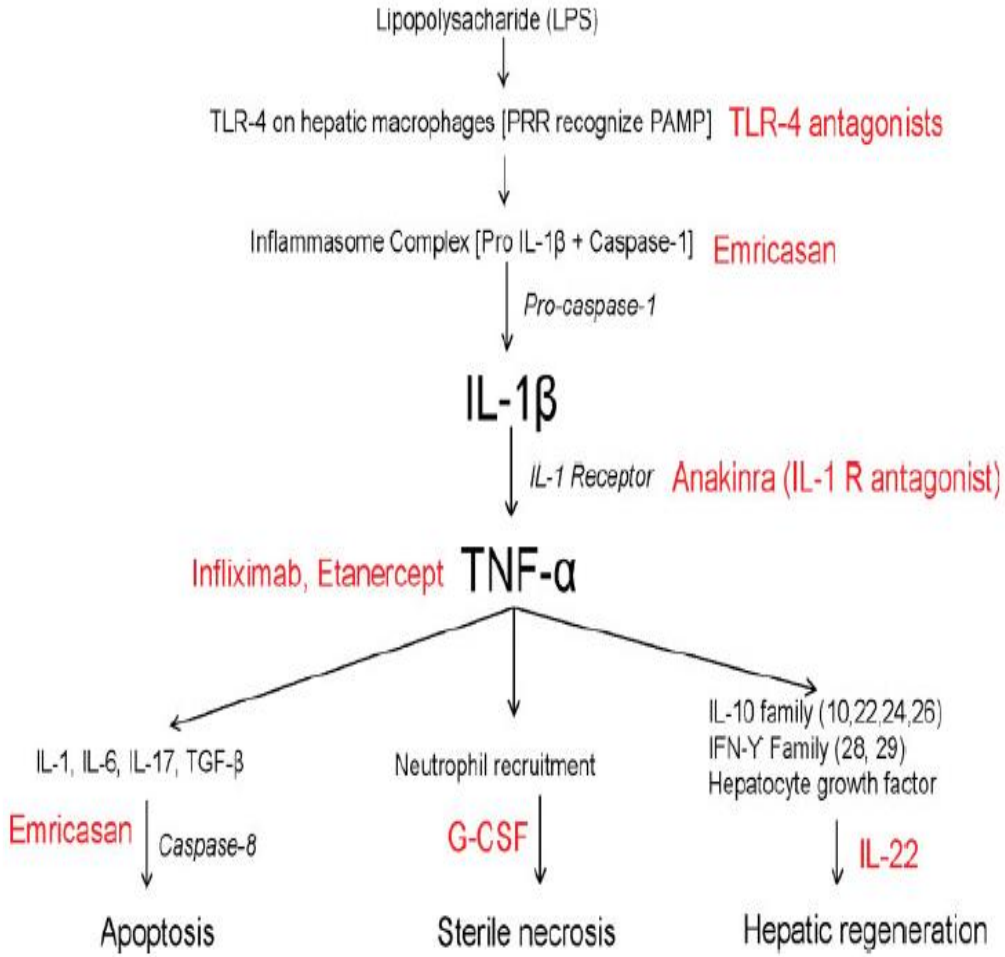
Ashwani K. Singal, MD, MS, FACG[1] Vijay H. Shah, MD[2]

Semin Liver Dis 2016;36:56–68.

Terapias emergentes:

1. Eixo intestino-fígado
2. Agentes anti-inflamatórios
3. Antioxidantes
4. Benefícios regenerativos





Agentes anti TNF

A Double-Blind Randomized Controlled Trial of Infliximab Associated With Prednisolone in Acute Alcoholic Hepatitis

Sylvie Naveau,[1,9] Sylvie Chollet-Martin,[2*] Sébastien Dharancy,[3*] Philippe Mathurin,[3] Pauline Jouet,[4] Marie-Astrid Piquet,[5] Thierry Davion,[6] Frédéric Oberti,[7] Philippe Broët,[8] and Dominique Emilie,[9] for the Foie-Alcool group of the Association Française pour l'Etude du Foie (AFEF)**

A Randomized, Double-Blinded, Placebo-Controlled Multi-Center Trial of Etanercept in the Treatment of Alcoholic Hepatitis

Nicholas C. Boetticher[1], Craig J. Peine[2], Paul Kwo[3], Gary A. Abrams[4], Tushar Patel[5], Bashar Aqel[6], Lisa Boardman[1], Gregory J. Gores[1], William S. Harmsen[8], Craig J. McClain[7], Patrick S. Kamath[1], and Vijay H. Shah[1]

Gastroenterology. 2008 December ; 135(6): 1953–1960. doi:10.1053/j.gastro.2008.08.057.

HEPATOLOGY, Vol. 39, No. 5, 2004

- Infecções graves
- Alto risco de óbito

Importância do TNF para regeneração parenquimatosa

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucocorticoids plus *N*-Acetylcysteine in Severe Alcoholic Hepatitis

Eric Nguyen-Khac, M.D., Ph.D., Thierry Thevenot, M.D., Marie-Astrid Piquet, M.D., Ph.D., Saïd Benferhat, M.D., Odile Goria, M.D., Denis Chatelain, M.D., Ph.D., Blaise Tramier, M.D., François Dewaele, M.D., Salah Ghrib, M.D., Marika Rudler, M.D., Nicolas Carbonell, M.D., Hervé Tossou, M.D., Abdeslam Bental, M.D., Brigitte Bernard-Chabert, M.D., and Jean-Louis Dupas, M.D., for the AAH-NAC Study Group*

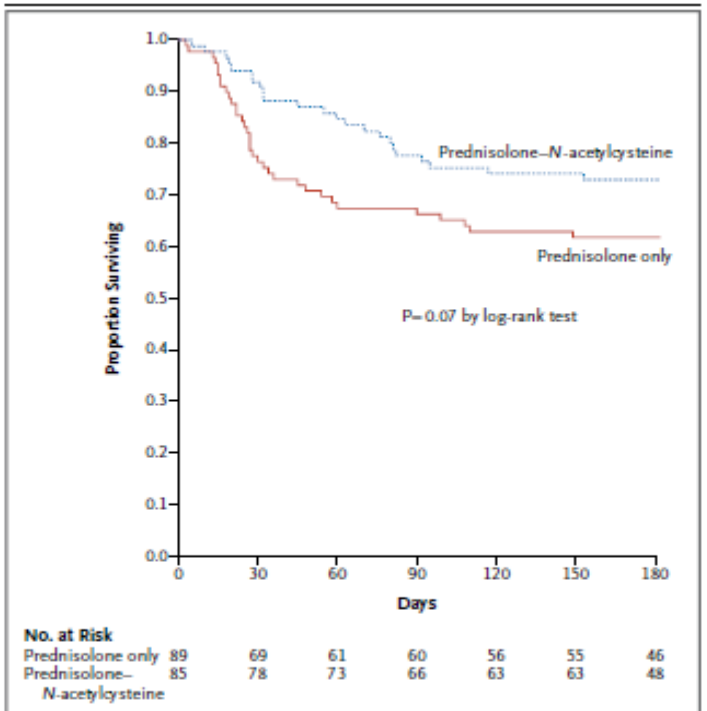


Figure 2. Kaplan–Meier Curves for 6-Month Survival in the Intention-to-Treat Population.

Prednisona + NAC

Sobrevida

- 1 mês: 8% vs 24%, p=0.006
- 3 meses 22% vs 34% , p= 0.06
- 6 meses 27 % vs 38%, p= 0.07
- SHR e infecções menos frequentes no grupo Pred+NAC

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

- In the absence of active infection, corticosteroids (prednisolone 40 mg/day or methylprednisolone 32 mg/day) should be considered in patients with severe AH to reduce short term mortality (**Grade A1**). However, corticosteroids do not influence medium to long term survival.

- N-acetylcysteine (for five days, intravenously) may be combined with corticosteroids in patients with severe AH (**Grade B2**)

Journal of Hepatology **2018** vol. 69 | 154–181

GASTROENTEROLOGY 2012;142:505–512

CLINICAL—LIVER

Granulocyte Colony–Stimulating Factor Mobilizes CD34+ Cells and Improves Survival of Patients With Acute-on-Chronic Liver Failure

VISHAL GARG,* HITENDRA GARG,‡ ARSHI KHAN,‡ NIRUPAMA TREHANPATI,‡ ASHISH KUMAR,‡ BARJESH CHANDER SHARMA,* PUJA SAKHUJA,§ and SHIV KUMAR SARIN*,‡

*Departments of *Gastroenterology and §Pathology, GB Pant Hospital, New Delhi; and ‡Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India*

G-CSF:

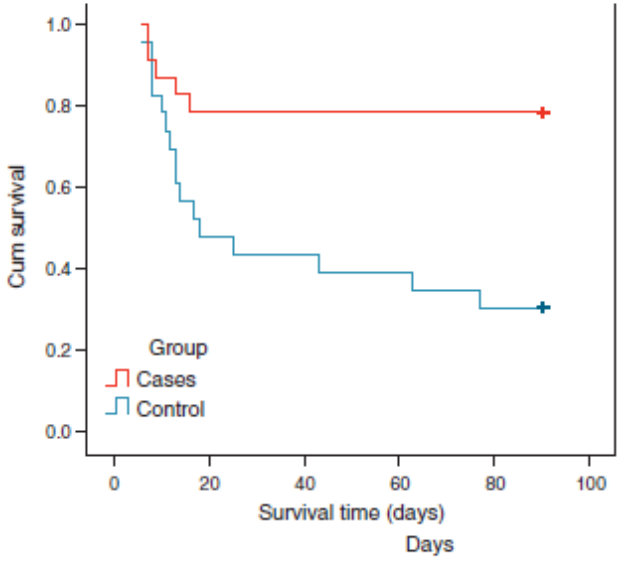
- Aumento neutrófilos periféricos (p<0.0001)
- Aumento de cél CD 34 no fígado (45% vs.27%, p=0.01)
- Menos SHR (19% vs. 71%, p=0.0002)
- Menos sepsis (14% vs. 41%, p=0.04)
- Melhor sobrevida (70% vs. 29%, p=0.001)

The American Journal of GASTROENTEROLOGY VOLUME 109 | SEPTEMBER 2014 www.amjgastro.com

Granulocyte Colony-Stimulating Factor in Severe Alcoholic Hepatitis: A Randomized Pilot Study

Virendra Singh, MD, DM, FASGE[1], Arun K. Sharma, MD, DM[1], R. Lakshmi Narasimhan, MD[2], Ashish Bhalla, MD[2], Navneet Sharma, MD[2] and Ratiram Sharma, MD[3]

- G-CSF 5 ug/Kg SC 12/12 h 5 dias
- Aumento cél CD 34+ (p=0.019)
- Diminuição CTP, MELD, Maddrey (p < 0.05)
- Melhora sobrevida 90 dias (p=0.001)

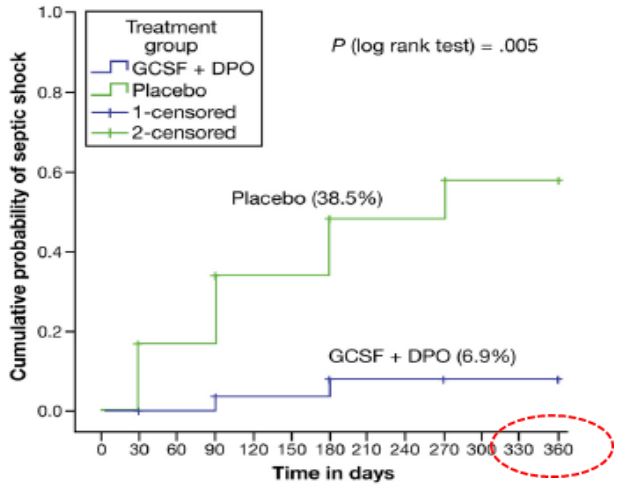


Days					
Patients at risk	20	40	60	80	90
G-CSF group (n=23)	18	18	18	18	18
Standard medical therapy group (n=23)	11	10	9	7	5

Gastroenterology 2015;148:1362–1370

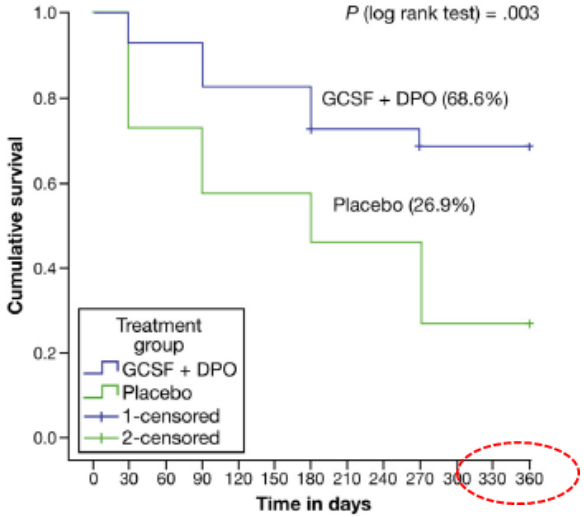
Combination of Granulocyte Colony-Stimulating Factor and Erythropoietin Improves Outcomes of Patients With Decompensated Cirrhosis

Chandan Kumar Kedarisetty,[1] Lovkesh Anand,[1] Ankit Bhardwaj,[2] Ajeet Singh Bhadoria,[2] Guresh Kumar,[2] Ashish Kumar Vyas,[2] Paul David,[2] Nirupama Trehanpati,[2] Archana Rastogi,[3] Chhagan Bihari,[3] Rakhi Maiwall,[1] Hitendra Kumar Garg,[1] Chitranshu Vashishtha,[1] Manoj Kumar,[1] Vikram Bhatia,[1] and Shiv Kumar Sarin[1]



Days		0	30	60	90	120	150	180	210	240	270	300	330	360
GDP gp	At risk	29	27	27	24	24	24	19	19	19	17	17	17	17
	Sepsis	0	0	0	1	1	1	2	2	2	2	2	2	2
CL gp	At risk	26	19	19	15	15	15	12	12	12	7	7	7	7
	Sepsis	0	4	4	7	7	7	9	9	9	10	10	10	10

Figure 4. The Kaplan-Meier curve showing cumulative probability of septic shock was significantly lower in GDP group compared with the control group.



Days		0	30	60	90	120	150	180	210	240	270	300	330	360
GDP gp	At risk	29	27	27	24	24	24	19	19	19	17	17	17	17
	Died	0	2	2	5	5	5	8	8	8	9	9	9	9
CL gp	At risk	26	19	19	15	15	15	12	12	12	7	7	7	7
	Died	0	7	7	11	11	11	14	14	14	19	19	19	19

Figure 1. Kaplan-Meier curve showing the overall survival at 12 months in GDP group compared with the control group.

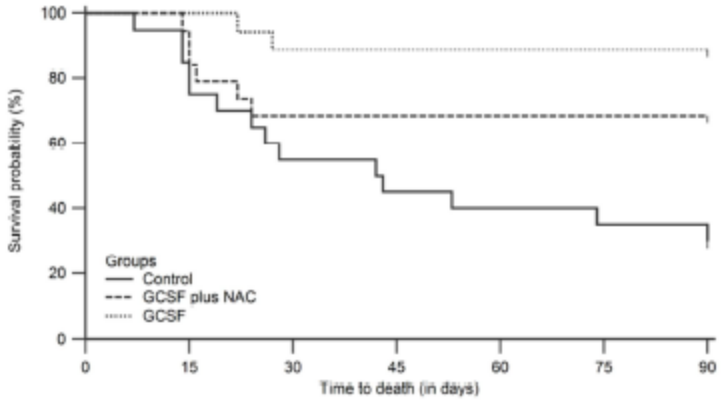
Efficacy of Granulocyte Colony Stimulating Factor and N-acetyl Cysteine Therapies in Patients with Severe Alcoholic Hepatitis

(Short title: G-CSF and NAC in alcoholic hepatitis)

Virendra Singh,[1] Amarjit Keisham,[2] Ashish Bhalla,[2] Navneet Sharma,[2] Ritesh Agarwal,[3] Ratiram Sharma,[4] Akash Singh[1]

PII: S1542-3565(18)30110-1
DOI: 10.1016/j.cgh.2018.01.040
Reference: YJCGH 55676

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 21 January 2018



- GCSF: melhora de função hepática e aumento de sobrevida

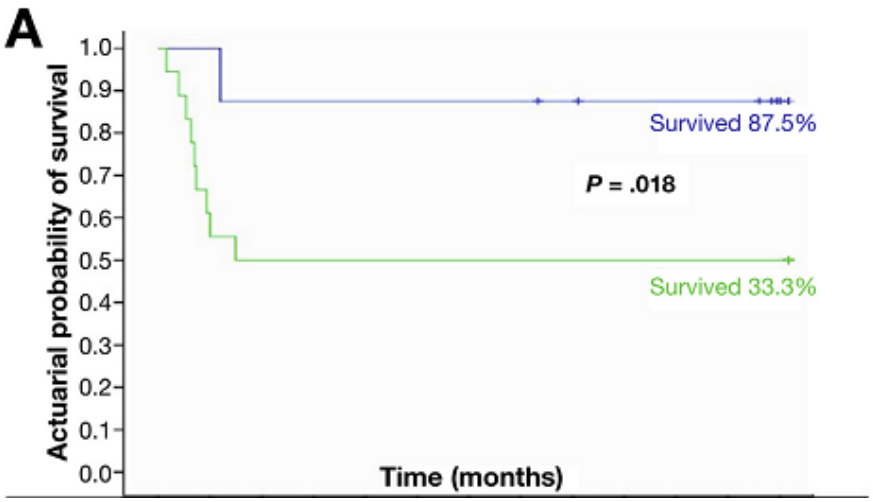
- Combinação GCSF +NAC: ausência de benefício adicional

Clinical Gastroenterology and Hepatology 2017;15:600–602

Healthy Donor Fecal Microbiota Transplantation in Steroid-Ineligible Severe Alcoholic Hepatitis: A Pilot Study

Cyriac Abby Philips,* Apurva Pande,* S. Murali Shasthry,* Kapil Dev Jamwal,* Vikas Khillan,‡ Shivendra Singh Chandel,* Guresh Kumar,§ Manoj K. Sharma,* Rakhi Maiwall,* Ankur Jindal,* Ashok Choudhary,* Md Shabbir Hussain,‖ Shvetank Sharma,‖ and Shiv K. Sarin*,‖

*Department of Hepatology and Transplant Medicine, ‡Department of Microbiology, §Department of Biostatistics, and ‖Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India



- TMF eficácia e segurança em HA grave
- Sobrevida 1 anos

Current trials and novel therapeutic targets for alcoholic hepatitis

Ashwani K. Singal[1,*], Vijay H. Shah[2]

Table 1. Current clinical trials with novel therapeutic agents for treatment of alcoholic hepatitis.

Pharmaceutical agent	Mechanism of action	Study design [N]	Main inclusion	Primary endpoint	Status
Bovine colostrum (IMM-124E)	IgG to LPS and reduces bacterial translocation	Placebo controlled RCT	MELD score ≥20 but ≤28	Decrease in serum endotoxin levels at 7 months	Phase II, active, not recruiting
Lactobacillus rhamnosus GG	Change in gut microbiome	Placebo controlled RCT	MELD score <21	Change in MELD score at 30 days	Phase II, active and recruiting
Augmentin	Antibiotic amoxicillin plus clavulanic acid	Placebo controlled RCT with CS	MELD score ≥21	Survival at 2 months	Phase III, active and recruiting
Faecal transplant	Change in gut microbiome	RCT FMT *vs.* CS[42]	Eligible for CS treatment	Survival at 3 months	Active and recruiting
Anakinra	Antagonist to IL-1 receptor	RCT Anakinra + Zn + PTX *vs.* CS[42]	MELD score ≥20 and Madre DF ≥32	Survival at 6 months	Phase II, active and recruiting
Obeticholic acid [INT-747]	FXR activation, bile acid agonist, and anti-inflammatory	Placebo controlled RCT	MELD score >11 and <20	Change in MELD score at 6 weeks	Phase II, completed
Selonsertib [GS-4997]	ASK-1 antagonist to inhibit MAPK, JNK, p38	Placebo controlled RCT with CS	Maddrey DF score ≥32	Safety and SAE at 28 days plus 30 days	Phase II, completed
Emricasan [IDN-6556]	Pan caspase inhibitor	Placebo controlled RCT[42]	MELD score >20 but <35 or 35–40 if SOFA score <10	Survival at 28 days	Phase II, terminated after 5 patients
Metadoxine	Antioxidant and promotes abstinence	Placebo controlled RCT with CS[42]	Severe alcoholic hepatitis	Survival at 30 days	Phase IV, completed
IL-22 [F-652]	Anti-inflammatory and hepatic regeneration	Open label	MELD score 11–28	Safety and SAE at 42 days	Phase I completed Phase II planned
G-CSF [Filgrastim]	Increase neutrophils, hepatic regeneration	Placebo controlled RCT with CS in partial responder and without CS in null responder	Maddrey DF score ≥32	Survival at 2 months in null responder to CS and at 6 months in partial responder	Phase IV, active and recruiting

CS, corticosteroid; MELD, model for end-stage liver disease; PTX, pentoxifylline; RCT, randomised controlled trial; SAE, serious adverse event; SOFA, sequential organ failure assessment.

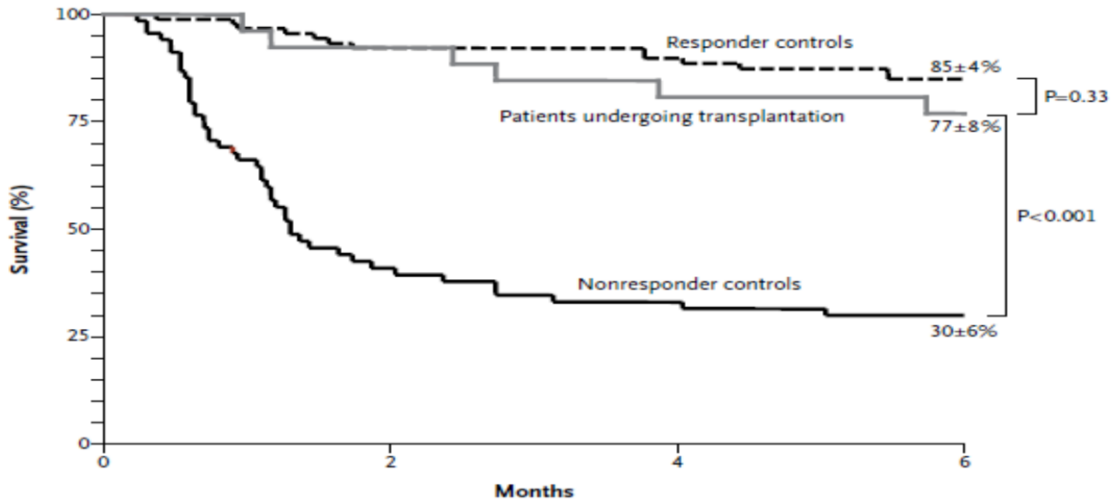
Transplante hepático para hepatite alcóolica

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D., Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S., François Durand, M.D., Ph.D., Hélène Castel, M.D., Alain Duhamel, M.D., Ph.D., Georges-Philippe Pageaux, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., Emmanuel Boleslawski, M.D., Ph.D., Valerio Lucidi, M.D., Thierry Gustot, M.D., Ph.D., Claire Francoz, M.D., Christian Letoublon, M.D., Denis Castaing, M.D., Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D., François-René Pruvot, M.D., and Jean-Charles Duclos-Vallée, M.D., Ph.D.



No. at Risk				
Responder controls	92	77	75	71
Patients undergoing transplantation	26	21	21	20
Nonresponder controls	69	21	21	19

Figure 2. Kaplan–Meier Estimates of Survival among the 26 Study Patients and Randomly Selected Matched Controls.

Outcomes After Liver Transplantation for Alcoholic Hepatitis Are Similar to Alcoholic Cirrhosis: Exploratory Analysis from the UNOS Database

Ashwani K. Singal,[1,2] Hmoud Bashar,[1] Bhupinderjit S. Anand,[3] Sarat C. Jampana,[1] Vineet Singal,[4] and Yong-Fang Kuo[5]

Data on liver transplantation for patients with alcoholic hepatitis are limited. Using the United Network for Organ Sharing database (2004-2010), adults undergoing liver transplantation for a listing diagnosis of alcoholic hepatitis were matched for age, gender, ethnicity, and model for endstage disease (MELD) score, donor risk index, and year of transplantation with three patients transplanted for a listing diagnosis of alcoholic cirrhosis. Study outcomes of graft and patient survival on follow-up were also analyzed for cohorts based on the diagnosis of the explant (46 alcoholic hepatitis and 138 alcoholic cirrhosis) and diagnosis at both listing as well as of the explant (11 alcoholic hepatitis and 33 alcoholic cirrhosis). Five-year graft and patient survival of alcoholic hepatitis and alcoholic cirrhosis patients were 75% and 73% ($P = 0.97$) and 80% and 78% ($P = 0.90$), respectively. Five-year graft and patient survival rates were also similar for cohorts based on diagnosis of the explant and diagnosis at listing as well as explant. Cox proportional regression analysis adjusting for other variables showed no impact of the etiology of liver disease (alcoholic hepatitis versus alcoholic cirrhosis) on the graft and patient survival. The causes of graft loss and patient mortality were similar in the two groups, and were not alcohol-related in any patient. *Conclusion:* Compared with alcoholic cirrhosis, patients with alcoholic hepatitis have similar posttransplantation graft and patient survival. Based on these preliminary findings, liver transplantation may be considered in a select group of patients with alcoholic hepatitis who fail to improve with medical therapy. Prospective studies are needed to assess the long-term outcome after liver transplantation in patients with alcoholic hepatitis. (HEPATOLOGY 2012;55:1398-1405)

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
AASLD

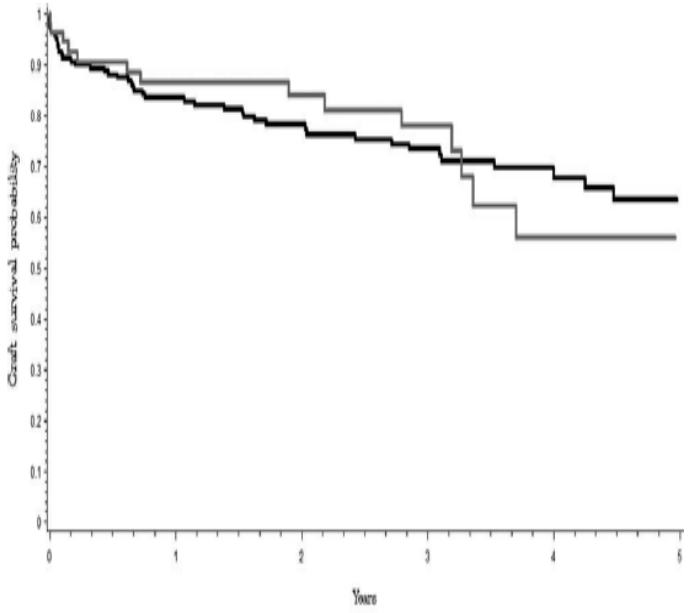


Fig. 2. Kaplan Meier survival curves comparing graft survival of patients transplanted for alcoholic hepatitis (gray line) and patients transplanted for alcoholic cirrhosis (black line). Results show similar graft survival between the two groups (Log rank $P = 0.97$).

Year of follow up	Alcoholic hepatitis	Alcoholic cirrhosis	Log Rank P
1 year	87	84	0.58
2 years	85	80	0.39
3 years	82	77	0.47
4 years	75	75	0.94
5 years	75	73	0.97

Impact of a first study of early transplantation in acute alcoholic hepatitis: results of a nationwide survey in French liver transplantation programs

Teresa Maria Antonini[1-4], Olivier Guillaud[5-6*], Jérôme Dumortier[5-6], Sébastien Dharancy[7], Faouzi Saliba[1-4], Philippe Mathurin[7], Jean-Charles Duclos-Vallée[1-4], Christophe Duvoux[8] and the "Groupe de Recherche Français en Greffe de Foie"*

LIVER TRANSPLANTATION
Official Journal of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society

'Accepted Article', doi: 10.1002/lt.25039

Questionário *online*

18 centros de transplante na França

- 88% mudança prática do TX para HA desde 2011
- 97% HA como possível indicação para TX
- 71% dos centros franceses fazendo Tx para HA
- 75% aplicavam regra de 6 meses de abstinência antes de 2011
- 65% regra de 3 meses de abstinência após 2011

"The seminal publication of Mathurin exerted a significant impact on French clinical practice"

Journal of Hepatology **2019** vol. 70 | 328–334

Review

JOURNAL
OF HEPATOLOGY

Liver transplantation for alcoholic hepatitis

Gene Y. Im[1,*], Andrew M. Cameron[2], Michael R. Lucey[3]

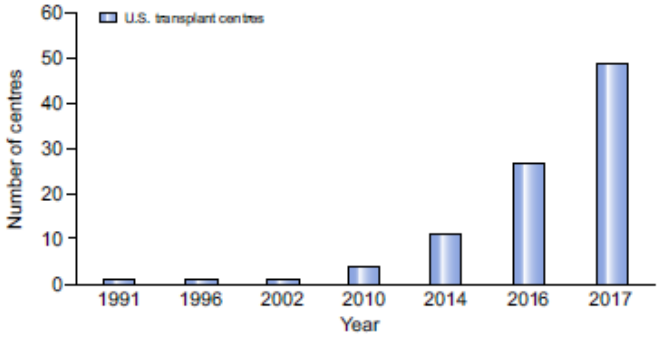


Fig. 1. Centres having performed liver transplantation for alcoholic hepatitis in the United States over time. Data based on references[2,14–15,26–28,48] and unpublished dat

Box 1. Common study criteria in liver transplantation for alcoholic hepatitis.

Inclusion criteria
- Maddrey Discriminant Function >32
- Non-responder to (according to Lille ≥0.45) or ineligible for medical therapies (mainly corticosteroids)
- First liver-decompensating event
- Favourable psychosocial profile
- Good social support
- Agreement of transplant selection committee

Exclusion criteria
- Uncontrolled infection
- Comorbid systemic illness likely to prevent recovery
- Poor prognostic profile: failure to accept addiction as a problem; history of previous failed alcohol use disorder treatments
- Lack of social support: no home, supporting family or friends, lack of transport
- Prior liver-decompensating events
- Severe, uncontrolled psychiatric disorder

<5% dos pacientes elegíveis para Tx

RESULTADOS DO INQUÉRITO DA SOCIEDADE BRASILEIRA DE HEPATOLOGIA PARA AVALIAÇÃO DO CRITÉRIO LEGAL DE ABSTINÊNCIA DE SEIS MESES PARA INCLUSÃO EM LISTA DE TRANSPLANTE DE FÍGADO

Liana Codes, Rita de Cássia M A da Silva, Mônica Viana, Janaína L. Narciso-Schiavon, Cláudia Ivantes, Maria Lúcia Gomes Ferraz, José Huygens Garcia, Paulo Bittencourt

E-mail para associados

Site “ tudosobrefigado.com.br”

105 clínicos, 44 cirurgiões e 48 multi-profissionais da saúde, 37 indivíduos da sociedade civil

12% concordam totalmente com o critério vigente

TH hepatite alcoólica: 155 concordaram, a maioria (n=129) em casos selecionados, valorizando apoio psiquiátrico e suporte social

Terapias para prevenir recidiva do álcool

- Recidiva do consumo etilico 70%
- STOPAH: mortalidade maior recidivantes
- Encaminhamento para psiquiatria
- TCC ou AA
- Baclofeno (40mg/d) por 6 meses: abstinência 97% (Yamini et al.2014)

Caso clínico:
Hepatite alcoólica grave => ACLF
Há benefício com o corticóide?

- Rastreio infeccioso, suporte nutricional oral, medidas para encefalopatia, tratamento empírico com tiabendazol, corticoterapia

- D2 corticóide: queda de bilirrubinas

- D3 corticóide: Hematêmese => IBP + Terlipressina + Ceftriaxone
  - EDA: Varizes esôfago com ponto de ruptura na TEG. Gastroplastia redutora tipo Capella. LE - 6 bandas
- Piora sensório, hipotensão, VM, modo A/C, trocas ruins (P/F: 170), piora de função renal, acidose metabólica. Noradrenalina. ACLF grau III
- Teicoplanina, meropenem, fluconazol empíricos
- Choque refratário , hipotermia. Assistolia e óbito

Mensagens importantes

- Hepatite alcóolica é uma condição grave, associada a complexas alterações imunológicas.
- Um dos principais fatores desencadeantes da ACLF
- Corticóide continua como primeira linha de tratamento.
- Identificação precoce de não resposta ao corticóide: mau prognóstico (Lille > 0.56: sobrevida 25-30 % em 6 meses).
- Corticóide é ineficaz em pacientes com HA - ACLF de alto grau.
- Novas opções terapêuticas estão sendo estudadas: G-CSF, rifaximina, AOC...
- Transplante como terapia de resgate em casos altamente selecionados.
- Abstinência melhora sobrevida de curto e longo prazo