MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Cirrosis II

Profilaxis y tratamiento de las infecciones bacterianas en la cirrosis. Sepsis en la cirrosis"

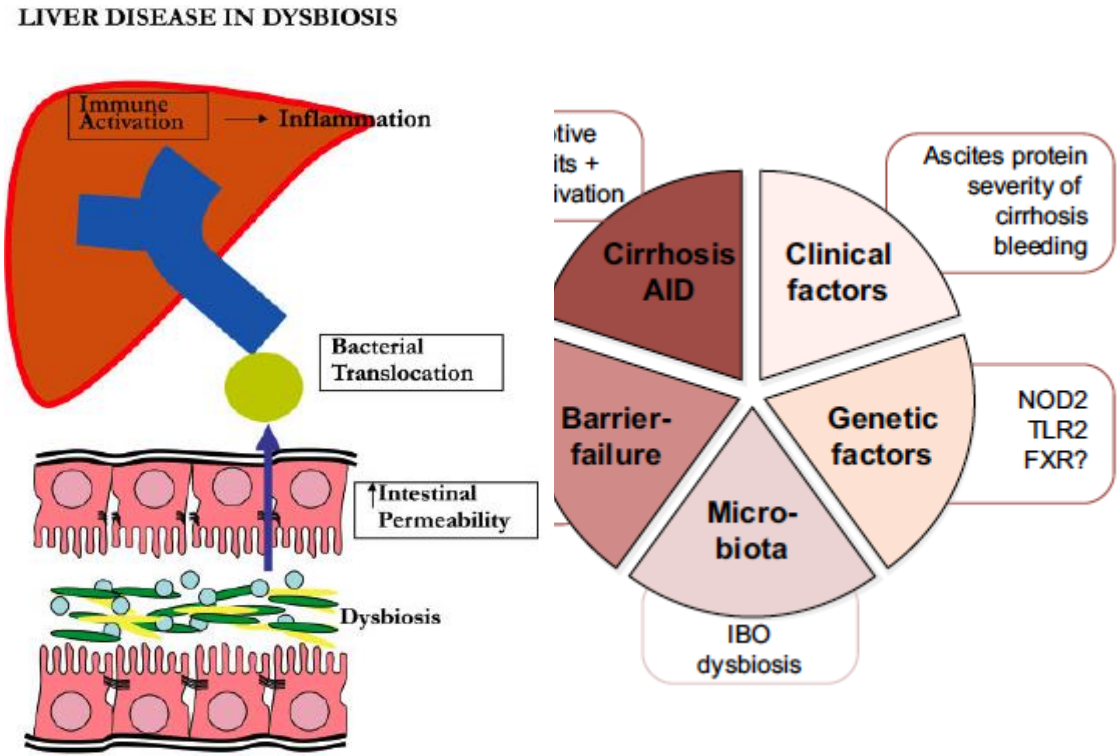
J. Fernández

Hospital Clinic de Barcelona, IDIBAPS, CIBERehd, EF-Clif

Índice

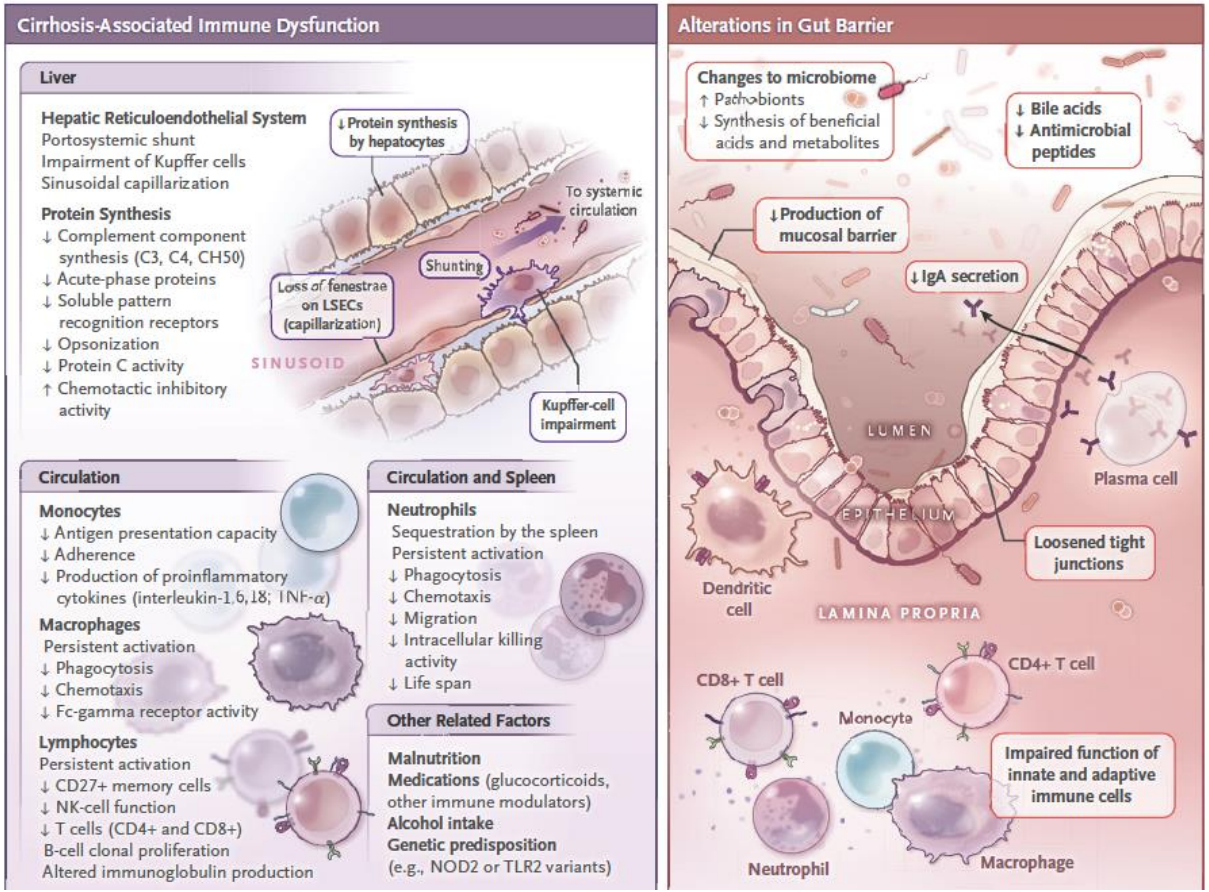
- Patogenia
- Prevalencia y tipos
- Impacto clínico/coberturas antibióticas empíricas
- Diagnóstico
- Resistencia antibiótica
- Optimización farmacocinética y nuevos antibióticos
- Vigilancia epidemiológica
- Profilaxis antibiótica
- Infección fúngica

Infección bacteriana en la cirrosis: un problema multifactorial



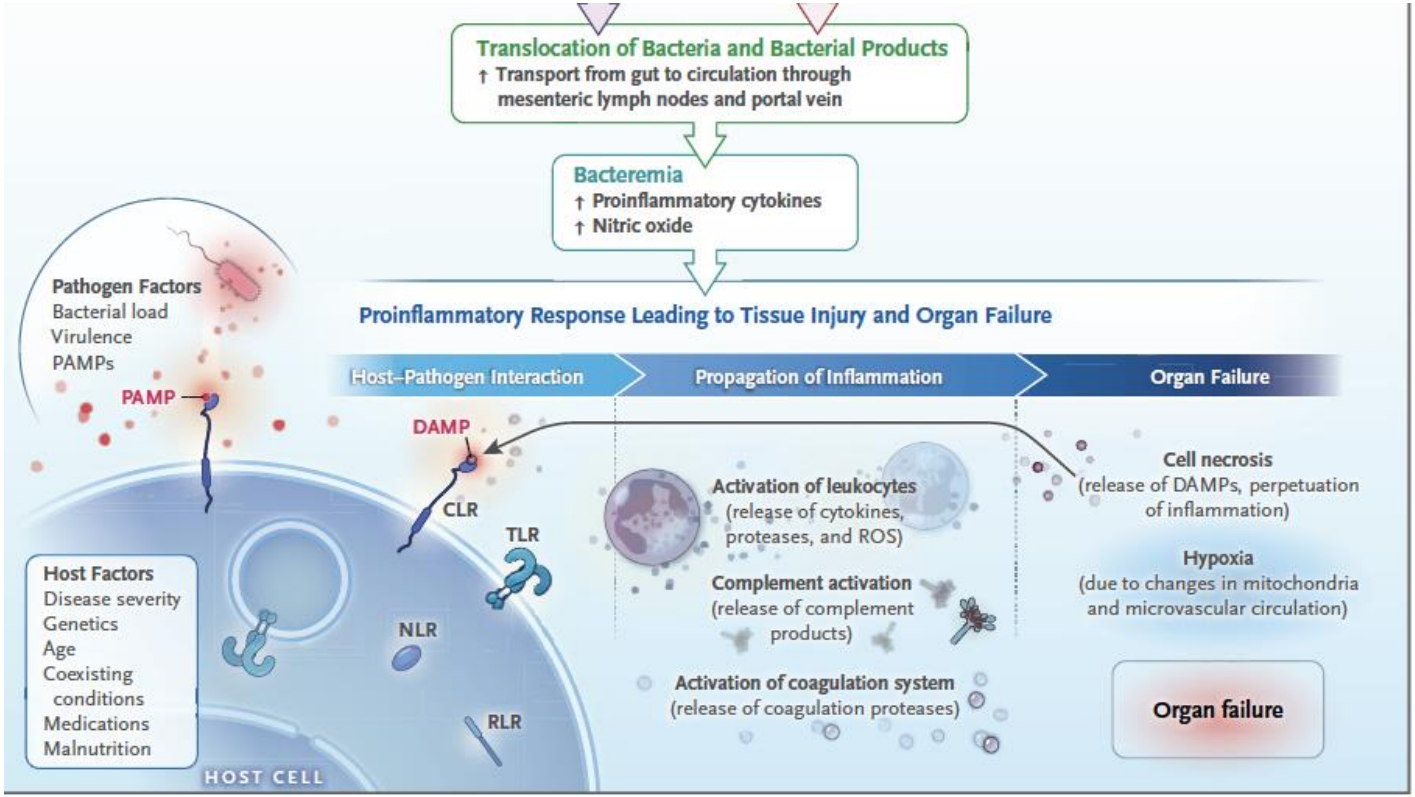
Jalan, Fernández, Wiest et al. J Hepatol 2014
Anand et al, Semin Liver Dis 2016

Infección en la cirrosis: patogenia



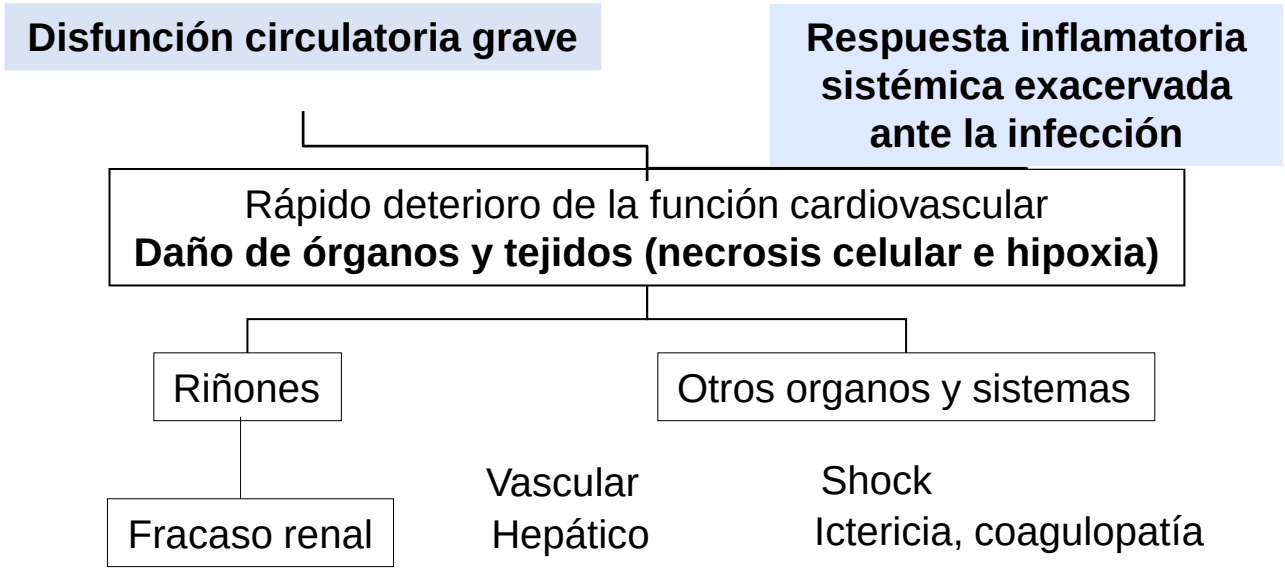
Bajaj et al. NEJM 2021

Infección en la cirrosis: patogenia



Bajaj et al. NEJM 2021

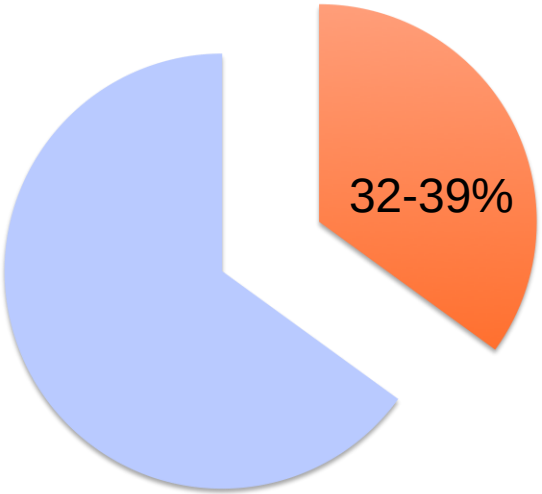
Bases fisiopatologicas del fracaso de órganos en la cirrhosis hepática



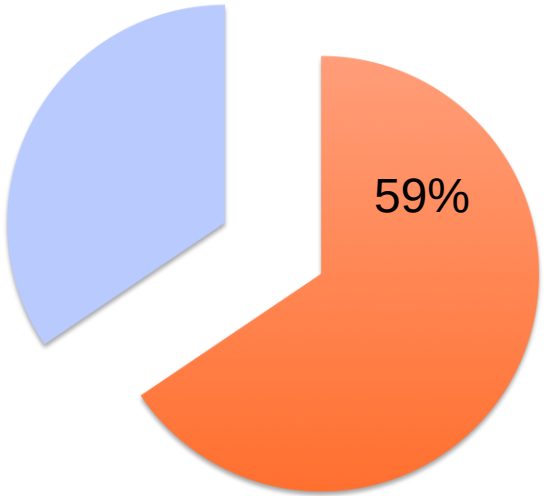
Adapted from Arroyo et al. Nat Rev Nephrol 2011

Prevalencia de las infecciones bacterianas en la cirrosis

GLOBAL

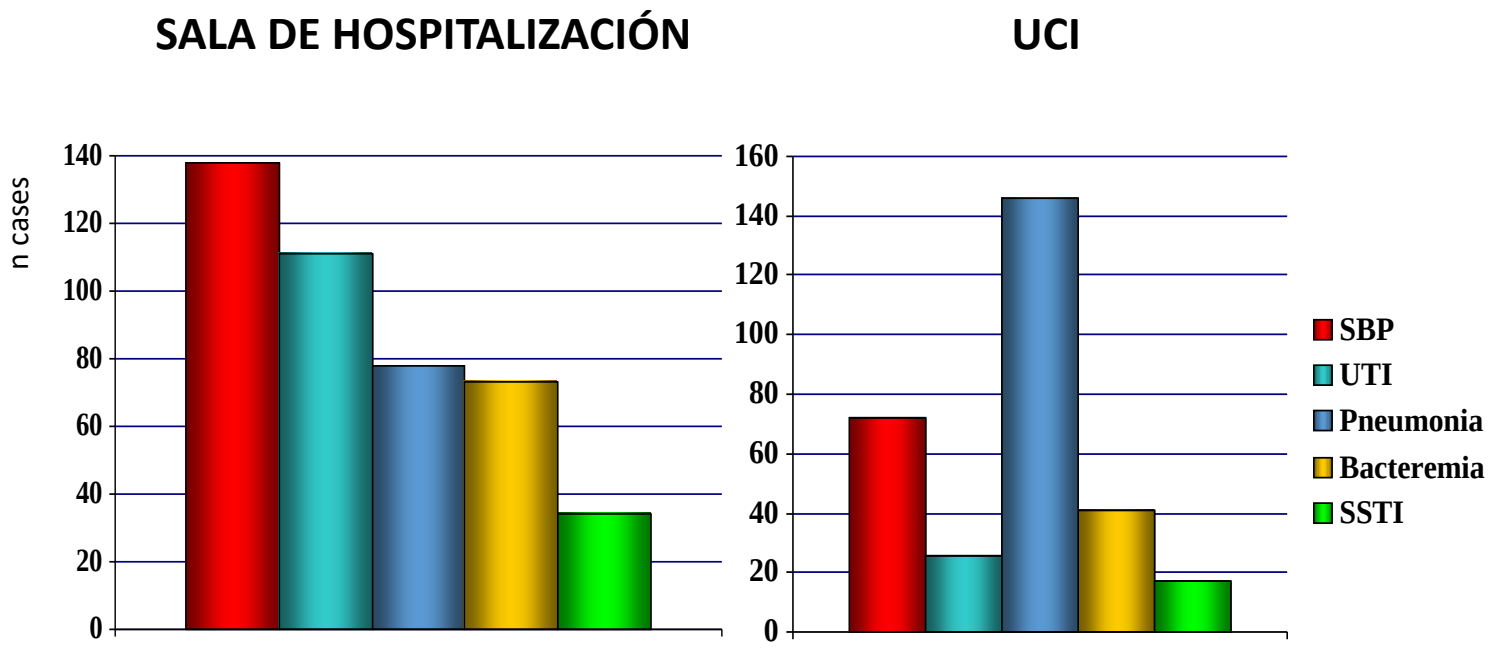


UCI



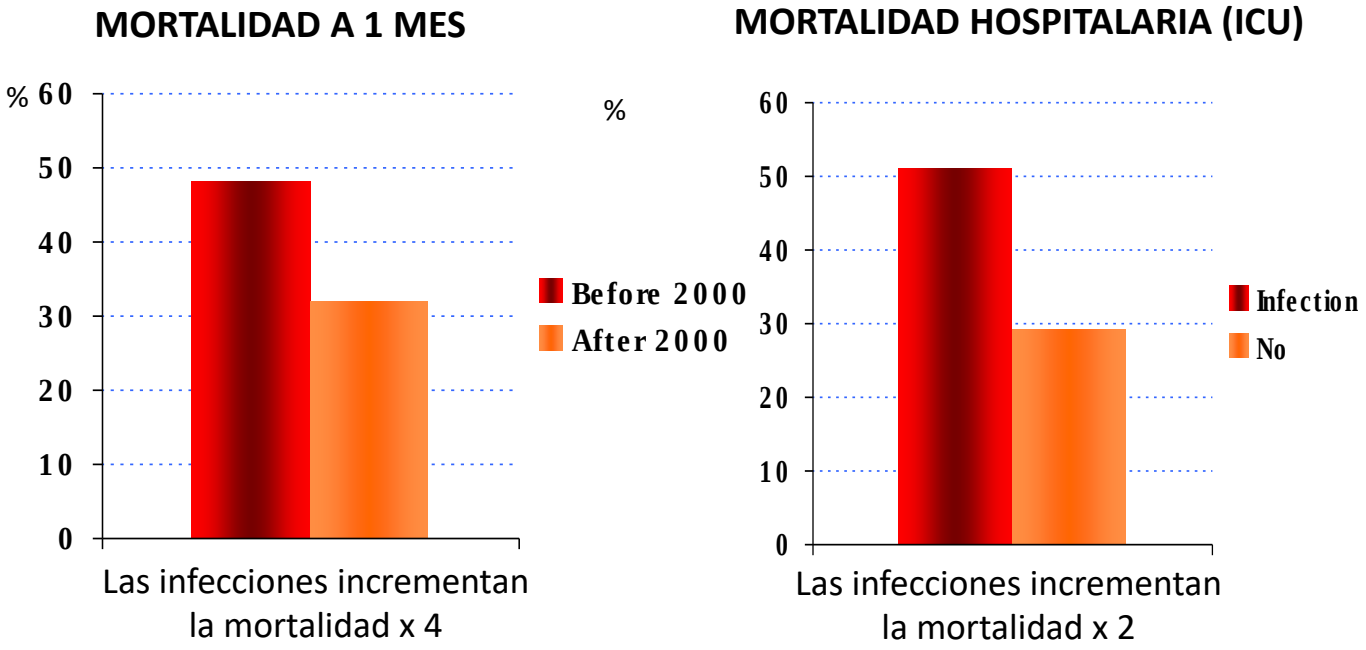
Fernández et al. J Hepatol 2019; Gustot et al. Liver Int 2014

Tipo de infecciones bacterianas



Fernández et al. Hepatology 2002; Gustot et al. Liver Int 2014

Impacto de la infección bacteriana sobre la mortalidad



Arvaniti et al. Gastroenterology 2010

Gustot et al. Liver Int 2014

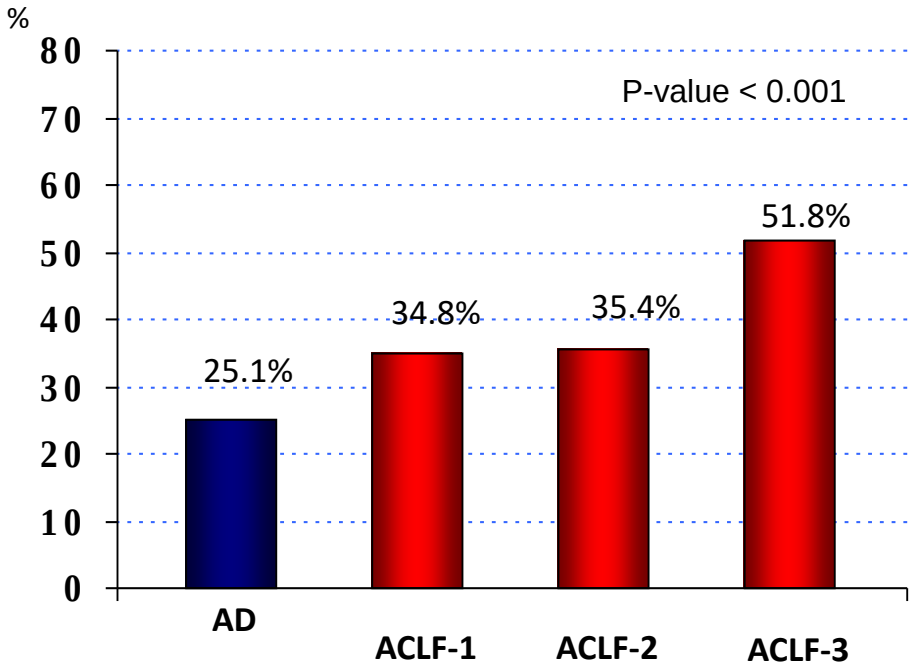
Impacto clínico
Eventos precipitantes del ACLF

	NO ACLF (N=871)	ACLF (N=417)	p
Infección bacteriana	218 (25%)	160 (38%)	<0.001
Hemorragia GI	99 (16%)	74 (18%)	Ns
Alcoholismo activo*	**115 (14%)**	**89 (23%)**	**0.0001**
Otros EP **	31 (4%)	38 (10%)	<0.001
No EP ***	483 (65%)	124 (43 %)	<0.001
Cualquier EP ***	327 (39.8%)	215 (54.4 %)	
>1 EP ***	43 (5.2 %)	48 (12.2 %)	<0.0001

* En los 3 meses previos a la inclusión;
** Otros EP: paracentesis evacuadora sin albúmina, TIPS, cirugía mayor, hepatitis aguda .
*** Infección bacteriana, alcoholismo activo u otro EP

Moreau Gastroenterology 2013

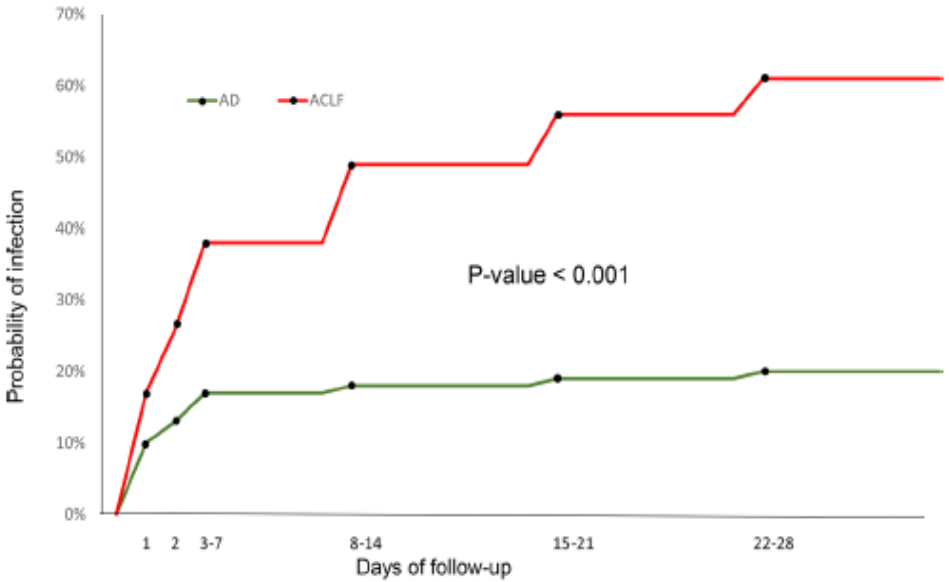
Prevalencia de infecciones bacterianas en pacientes con AD y con ACLF



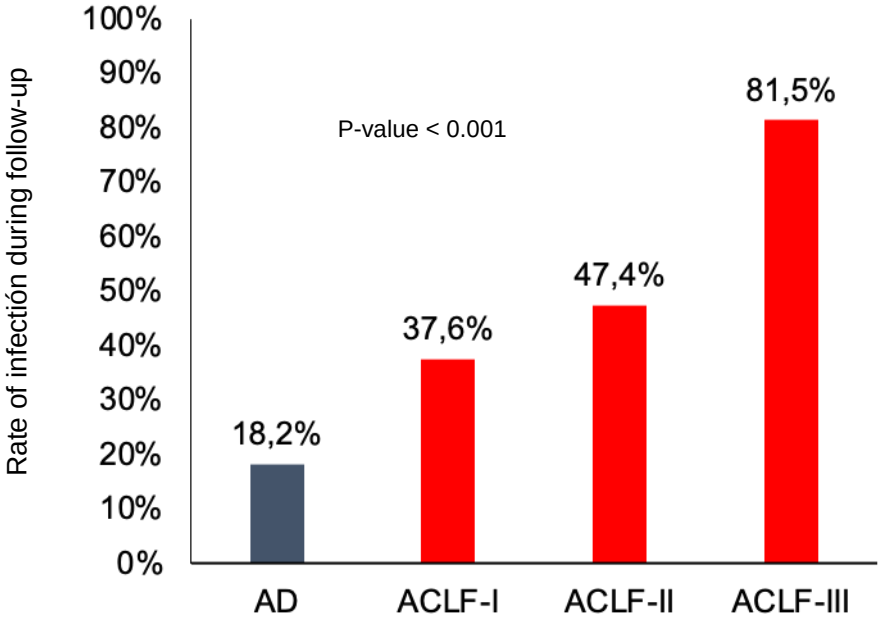
Fernandez et al. Gut 2018

Riesgo de desarrollar infecciones bacterianas en pacientes con AD o ACLF no infectados al ingreso

PROBABILIDAD DE INFECCIÓN



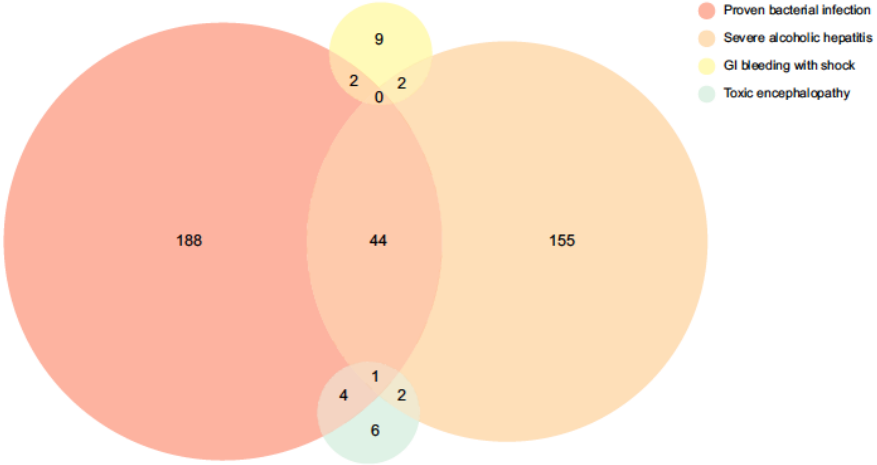
TASA DE INFECCIÓN



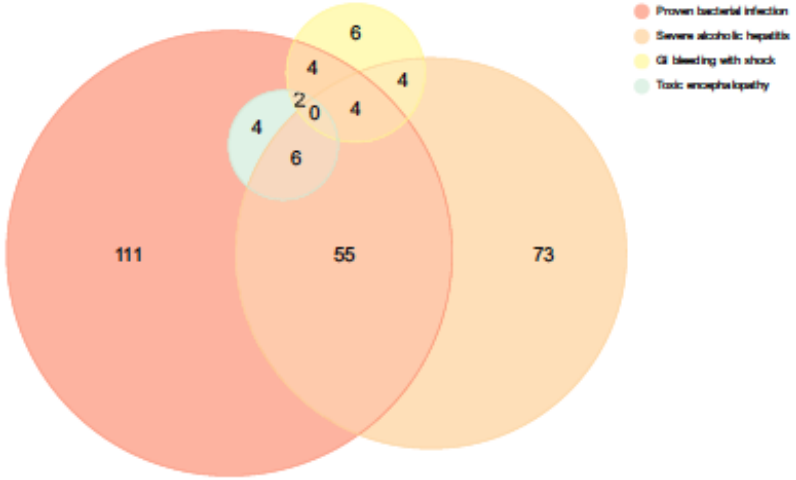
Fernandez et al. Gut 2018

Infecciones bacterianas
Un evento precipitante mayor en pacientes con AD y ACLF

DESCOMPENSACIÓN AGUDA



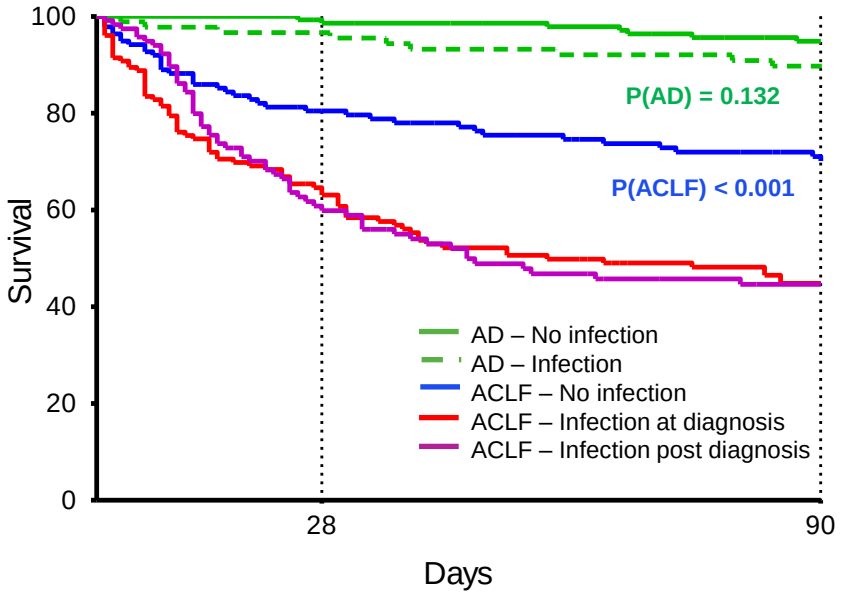
ACLF



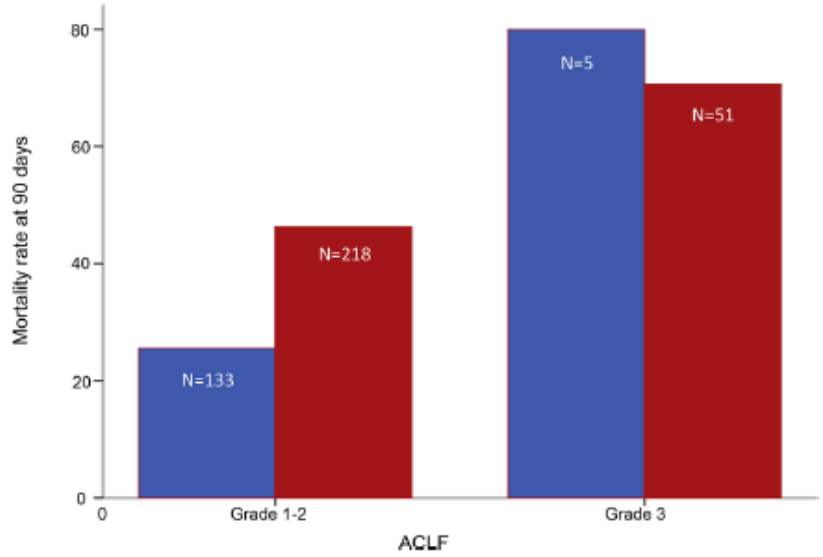
Trebicka and Fernandez et al. J Hepatol 2021

Impacto clínico
Infección bacteriana y supervivencia en pacientes con AD o ACLF

PROBABILIDAD DE SUPERVIVENCIA A 90 DIAS



MORTALIDAD A 90 DIAS



Fernandez et al. Gut 2018

Algoritmo diagnóstico

Physical Examination

- Vital signs: body temperature (fever/hypothermia), respiratory and heart rates, mean arterial pressure
- Look for abnormal findings at examination:
  - Abdominal pain, tenderness, Blumberg sign, ileus (SBP or secondary peritonitis)
  - Respiratory signs (pneumonia/spontaneous empyema)
  - Skin inflammation (cellulitis)

Assess the Source of Infection

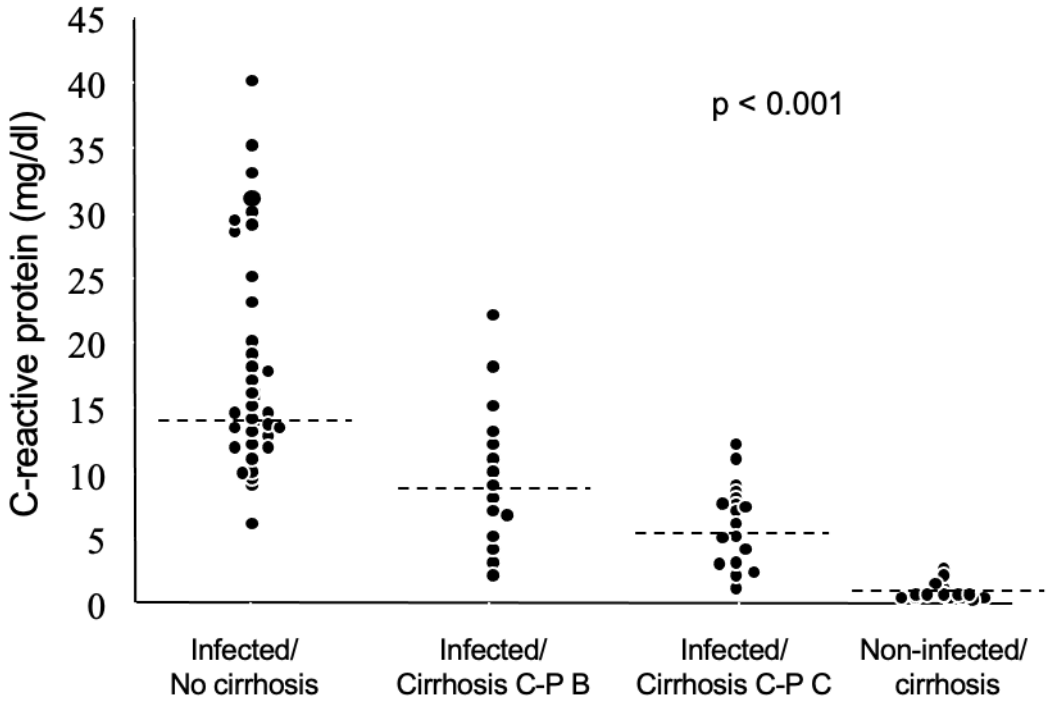
- Blood leukocyte cell count and cultures
- Source of infection:
  - Chest-X ray
  - Ascitic/pleural fluid cell count and cultures
  - Urine sediment and culture
  - Gram staining of sputum and culture
  - Consider abdominal ultrasonography

Evaluate possible Organ Failures

- Cardiovascular system: lactate levels
- Kidney: serum creatinine, electrolytes, venous blood gases
- Liver: ascites, encephalopathy, serum bilirubin
- Brain: mental status
- Coagulation: bleeding, INR, fibrinogen, platelet count
- Metabolism: serum glucose levels

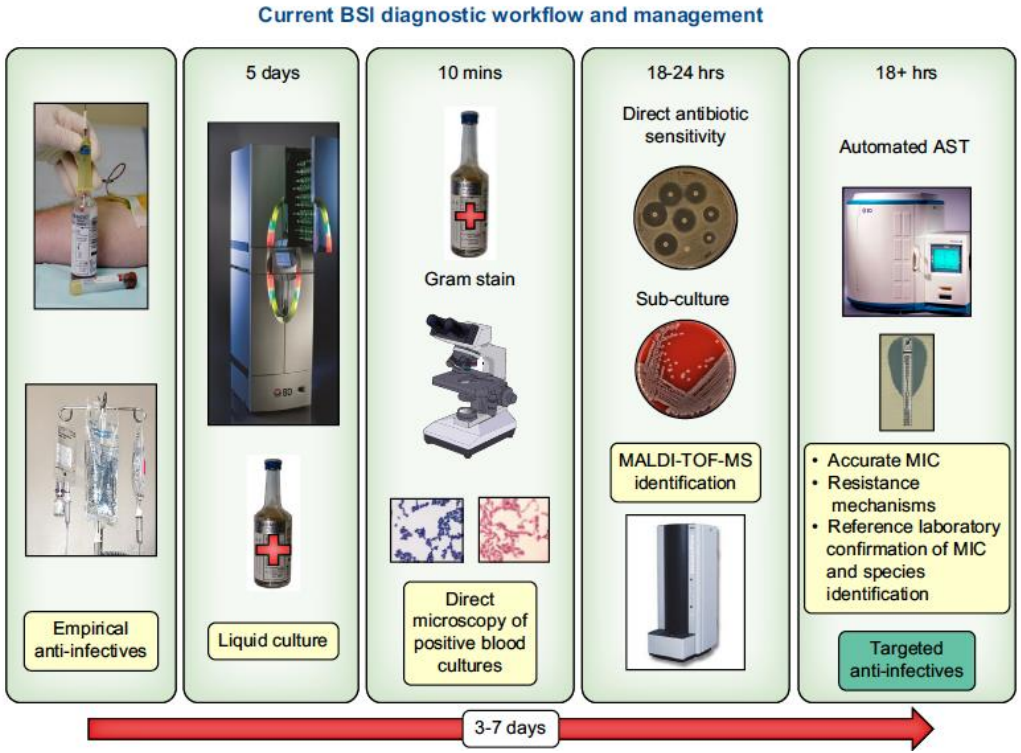
Fernández et al. J Hepatol 2012

Proteina C-reactiva: *E. coli* bacteremia



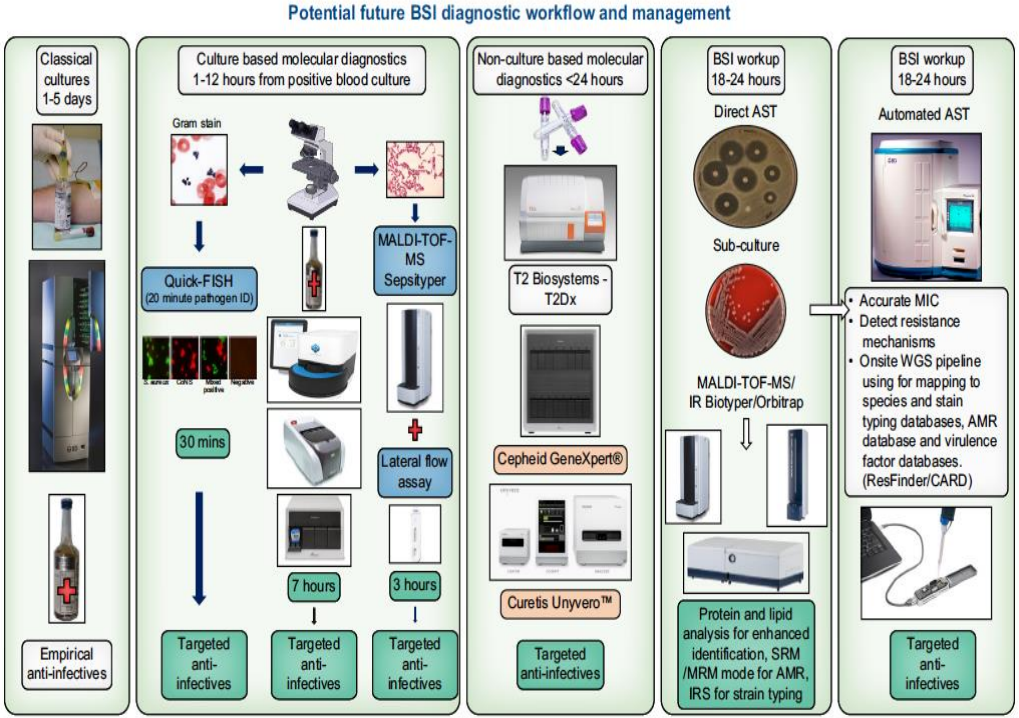
Park et al. Diagnostic Microbiology and Infectious Disease 2005

Métodos diagnósticos



Fernández et al. J Hepatol 2021

Métodos diagnósticos



Fernández et al. J Hepatol 2021

Métodos diagnósticos

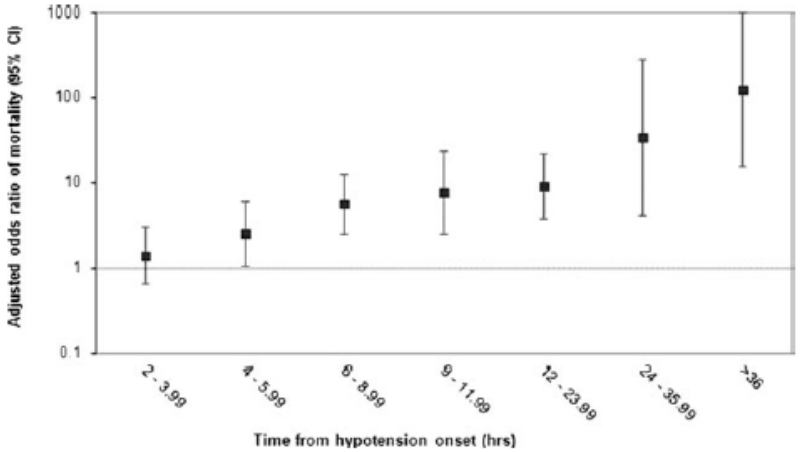
Table 2. New rapid diagnostic adjuncts for culture-based and non-culture-based identification deployed to reduce times of microbiological tests.

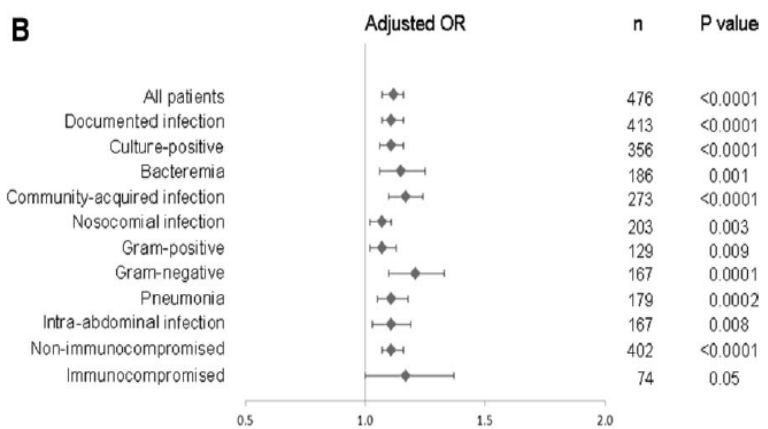
Diagnostic technique	Species/strain identification	Antibiotic sensitivity identification	Antimicrobial resistance identification	Sample type	Turnaround time
Currently available in clinical practice					
Culture-based diagnostics					
MALDI-TOF-MS	✓			Positive blood or urine cultures, bacterial subcultures	< 1 hour
MAST diagnostics: CARBAPAcE (Chromogenic/colorimetric media)			✓	Bacterial subcultures	< 1 hour
Lateral flow assays			✓	Bacterial subcultures	< 1 hour
- NG-Test CARBA 5 [NG Biotech]					
- RESIST-4 O.K.N.V. plus IMP K-SeT [Coris BioConcept] (Immunochromatographic lateral flow assays)					
Accelerate Diagnostics (Real-time microscopy-based)	✓	✓		Positive blood culture	6 hours
Quantamatrix (Real-time microscopy-based)	✓	✓		Positive blood culture	6 hours
QuickFISH (Direct microscopy visualization of fluorophore)	✓			Positive blood culture	30 mins
IRS (Infrared spectroscopy)	✓			Bacterial subcultures	30 mins
BioFire (Multiplexed, syndrome-oriented PCR, Molecular, Film Array)	✓		✓	Positive blood culture	< 1 hour
Non-culture-based diagnostics					
T2 Biosystems – T2Dx/T2MR (Magnetic resonance nanotechnology)	✓			Whole blood	4 hours
Adjuncts for culture-based and non-culture-based diagnostics					
Curetis Unyvero™ BCU (Multiplex-PCR and bi-directional sequencing)	✓		✓	Positive blood cultures, bacterial subcultures/ clinical samples	4 hours
Cepheid GeneXpert (Multiplex real-time PCR)	✓		✓		1 hour
At research/development stage					
Culture-based diagnostics					
IRS (infrared spectroscopy)			✓	Bacterial subcultures	30 mins
Non-culture-based diagnostics					
Nanopore Diagnostics LLC (iNDxer, a nanopore sensor for detecting nucleic acid biomarkers directly in minimally processed samples)	✓	✓	✓	Bacterial subcultures	3 hours
Oxford Nanopore Technologies (Long read WGS)	✓	✓	✓	Bacterial subcultures	3 hours
Adjuncts for culture-based and non-culture-based diagnostics					
MALDI-TOF-MS/MS (SRM/MRM)		✓	✓	Bacterial cultures/clinical samples	3 hours

FISH, fluorescent *in situ* hybridization; MALDI-TOF MS, matrix-assisted laser desorption ionization-time of flight mass spectrometry; MRM, multiple reaction monitoring methods; SRM, single reaction monitoring method; WGS, whole-genome sequencing.
Entries in brackets describe the basis of the diagnostic test.

Fernández et al. J Hepatol 2021

Tratamiento antibiótico empírico precoz y adecuado en el paciente cirrótico con shock séptico. "El concepto de la hora de oro"





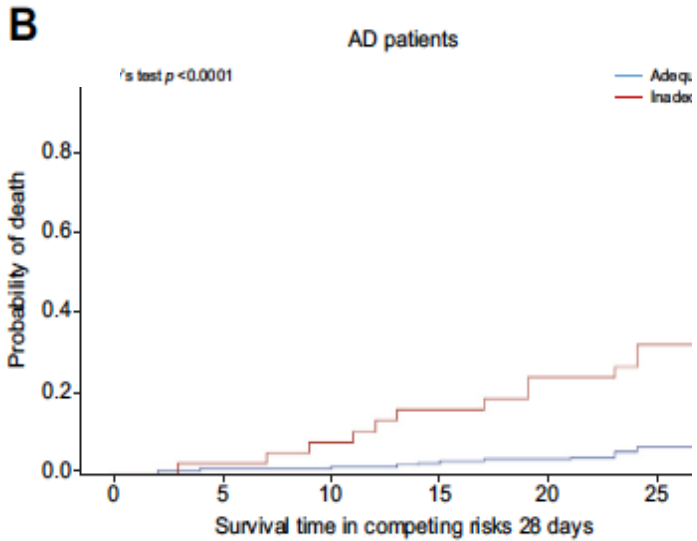
Tratamientos iniciales inadecuados o tardíos aumentan la mortalidad**:**

8% por hora

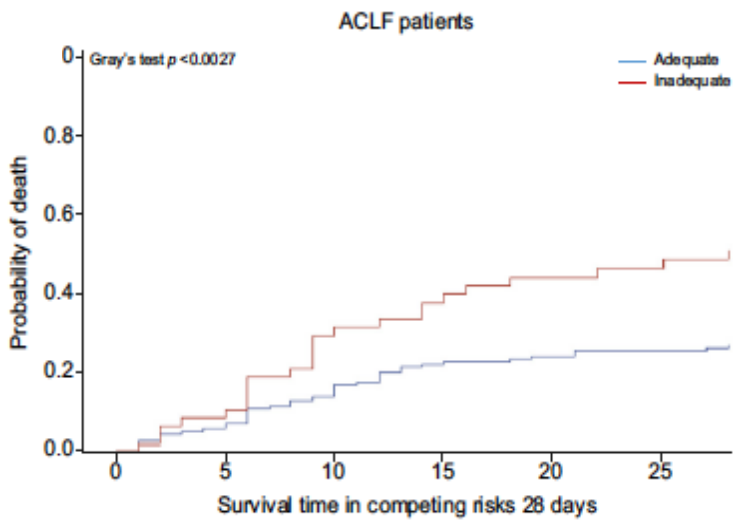
Arabi et al. Hepatology 2012

Impacto en la supervivencia de coberturas antibióticas empíricas inadecuadas en pacientes infectados con AD y ACLF

DECOMPENSACIÓN AGUDA



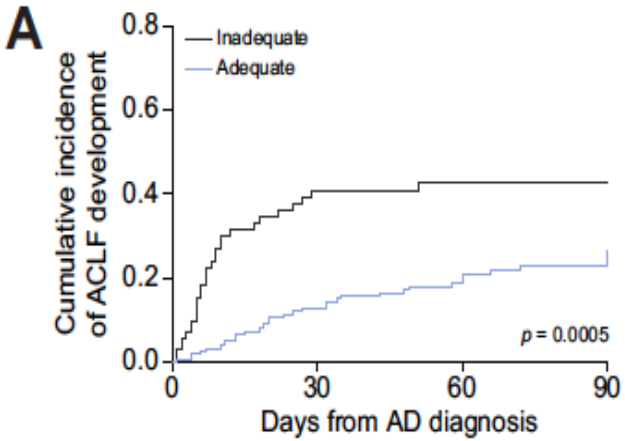
ACLF



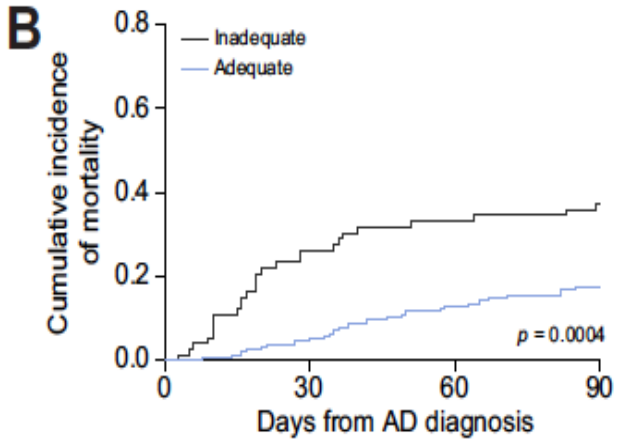
Fernandez et al. J Hepatol 2019

Impacto clínico de coberturas antibióticas empíricas inadecuadas en pacientes infectados con AD y ACLF

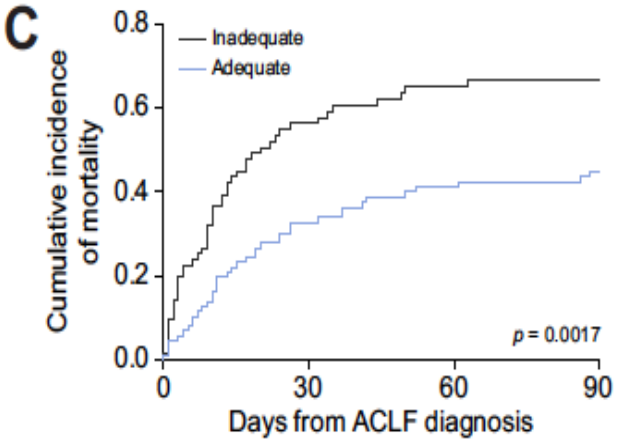
RIESGO DE ACLF



MORTALIDAD AD

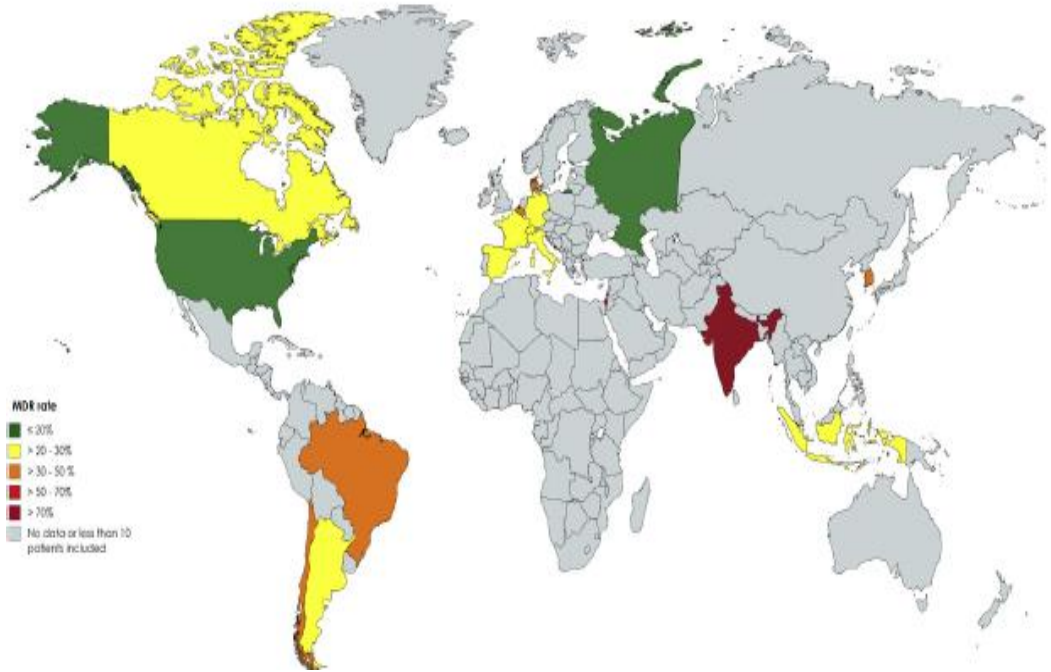


MORTALIDAD ACLF



Trebicka and Fernandez et al. J Hepatol 2021

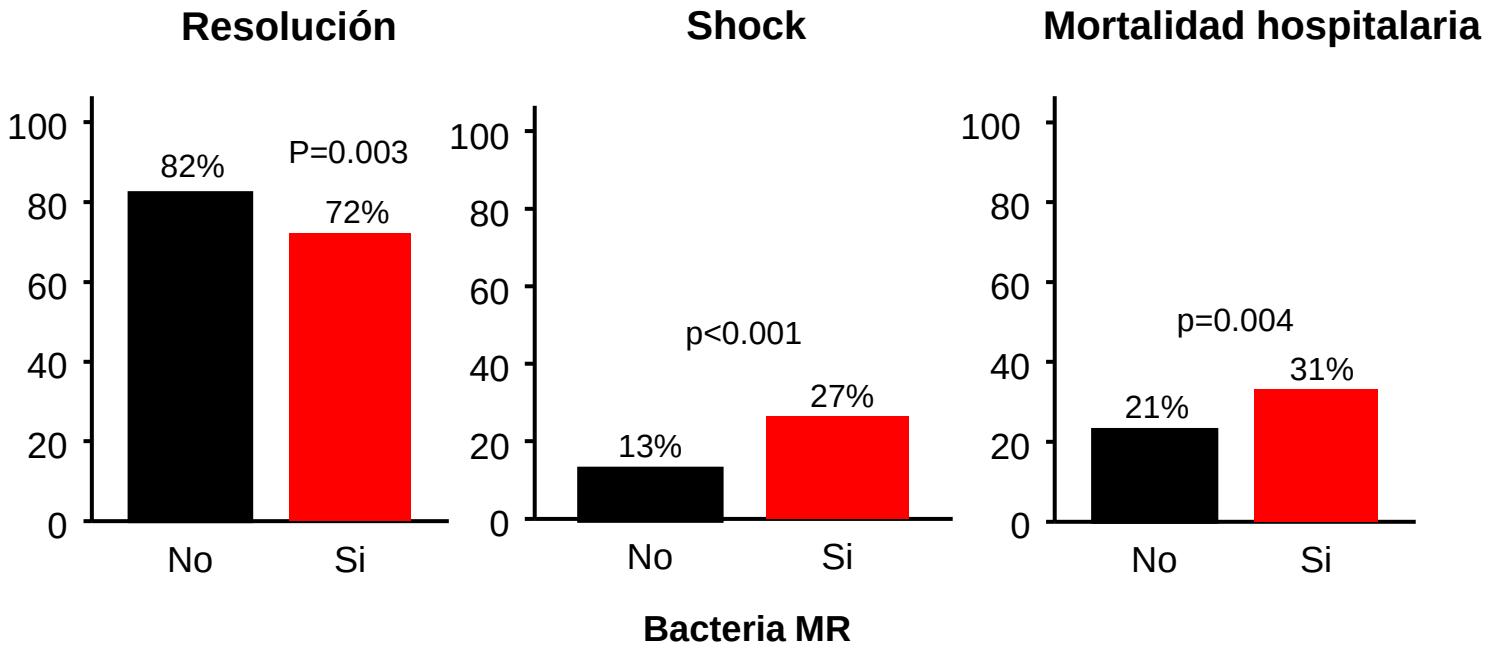
Resistencia antibiótica en la cirrosis
Datos globales del estudio del IAC



PREVALENCIA GLOBAL : 34%

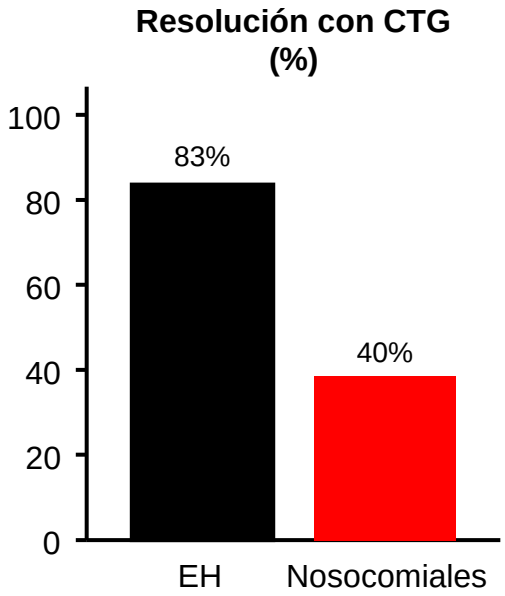
Piano et al. Gastroenterology 2019

Impacto clínico de la resistencia antibiótica: global data



Piano et al. Gastroenterology 2019

Fracaso de las guías basadas en cefalosporinas de tercera generación (CTG)



	EH	Nosocomial	p
PBE	78%	26%	<0.001
ITU	90%	29%	<0.001
Bacteriemia	67%	18%	0.05
Celulitis	82%	50%	ns
Neumonía	67%	44%	ns
Otras	91%	65%	0.005

Fernández et al., Hepatology 2012

Tratamiento antibiótico empírico recomendado en la actualidad

Type of infection	Community-acquired infections	Nosocomial infections*
SBP, SBE and spontaneous bacteremia	Cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	Piperacillin/tazobactam$^{\Delta}$ **or** meropenem§ ± glycopeptide$^{\#}$
Urinary infections	**Uncomplicated:** ciprofloxacin **or** cotrimoxazole **If sepsis:** cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	**Uncomplicated:** nitrofurantoin or fosfomycin **If sepsis:** piperacillin/tazobactam$^{\Delta}$ **or** meropenem§ ± glycopeptide$^{\#}$
Pneumonia**	Amoxicillin/clavulanic acid **or** ceftriaxone + macrolide **or** levofloxacin **or** moxifloxacin	Piperacillin/tazobactam$^{\Delta}$ **or** meropenem/ceftazidime + ciprofloxacin ± glycopeptide$^{\#}$ should be added in patients with risk factors for MRSA¶
Cellulitis	Amoxicillin/clavulanic acid **or** ceftriaxone + oxacillin	Meropenem/ceftazidime$^{\&}$ + oxacillin **or** glycopeptides$^{\#}$

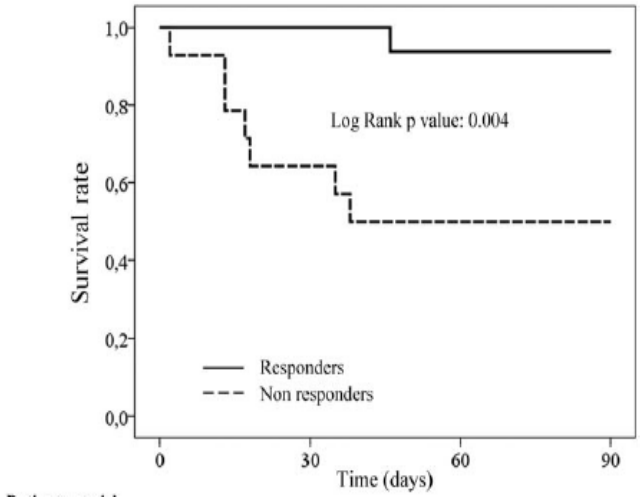
SBP, spontaneous bacterial peritonitis; SBE, spontaneous bacterial empyema; MRSA, methicillin-resistant *Staphylococcus aureus*.
Dosages of antibiotics have not been formally investigated or defined in cirrhotic population and it is advisable to follow standard recommended dosages.
*Recommended empirical treatment also for health-care associate (HCA) urinary infections and pneumonia. Empirical antibiotic treatment of HCA spontaneous infections and cellulitis will be decided on the basis of the severity of infection (patients with severe sepsis should receive the schedule proposed for nosocomial infections) and on the local prevalence of multiresistant bacteria in HCA infections.
$^{\Delta}$In areas with a low prevalence of multiresistant bacteria.
§To cover extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*.
$^{\#}$IV vancomycin or teicoplanin in areas with a high prevalence MRSA and vancomycin-susceptible enterococci (VSE). Glycopeptides must be replaced by IV linezolid in areas with a high prevalence of vancomycin-resistant enterococci (VRE).
**Liver disease is considered as severe comorbidity for community-acquired pneumonia in guidelines.
$^{\&}$Antibiotics active against *Pseudomonas aeruginosa*.
¶Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage.

Jalan and Fernández et al. J Hepatol 2013; Angeli at al J Hepatol 2018

Impacto clínico de coberturas antibióticas activas frente a bacterias multirresistentes adaptadas a la epidemiología local

PBE NOSOCOMIAL

Cefepime vs meropenem+daptomicina



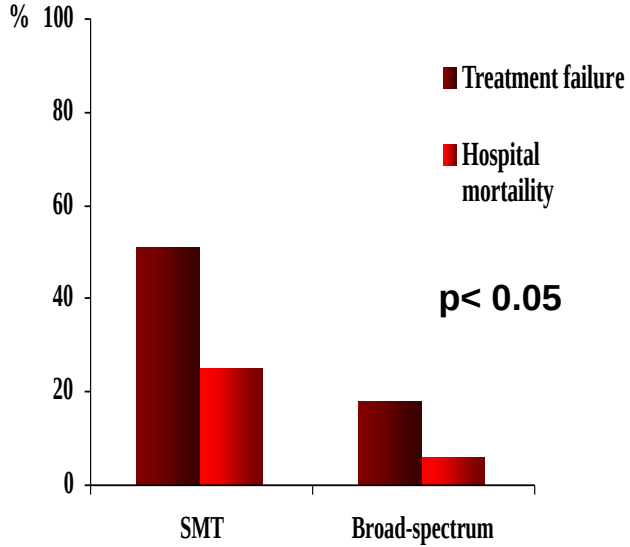
RESOLUTION RATE:

Cefepime: 25%

Meropenem+daptomicina: 87%

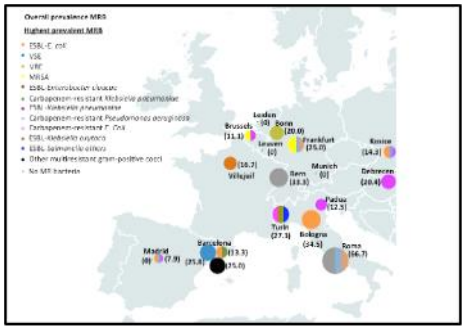
INFECCIONES HCA

B-lactámicos vs Imipenem+GPC

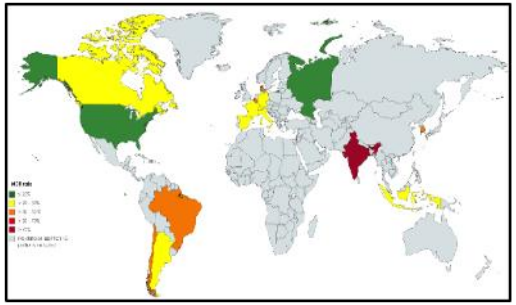


Piano et al, Hepatogy 2015, Jindal et al. Liver int 2015

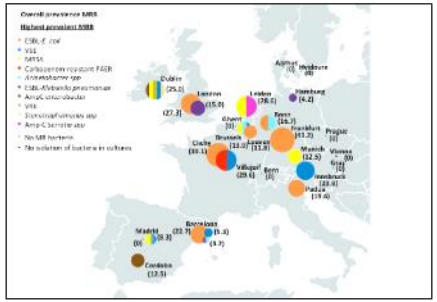
Incremento de la resistencia antibiótica en la cirrosis



2017-2018: 38%



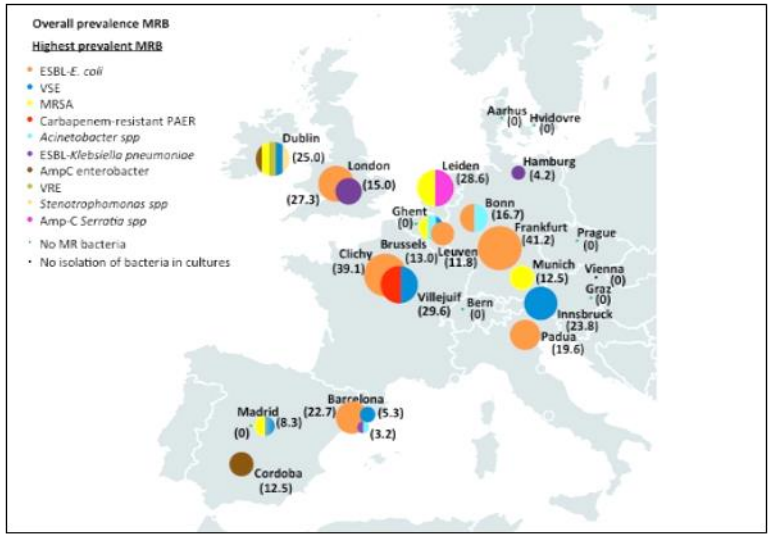
2015-2016: 34%



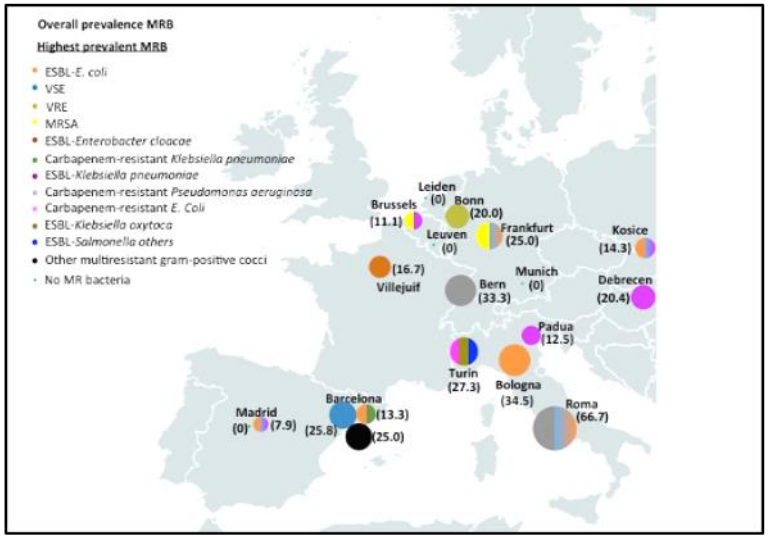
2011: 29%

Fernandez et al. J Hepatol 2021

Incremento de la resistencia antibiótica en la cirrosis



2011: 29%



2017-2018: 38%

Fernandez et al. J Hepatol 2021

Factores de riesgo de infecciones causadas por bacterias multirresistentes en la cirrosis

Factores de riesgo indiscutibles
Episodio nosocomial
Hospitalización reciente (3 meses)
Antibióticos sistémicos recientes(1 -3 meses)
Procedimiento invasivo reciente (1 mes)
Ingreso en UCI
Infección o colonización reciente por BMR (6 meses)

Potenciales
Decontaminación a largo plazo con norfloxacino
ACLF
Diabetes mellitus

Fernandez et al. J Hepatol 2021

Principales bacterias MR

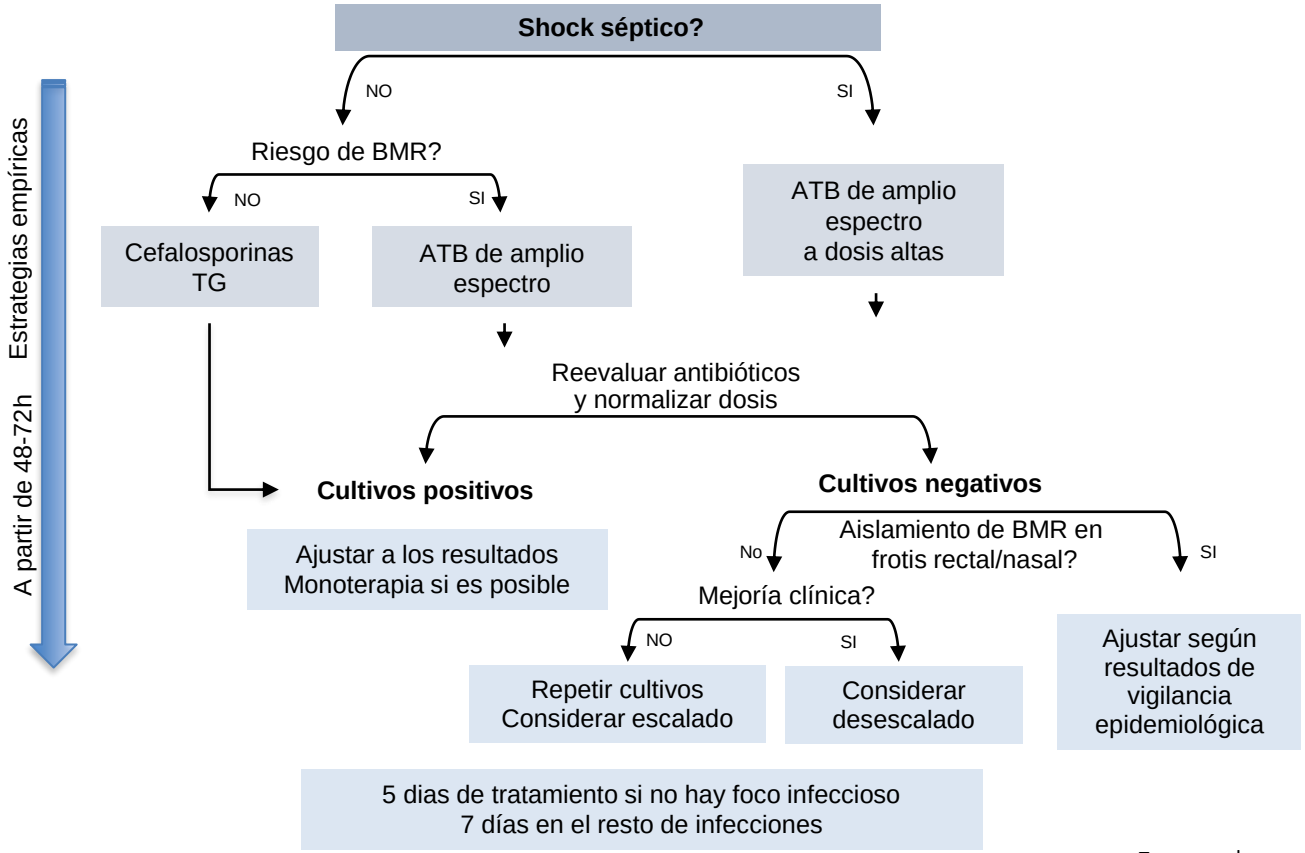
Bacteria MR	ESBL-producing Enterobacteriaceae	Carbapenemase-producing Enterobacteriaceae	Carbapenem-resistant non-fermentative bacteria		MRSA	VRE
Main species	*E. coli,* *K. pneumoniae*	*E. coli,* *K. pneumoniae*	*Pseudomonas aeruginosa*	*Acinetobacter baumanii*	*S. aureus*	*E. faecium*
Resistance mechanism	β-lactam hydrolysis	β-lactam hydrolysis	Restricted permeability Efflux pumps β-lactam hydrolysis	β-lactam hydrolysis	Target modification	Target modification
Main reservoir	Intestinal tract	Intestinal tract	Intestinal tract	Intestinal tract	Oropharynx	Intestinal tract

Fernandez et al. J Hepatol 2016

Estrategias sugeridas para prevenir el desarrollo de la resistencia antibiótica en la cirrosis

Fernández and Berg et al, J Hepatol 2016

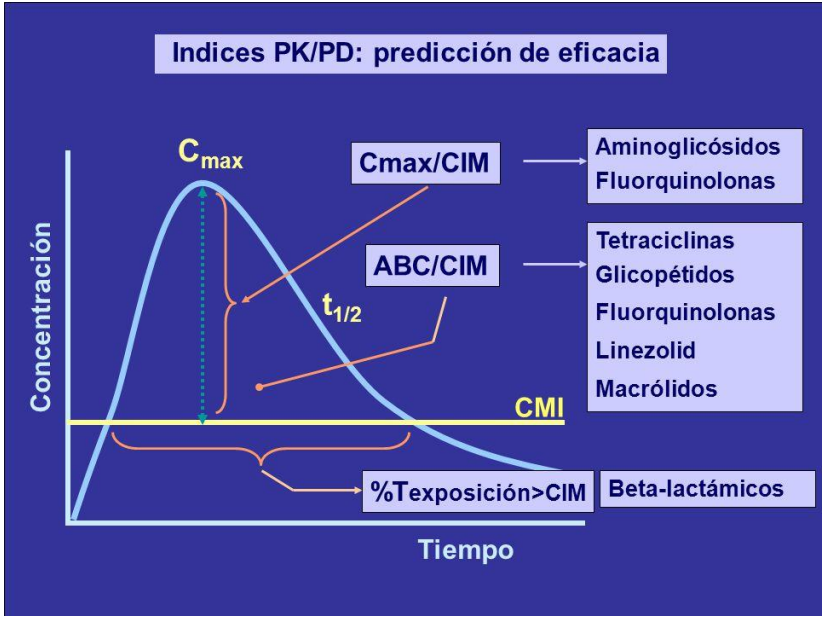
Esquemas empíricos sugeridos en pacientes con shock séptico y reglas de desescalado



Fernandez et al, J Hepatol 2021

Indices PK/PD

Relacionan parámetros PK del antibiótico con su capacidad de inhibir el crecimiento bacteriano

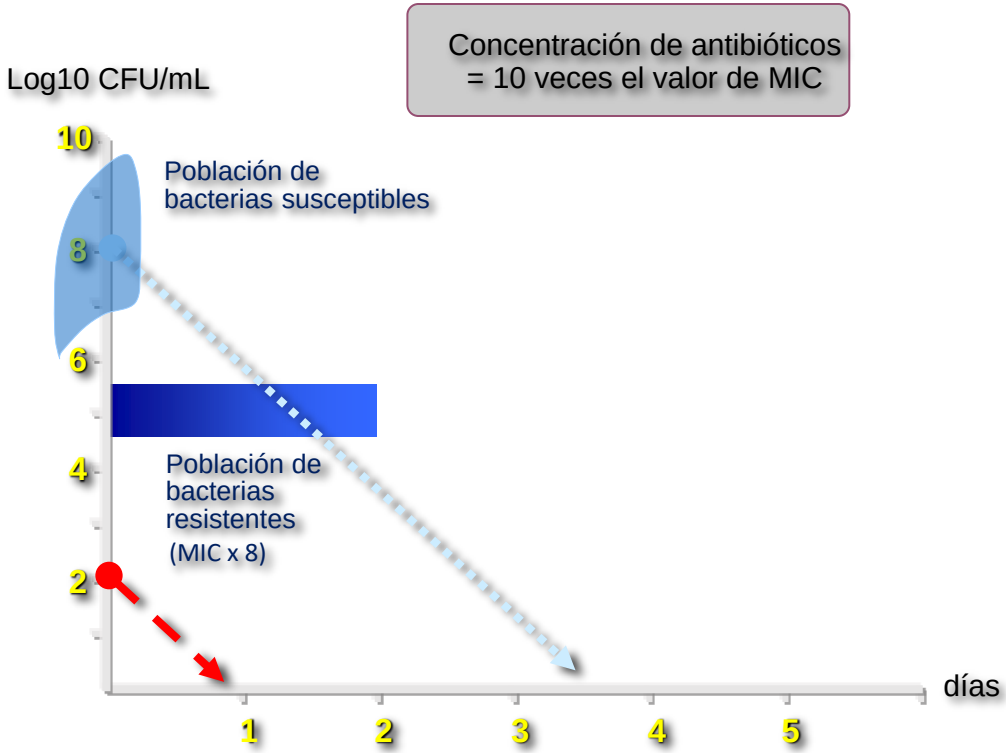


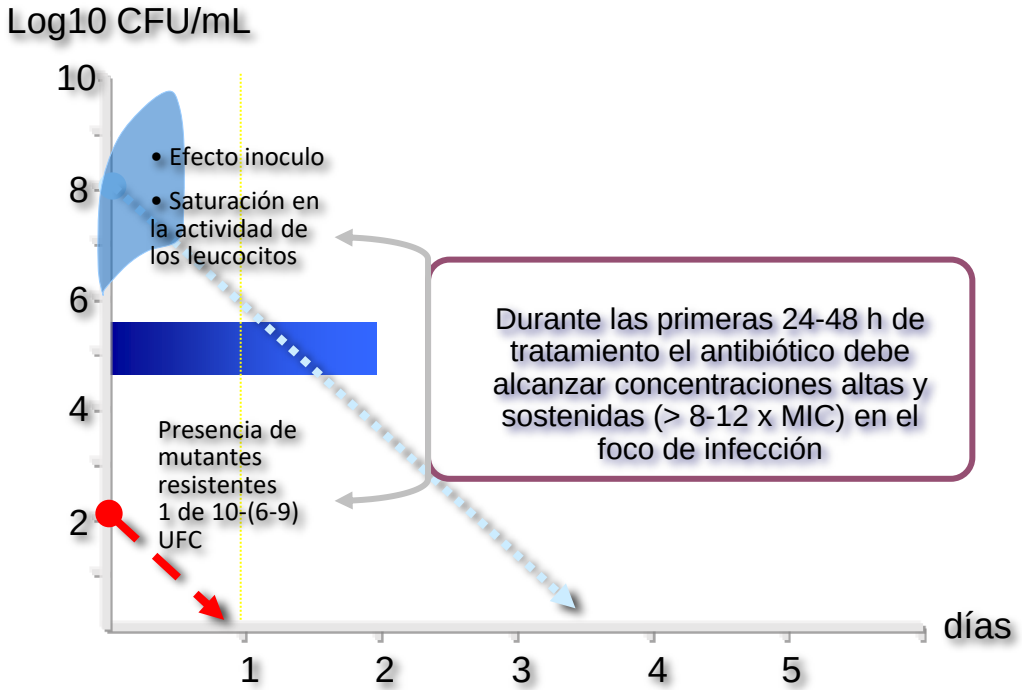
Cmax o pico/CMI

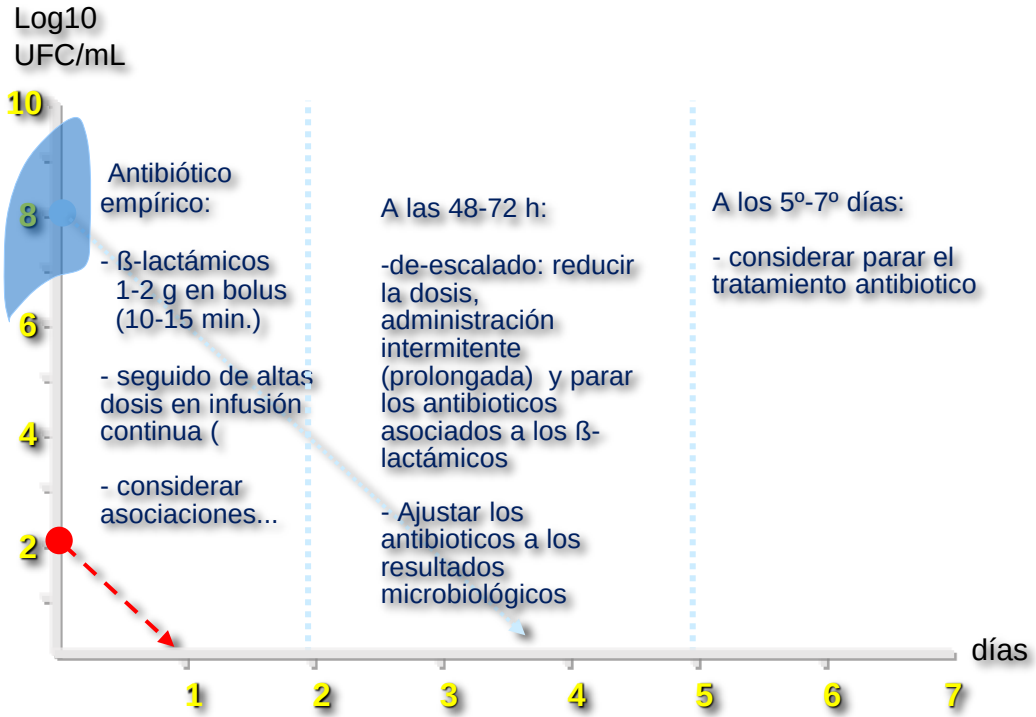
AUC/CMI

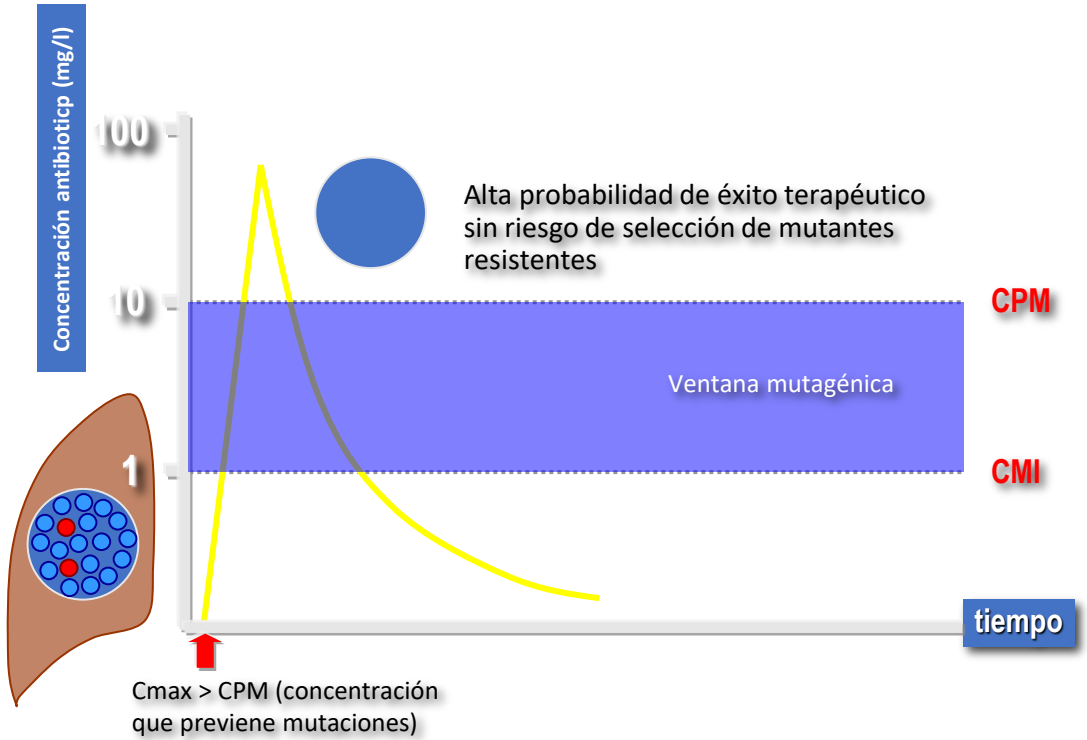
%t > CMI tiempo entre dos dosis en el que la concentración del fármaco está por encima de la CMI: 50-100%

Optimización farmacocinética de las dosis de antibioticos y de su eficacia




Log10 CFU/mL
10
8
6
4
2
• Efecto inoculo
• Saturación en la actividad de los leucocitos
Presencia de mutantes resistentes 1 de 10-(6-9) UFC
Durante las primeras 24-48 h de tratamiento el antibiótico debe alcanzar concentraciones altas y sostenidas (> 8-12 x MIC) en el foco de infección
días
1
2
3
4
5


Log10
UFC/mL
10
8
6
4
2
Antibiótico empírico:
- ß-lactámicos 1-2 g en bolus (10-15 min.)
- seguido de altas dosis en infusión continua (
- considerar asociaciones...
A las 48-72 h:
-de-escalado: reducir la dosis, administración intermitente (prolongada) y parar los antibioticos asociados a los ß-lactámicos
- Ajustar los antibioticos a los resultados microbiológicos
A los 5º-7º días:
- considerar parar el tratamiento antibiotico
días
1
2
3
4
5
6
7


Concentración antibioticp (mg/l)
100
10
1
Alta probabilidad de éxito terapéutico
sin riesgo de selección de mutantes
resistentes
CPM
Ventana mutagénica
CMI
tiempo
Cmax > CPM (concentración
que previene mutaciones)

Optimización farmacocinética en el paciente grave

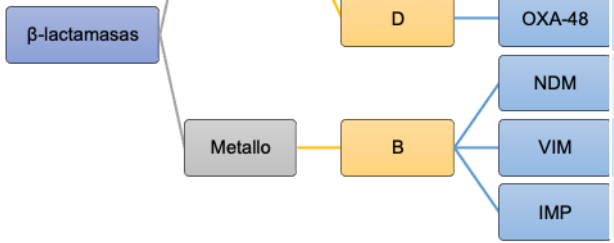
Table 6. Proposed empirical doses and ways of administration of the main antibiotics in patients with septic shock.

Antibiotic and initial dose*	Doses during the first 48-72 hours and mode of administration	De-escalation after 72 hours◇
Ceftriaxone 2 g	1 g/12 hours	1 g/12-24 hours
Cefotaxime 2 g	6-8 g/day in continuous infusion@	1-2 g/8 hours
Ceftazidime 2 g	6 g/day in continuous infusion@	1-2 g/8 hours
Meropenem 2 g	6 g/day in continuous infusion@	1-2 g/8 hours
Piperacillin-tazobactam 4 g-0.5g	16-2 g/day in continuous infusion@	4 g/6-8h
Ceftazidime-avibactam 2.5 g	7.5 g/day in continuous infusion@	7.5 g/day in continuous infusion@
Ceftolozane-tazobactam 1.5g (3 g in case of pneumonia)	4.5 or 9 g in continuous infusion@	4.5 or 9 g in continuous infusion@
Levofloxacin 1,000 mg	500 mg/12 hours	500 mg/24 hours
Ciprofloxacin 600 mg	400 mg/8 hours	400 mg/12 hours
Tigecycline 200 mg#	100 mg/12 hours#	50 mg/12 hours#
Metronidazole 1,000 mg	500 mg/6 hours	500 mg/8 hours
Clindamycin 900 mg	600 mg/6 hours	600 mg/6 hours
Vancomycin 20 mg/kg	15-20 mg//kg/12 hours	Adjust by TDM
Teicoplanin 12-15 mg/kg	8-12 mg/kg/day	8 mg/kg/day
Linezolid 600 mg	600 mg/12 hours	600 mg/12 hours
Daptomycin 10-12 mg/kg§	8-12 mg/kg/day	6-12 mg/kg/day
Amikacin 25 mg/kg-	20 mg/kg/day	Consider stopping or adjust by TDM
Gentamicin 7-9 mg/kg-	7 mg/kg/day	Consider stopping or adjust by TDM
Tobramycin 7-9 mg/kg-	7 mg/kg/day	Consider stopping or adjust by TDM
Fosfomycin 4 g	200-300 mg/kg/day in continuous infusion@	2 g/6 hours
Colistin 6-9 MIU	4.5 MIU/12 hours	3 MIU/12 hours

MIU, million international units; TDM, therapeutic drug monitoring.

Fernandez et al, j Hepatol 2021

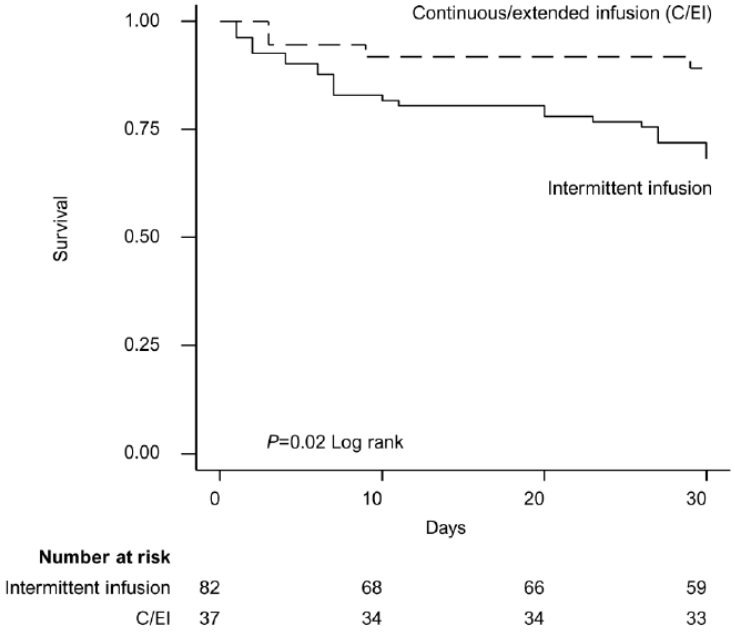
Nuevos antibióticos activos frente a bacterias MR

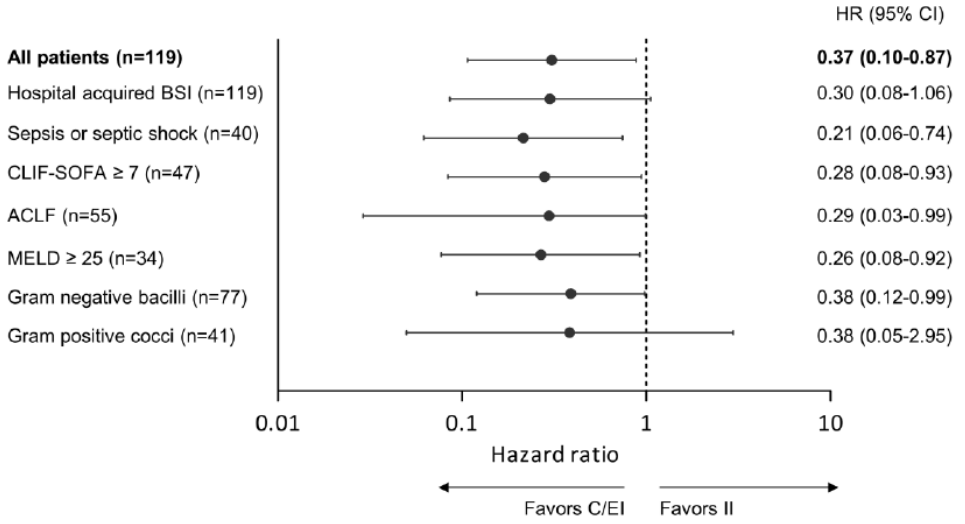


Ambler Class	Enzimas	Fármacos con actividad in vitro						
		Beta-láctamicos clásicos	Carbapenems	Ceftazidima-avibactam	Ceftolozano-tazobactam	Cefiderocol	Meropenem vaborbactam	Aztreonam-avibactam
A	KPC			✔		✔	✔	✔
A	CTX-M	+/-	✔	✔	+/-	✔	✔	✔
A	TEM, SHV	+/-	✔	✔	+/-	✔	✔	✔
C	AmpC	+/-	✔	✔	+/-	✔		✔
D	OXA-48			✔		✔		✔
B	NDM					✔		✔
B	VIM					✔		✔
B	IMP					✔		✔

Fernandez et al, J Hepatol 2021

Infusiones extendidas de Beta-lactámicos: impacto clinico





Bartoletti et al, CID 2019

Colonización rectal por BMR en el paciente cirrótico crítico

PREVALENCE

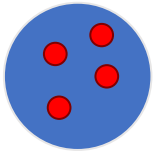
HOSPITAL CLINIC BARCELONA
2015-2016

486 critically ill patients, 129 with cirrhosis
Prevalence of MDRO rectal colonization: 32.7%
Prevalence in patients with cirrhosis: 42.6%

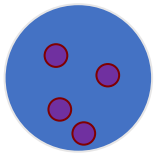
GOETHE UNIVERSITY FRANKFURT
2010-2018

421 critically ill cirrhotic patients
Prevalence of MDRO rectal colonization: 47%

PREDOMINANT COLONIZING STRAIN

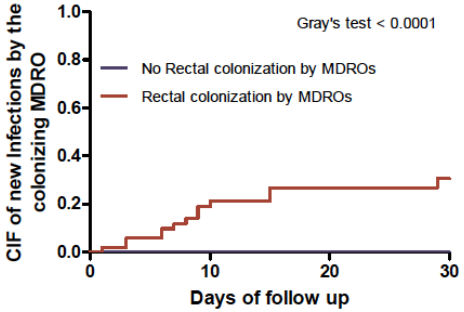


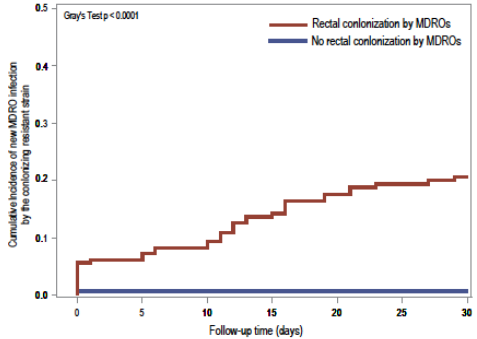
Extended-spectrum
beta-lactamase-*Enterobacterales*



Vancomycin-resistant enterococci

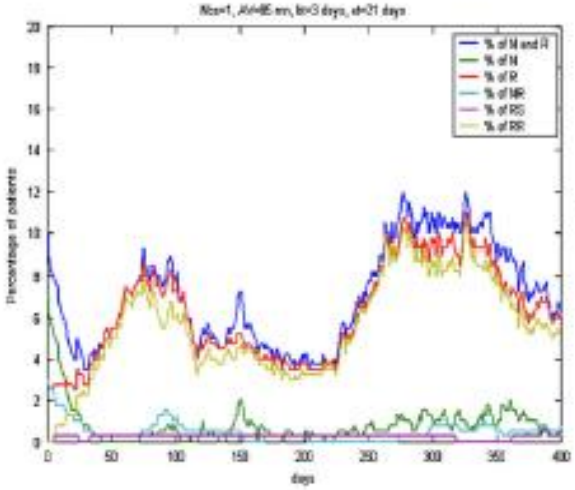
HIGHER RISK OF INFECTION BY THE COLONIZING BACTERIA

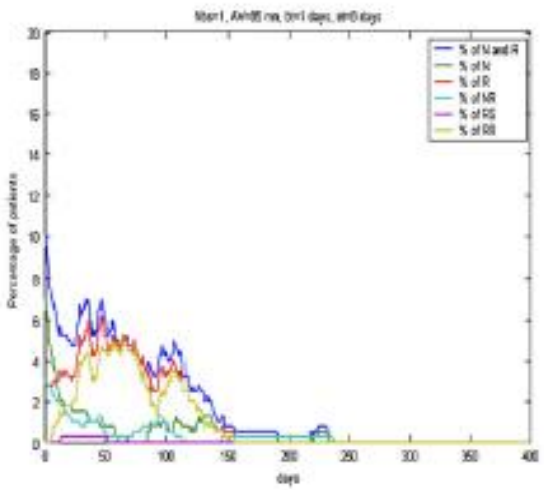




Prado et al. Submitted

Modelando la resistencia antibiótica
Impacto de minimizar la duración del tratamiento antibiótico



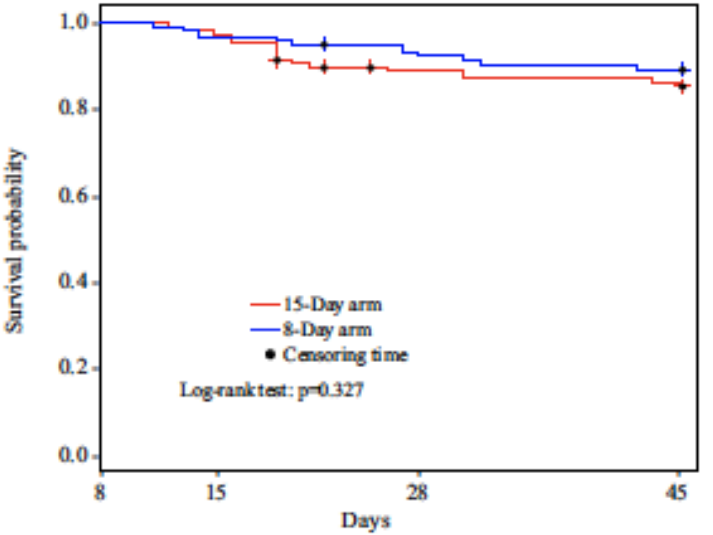


ATB se inician el día 3 y se paran el 21 ➡
Las cepas resistentes se se convierten en endémicas

ATB se inician el día 1 y se paran el 8 ➡
Cepas sensibles y resistentes son eliminadas

D'Agata et al, J Theor Biol. 2007

Antibioterapia de corta duración en el paciente crítico
Infecciones intra-abdominal



Number at risk (number censored)				
8-Day arm	120 (0)	118 (0)	111 (1)	107 (100)
15-Day arm	116 (0)	114 (0)	101 (3)	97 (92)

Fig. 3 Kaplan-Meier curves of the probability of survival from randomisation to day 45 according to treatment arm

Montraves et al. Intensive Care Med 2018

Indicaciones actuales de la profilaxis antibiótica en la cirrosis

Indication	Antibiotic and dose	Duration
Secondary prophylaxis of SBP	Norfloxacin 400 mg/d or ciprofloxacin 500 mg/d PO	Long-term: until LT
Upper gastrointestinal bleeding	Norfloxacin 400mg/12h or ciprofloxacin 500 mg/12h PO in compensated cirrhosis IV ceftriaxone 1gr/d in patients with: - Ascites, jaundice, hepatic encephalopathy or malnutrition - Those already on quinolone prophylaxis - In areas with a high prevalence of quinolone-resistant bacteria - Active bleeding IV ertapenem 1gr/d in patients colonized by ESBL-*Enterobacteriaceae*	Short-term: 5-7 days
Primary prophylaxis of SBP Patients with low protein ascites (<15g/l) and advanced cirrhosis*	Norfloxacin 400mg/d or ciprofloxacin 500 mg/d PO	Long-term: until LT or clinical improvement

Legend: SBP: spontaneous bacteria peritonitis; LT: liver transplantation;
*Child-Pugh C or Child- Pugh ≥ 9 points with serum bilirubin ≥ 3 mg/dl and/or serum creatinine ≥ 1.2 mg/dl, BUN ≥ 25 mg/dl, serum sodium ≤ 130 mEq/L

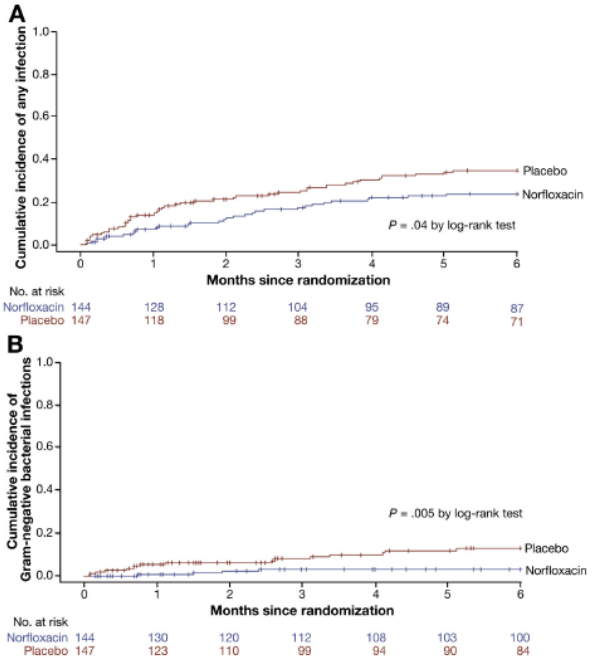
Fernandez et al. J Hepatol 2021

Profilaxis de la PBE en pacientes con cirrosis avanzada

STUDY DESIGN

- ✓ Double-blind randomized placebo controlled trial (norfloxacin 400 mg/d vs. placebo)
- ✓ N=291
- ✓ Target: Child-Pugh C patients with (4%) or without (96%) previous SBP with low or high protein ascites
- ✓ Main end-point: survival at 6 months
- ✓ Lenght of treatment: 6 months

BACTERIAL INFECTIONS



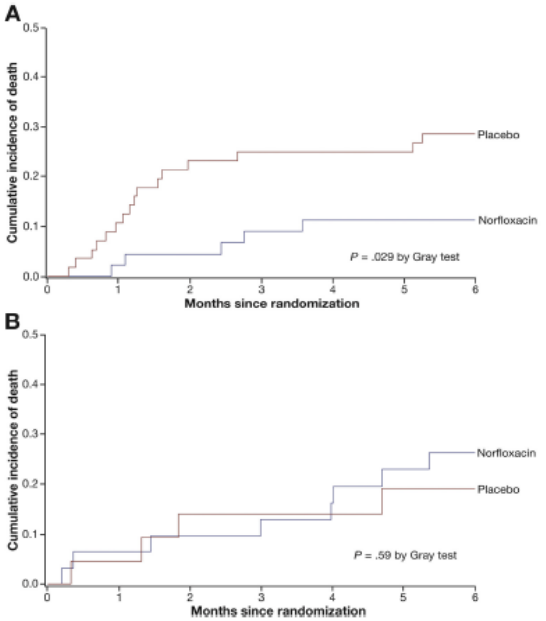
Moreau et al. *Gastroenterology* 2018

Profilaxis de la PBE en pacientes con cirrosis avanzada

SBP and MDR infections

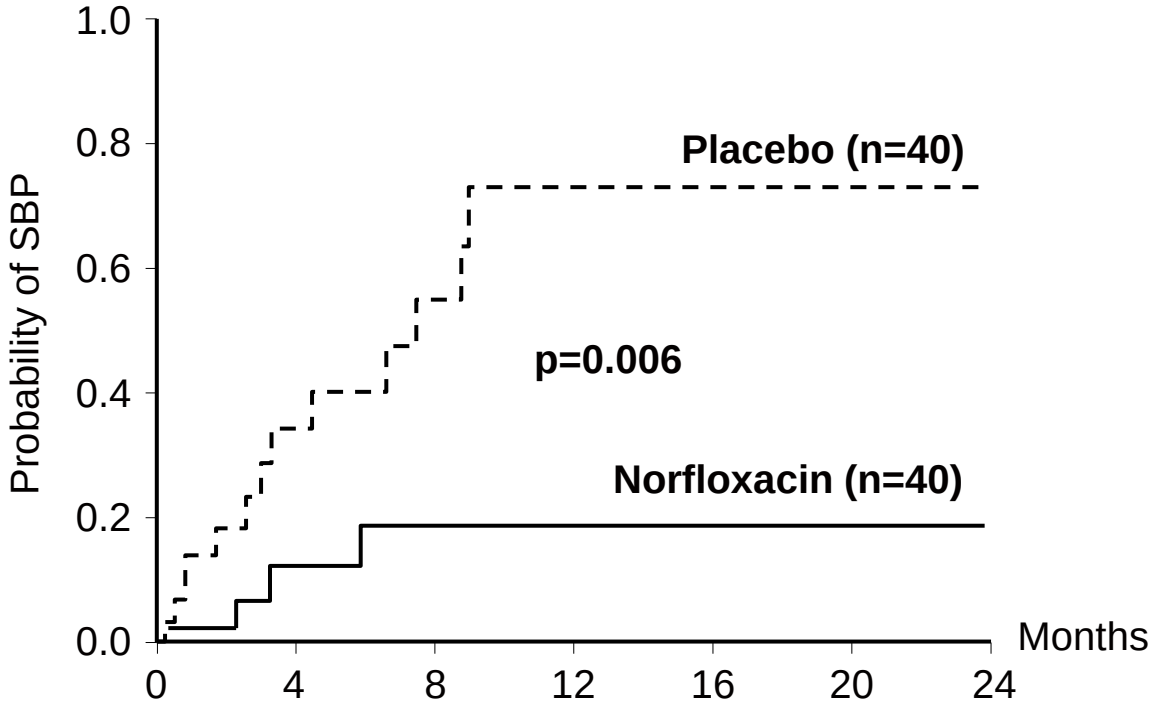
Characteristics	Chronological analysis: Norfloxacin (n = 144)	Chronological analysis: Placebo (n = 147)	*P* value
First infectious episode			
Patients, n (%)	31 (21.5)	46 (31.3)	.06[a]
Site of infection, no. of patients (%)			
Ascites	9 (29.0)	16 (34.8)	.60[a]
Lung	4 (12.9)	8 (17.4)	.75[b]
Urine	4 (12.9)	6 (13.0)	1.00[b]
Blood	3 (9.7)	5 (10.9)	1.00[b]
Soft tissue	5 (16.1)	6 (13.0)	.75[b]
Documented pathogen, no. of patients (%)			
Gram-negative bacteria	3 (9.7)	15 (32.6)	.02[a]
Gram-positive bacteria	4 (12.9)	7 (15.2)	1.00[b]
Mixed bacteria	1 (3.2)	3 (6.5)	.64[b]
Multidrug-resistant bacteria	2 (6.5)	1 (2.2)	.56[b]
Other	2 (6.5)	0 (0.0)	.16[b]

MORTALITY



Moreau et al. Gastroenterology 2018

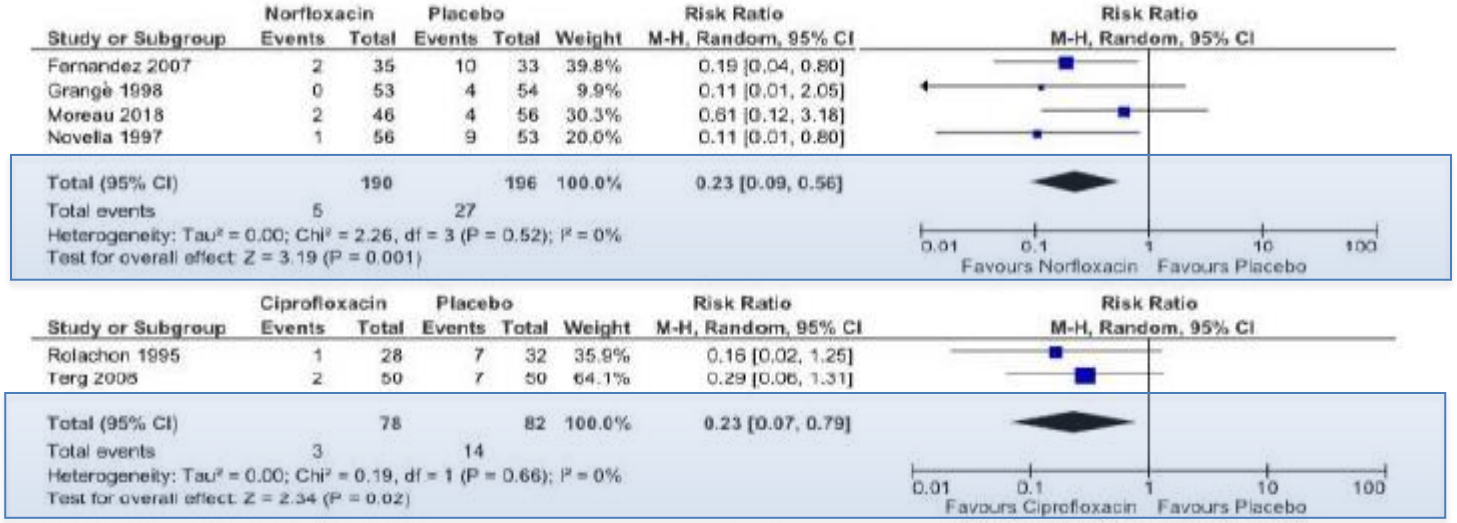
Profilaxis secundaria de la PBE



Gines et al. Hepatology 1990

Impacto de la profilaxis de la PBE Nuevo meta-analysis

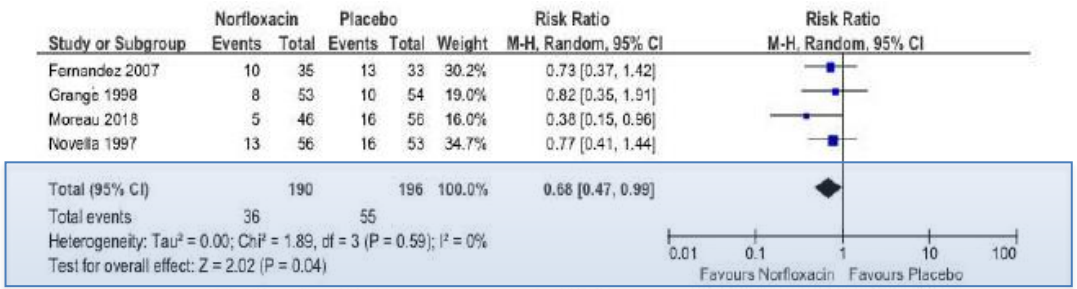
PREVENTION OF SBP

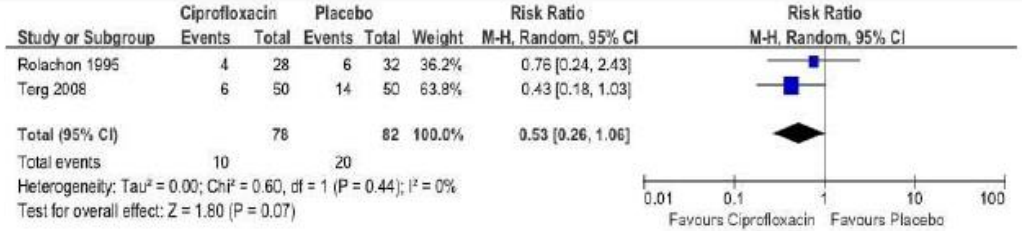


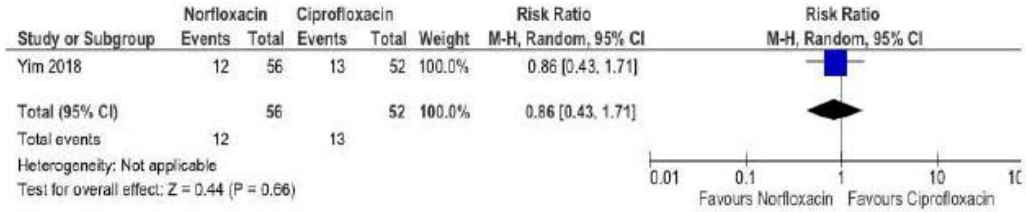
Facciorusso et al. Liver Int 2019

Impacto de la profilaxis de la PBE Nuevo meta-analysis

MORTALITY

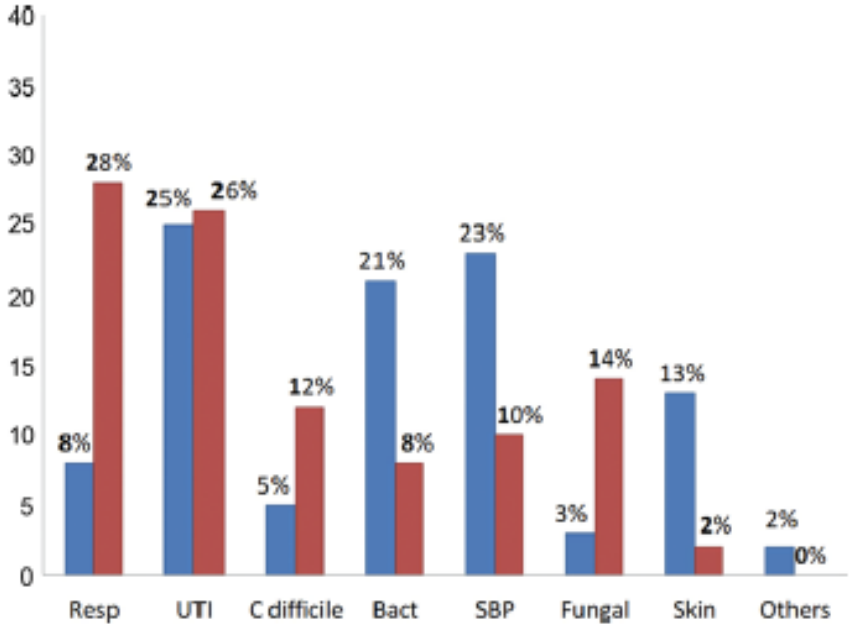






Facciorusso et al. Liver Int 2019

Infecciones fúngicas: prevalencia



Bajaj et al. Hepatology 2012

Colonización/Infección por hongos

	No ACLF (n=235)	ACLF All grades (n=407)	p
Fungal isolation (n/%)	1(0.4)	16(3.9%)	0.005
Fungal infection (n/%)	-	8(1.96%)*	0.01
Invasive candidiasis	-	7(2%)	
Candidemia		5	
Secondary peritonitis		2	
Invasive aspergillosis	-	1(0.2%)	
Colonization (n/%)	1 (0.4%)	8(2.5)	

* Six out of 8 occurred during follow-up

Fernandez et al. Gut 2018

Factores de riesgo de infección fúngica

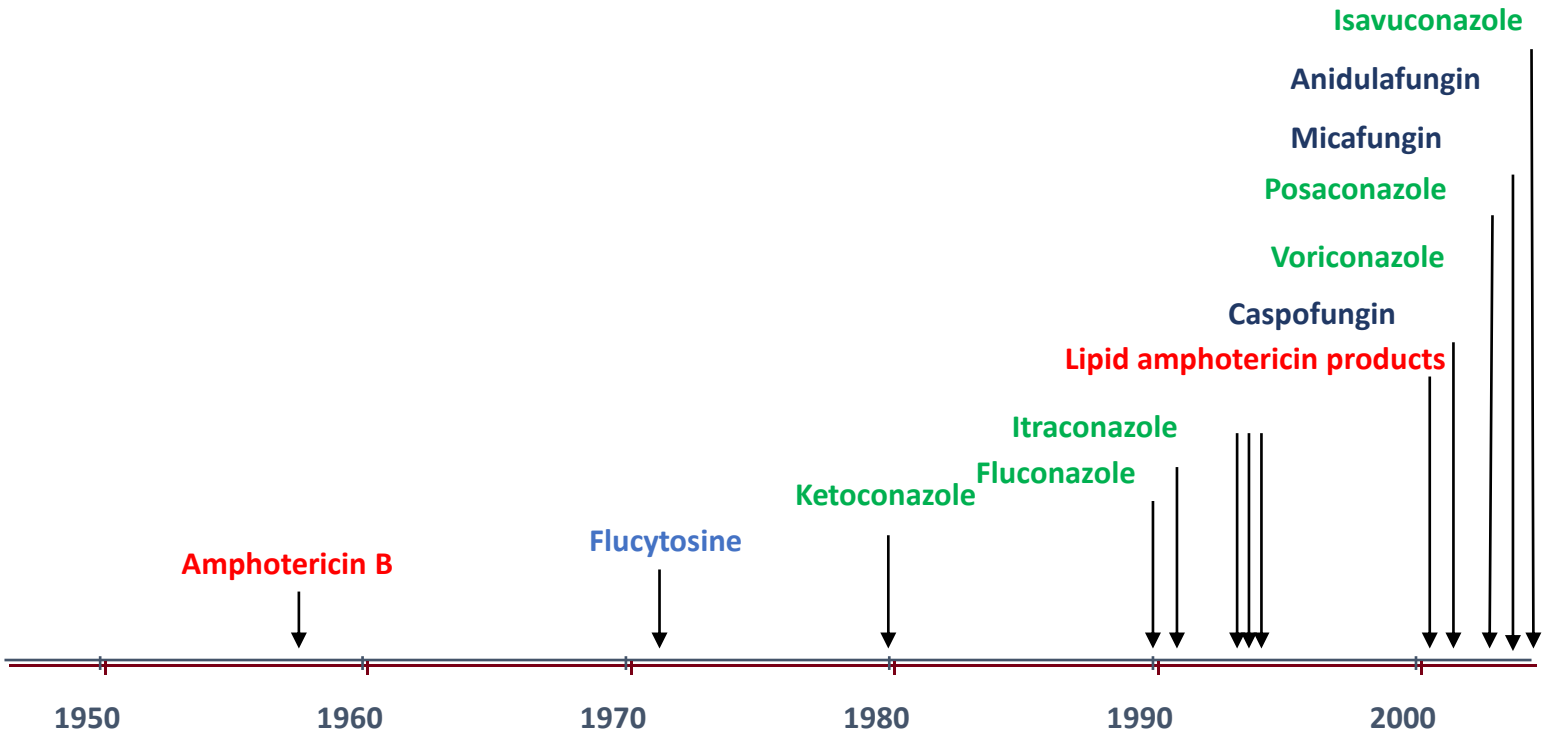
Table 3. Risk factors for infections caused by MDRO and fungi in cirrhosis.

	Major risk factors	Potential risk factors
Bacterial infection by MDROs	Nosocomial episode Recent hospitalisation (3 months) Recent systemic antibiotics exposure (1 to 3 months) Recent invasive procedures (1 month) ICU admission Recent infection or colonisation by MDROs (6 months)	Long-term norfloxacin prophylaxis Heath care-associated infections ACLF Diabetes mellitus
Invasive candidiasis*	Abdominal surgery Recent broad-spectrum antibiotic exposure Central venous catheter, total parenteral nutrition AKI-Renal replacement therapy Prolonged stay in the ICU Diabetes mellitus	Multifocal colonization by *Candida* ACLF Steroid therapy Malnutrition
Invasive aspergillosis*	Prolonged steroid therapy Poor liver function Prolonged stay in the ICU	ACLF Renal replacement therapy Malnutrition

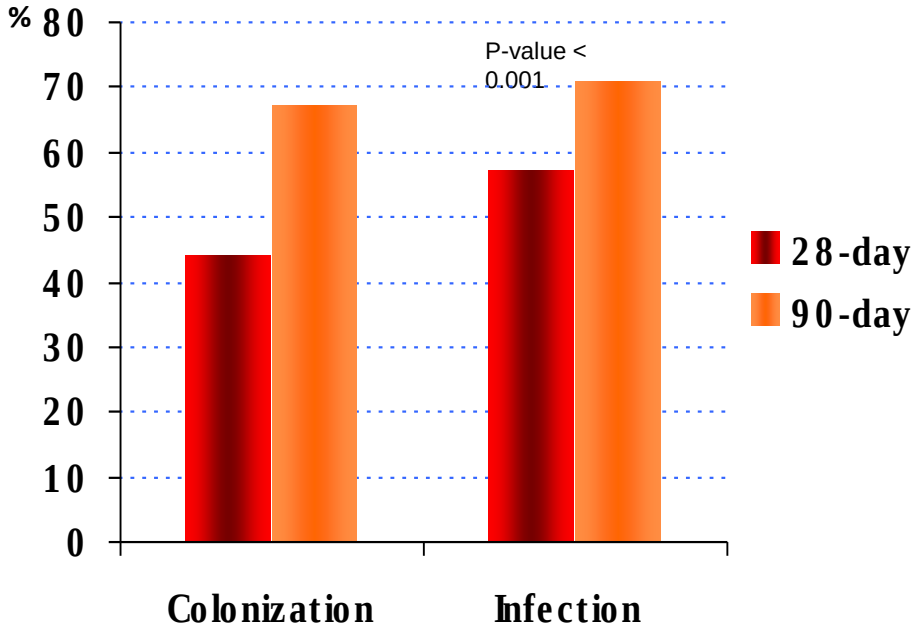
ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ICU, intensive care unit; MDROs, multidrug-resistant organisms.
*Described mainly in the general population.

Fernandez et al, J Hepatol 2021

Armamentarium antifúngico

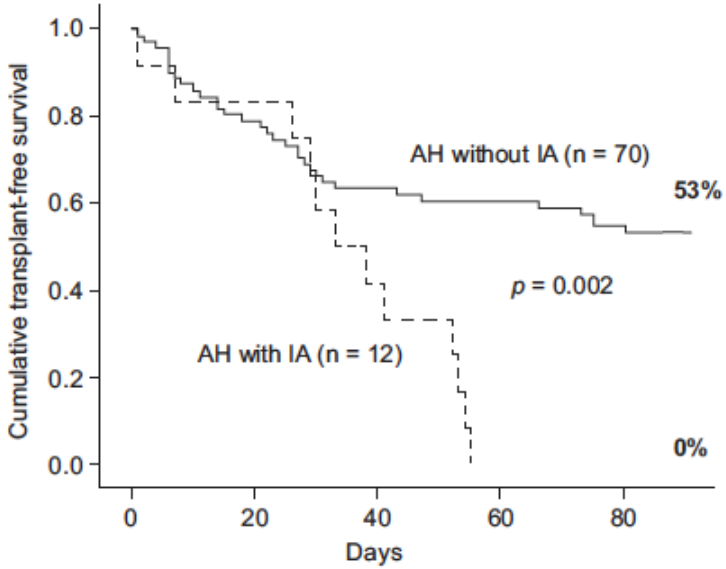


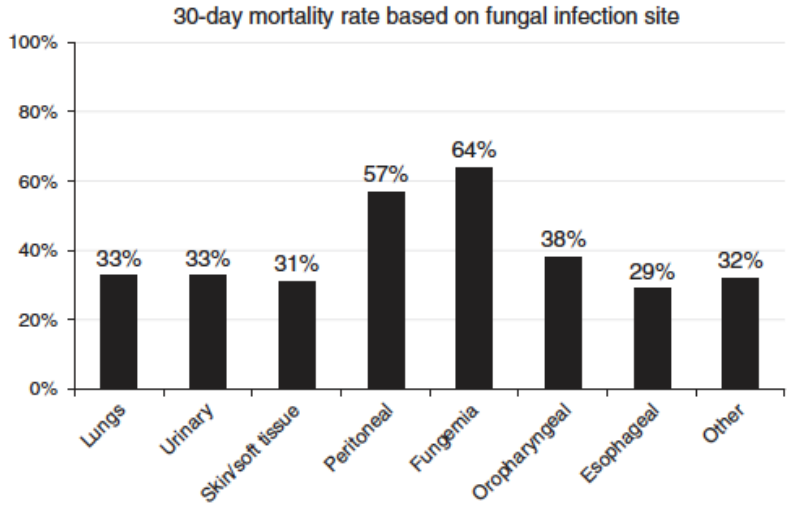
Mortalidad asociada con la infección/colonización por hongos en el ACLF



Fernandez et al. Gut 2018

IFI: pronóstico





Gustot et al, J Hepatol 2014, Bajaj et al Am J Gastroenterol 2017

Conclusiones

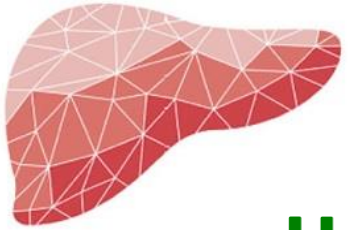
- Las infecciones bacterianas son extremadamente frecuentes en la cirrosis descompensada y frecuentemente causan o complican la evolución de los pacientes con AD y ACLF.
- Su patogenia es multifactorial. Elemento primordial en infecciones espontáneas: translocación bacteriana.
- Su prevalencia es especialmente alta en pacientes con ACLF grave.
- La resistencia antibiótica constituye un problema especialmente prevalente y relevante en el paciente cirrótico. Estas infecciones aumentan el riesgo de shock, ACLF y la mortalidad a corto plazo
- El tipo de BMR varía de manera marcada entre regiones y hospitales. Las coberturas antibióticas empíricas deben adaptarse a la epidemiologia local y a la gravedad de la infección

Conclusiones

- Los pacientes con shock séptico deben recibir coberturas de amplio espectro adaptadas al patrón local de resistencia antibiótica
- Pautas de optimización antibiótica (empleo de altas dosis en las primeras 48-72h; infusiones continuas o extendidas de β-lactámicos) son recomendadas en la actualidad en el paciente grave.
- Los esquemas empíricos deben ser desescalados rápidamente. La duración del tratamiento debe reducirse a 5-7 días en la mayor parte de las infecciones para prevenir el desarrollo de BMR.
- Las políticas de desescalado deben basarse en pruebas microbiológicas rápidas y probablemente en la vigilancia epidemiológica.
- El tratamiento de las BMR puede requerir el empleo de nuevos antibióticos activos frente a bacilos gram-negativos (ceftazidima-avibactam, ceftolozano-tazobactam, cefiderocol, etc.) o CGP (ceftarolina, ceftobiprole, tedizolid, etc.).
- La infección fúngica suele complicar la evolución de los pacientes con ACLF y se asocia a un mal pronóstico.

Bibliografía principal

- Fernández J, Piano S, Bartoletti M, Wey EQ. Management of bacterial and fungal infections in cirrhosis: the MDRO challenge. J Hepatol 2021; in press.
- Fernández J, Bert F, Nicolas-Chanoine MH. The challenges of multi-drug-resistance in hepatology. J Hepatol 2016;65:1043-1054.
- Rajiv Jalan; Javier Fernández; Reiner Wiest; et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013.Journal of hepatology. 60 - 6, pp. 1310 - 1334. 06/2014. ISSN 1600-0641.
- EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406-460.
- https://easl.eu/publications/clinical-practice-guidelines/.
- https://www.aasld.org/publications/practice-guidelines.
- http://ww2.aeeh.es/guías-clínicas/



MÁSTER EN HEPATOLOGÍA

UAM
Universidad Autónoma de Madrid

Universidad de Alcalá