PHC 2018 – www.aphc.info

Bacterial infections complicating cirrhosis

P. Angeli, Dept. of Medicine,
Unit of Internal Medicine and Hepatology (UIMH),
University of Padova (Italy)
pangeli@unipd.it

Agenda

- Epidemiology
- Risk factors and prevention
- Impact on outcome
- Treatment

Inernational Club of Ascites: “The Global Study”

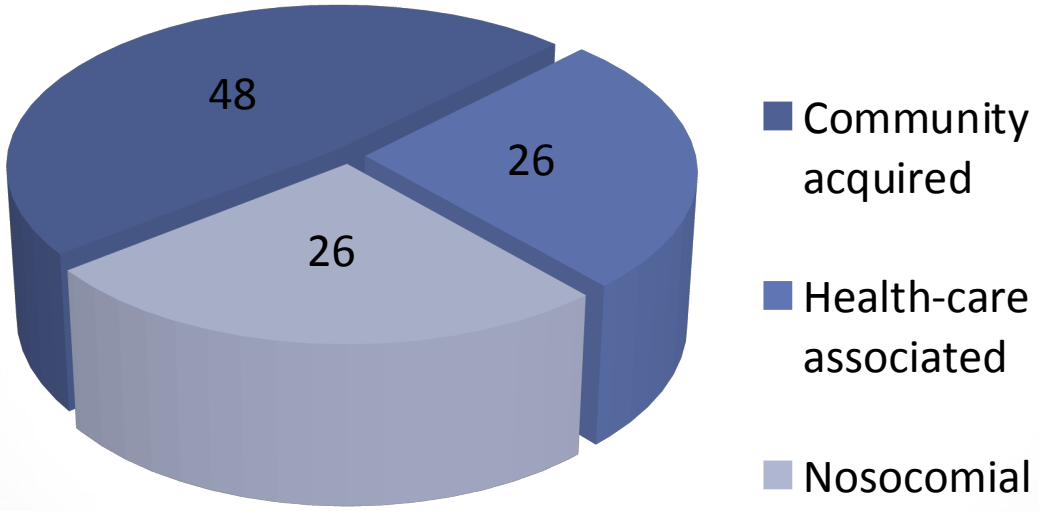
"The Global Study": Baseline features

Variables	N= 1,302
Geographic area – n (%) America Asia Europe	 321 (25) 416 (32) 565 (43)
Age (years) – mean (SD)	57 (13)
Gender (Male) – n (%)	898 (69)
Etiology of cirrhosis – n (%) Alcohol HCV HBV NASH	 674 (52) 193 (20) 96 (8) 128 (10)
Ascites – n (%)	1,002 (77)
ACLF – n (%)	460 (35)
MELD score – mean (SD)	21 (8)

(data from S. Piano et al. "Global study" ; EASL : 2017)

“The Global Study”: Classification of bacterial and/or fungal infections

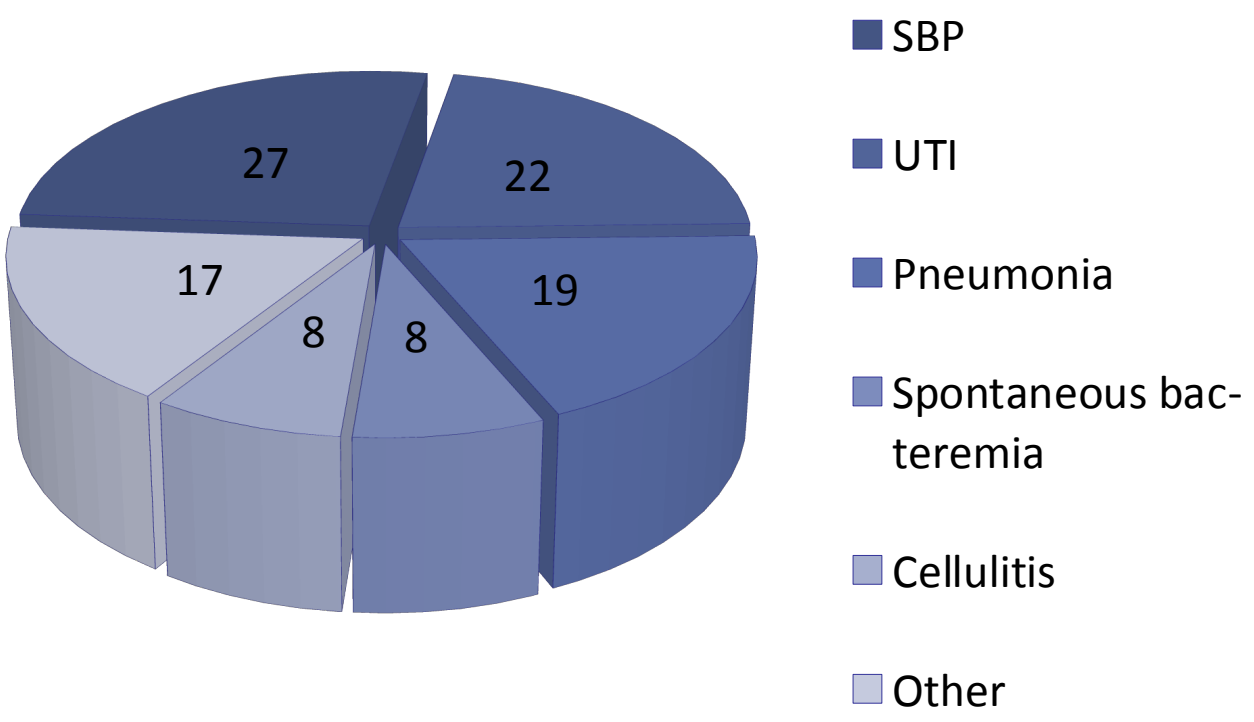
%



(data from S. Piano et al. “Global study” ; EASL : 2017)

"The Global Study": Classification of bacterial and/or fungal infections

%



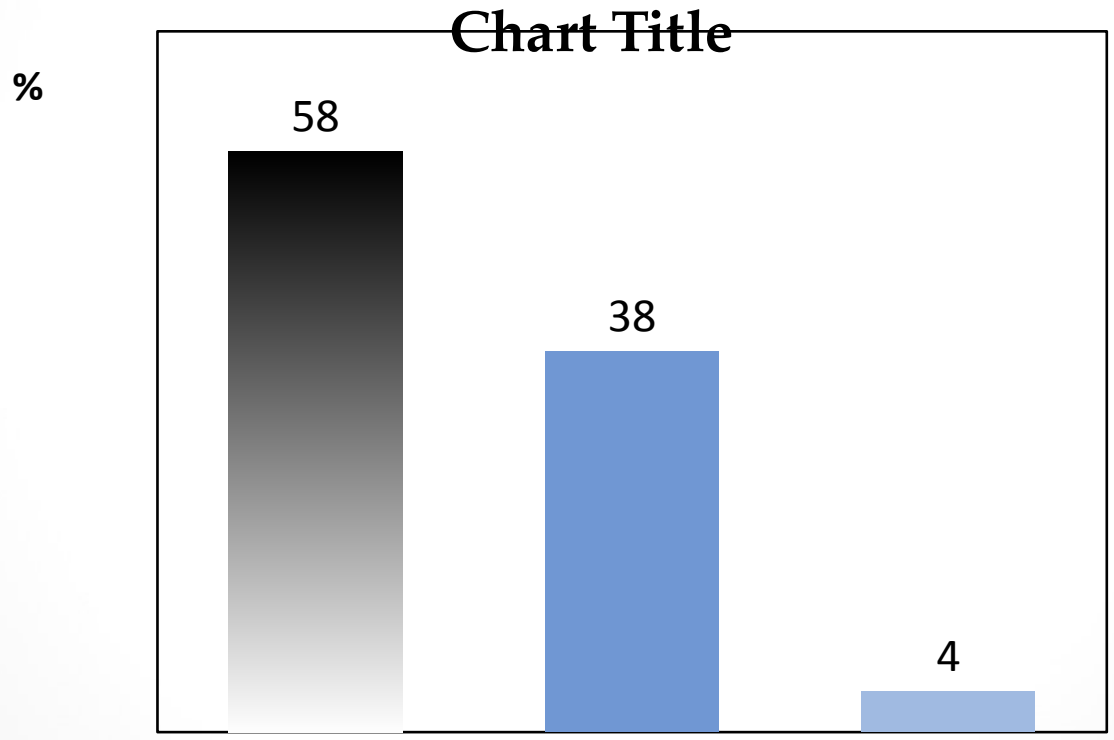
(data from S. Piano et al. "Global study" ; EASL : 2017)

"The Global Study": Characteristics of bacterial and/or fungal infections

Variables	N= 1,302
SIRS – n (%)*	405 (36)
qSOFA – n (%)*	255 (23)
Septic shock – n (%)	174 (13)
Positive cultures – n (%)	740 (57)
Number of bacteria per patient – n (%) - one - more than one	 592 (80) 148 (20)
Number of bacteria isolated (available in 1,119 patients) – n	959

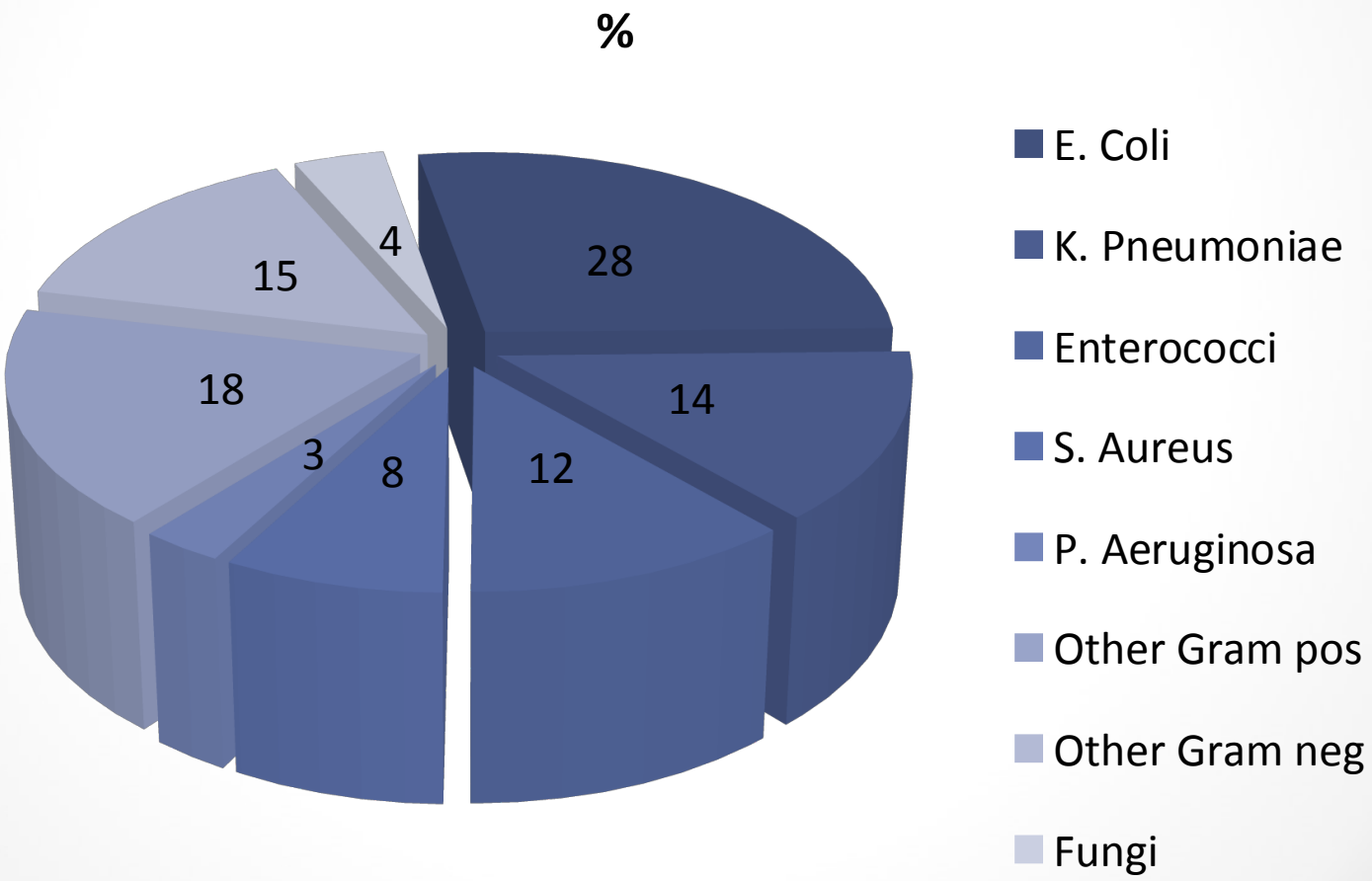
(data from S. Piano et al. "Global study" ; EASL : 2017)

"The Global Study": Type of microrganisms isolated



(data from S. Piano et al. "Global study" ; EASL : 2017)

"The Global Study": Etiology of bacterial and/or fungal infections



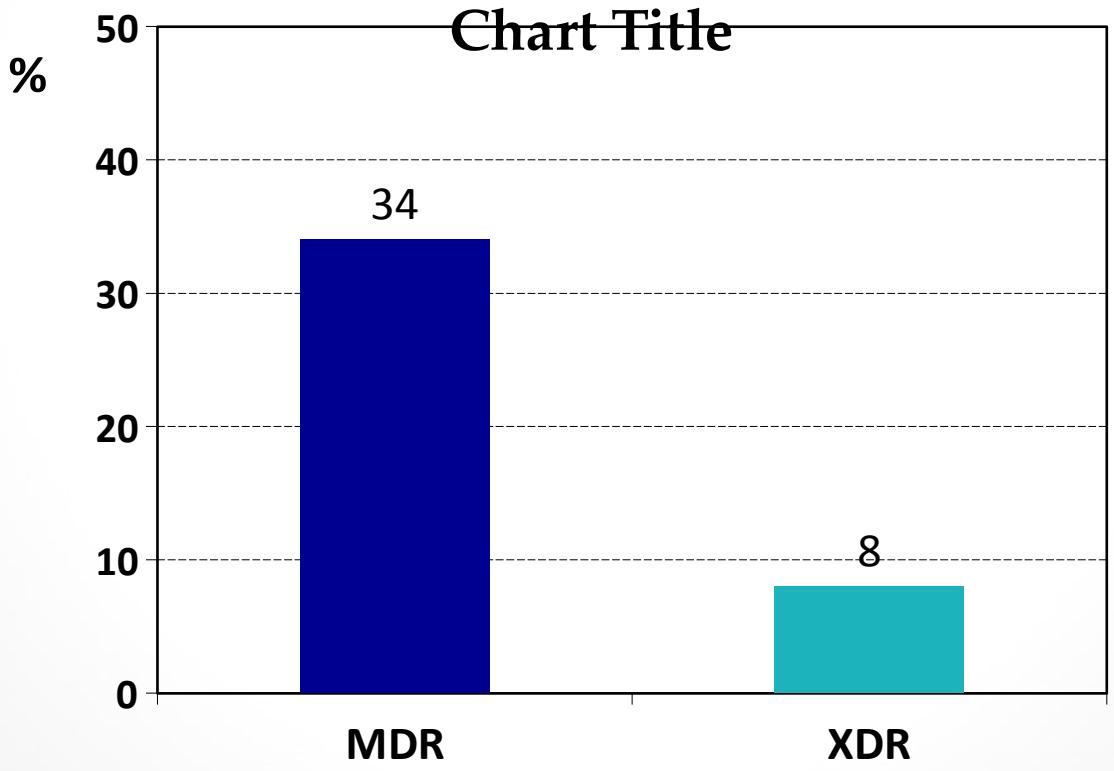
(data from S. Piano et al. "Global study" ; EASL : 2017)

Definitions of drug-resistant bacteria

- **MDR** was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories**.**
- **XDR** was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories**.**
- **PDR** was defined as non-susceptibility to all agents in all antimicrobial categories.

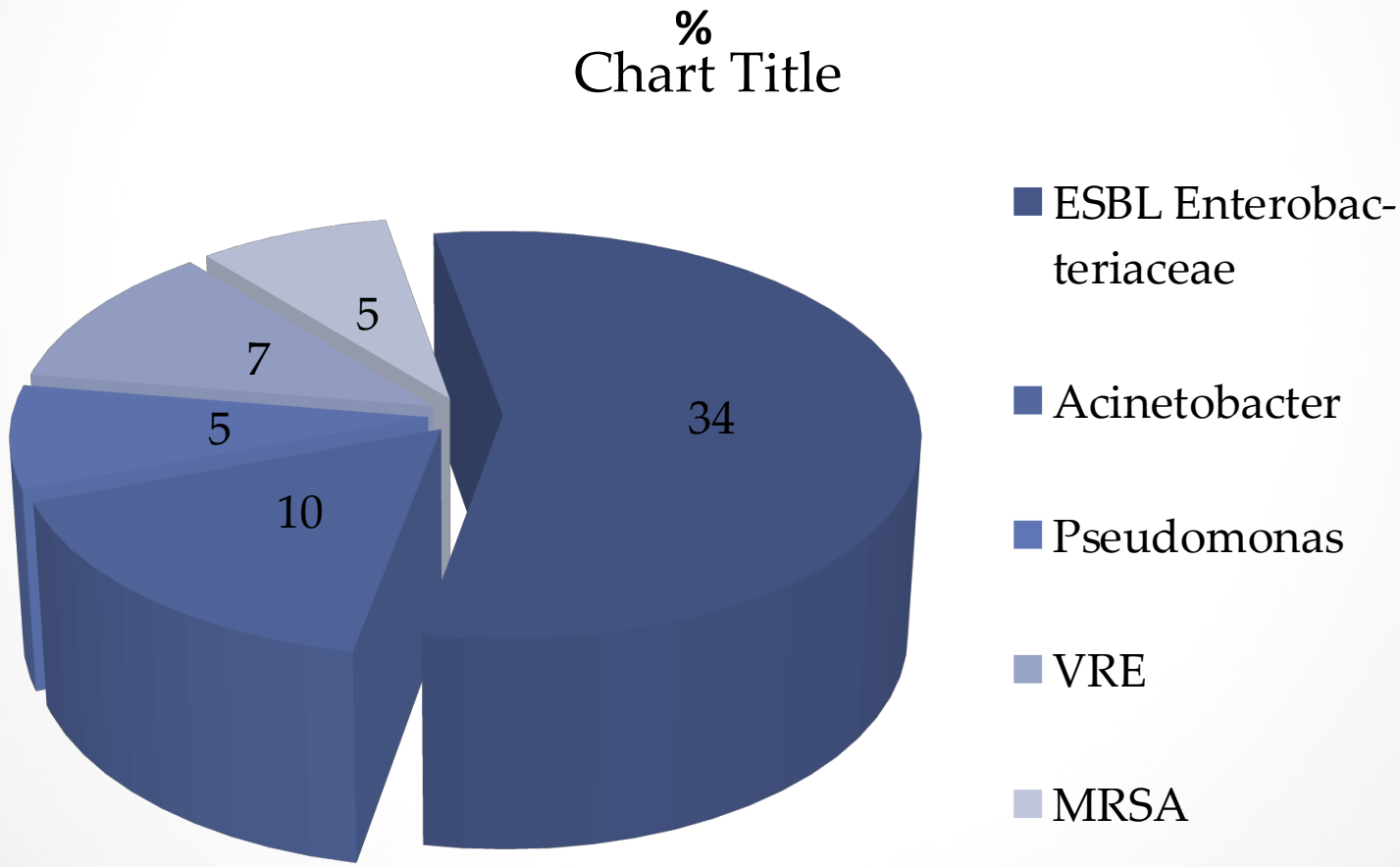
A.P. Magiorakos et al. Clin Microbiol Infect 2012 ; 18 : 268–281

Prevalence of multi drug resistant (MDR) and extensively drug resistant (XDR) bacteria

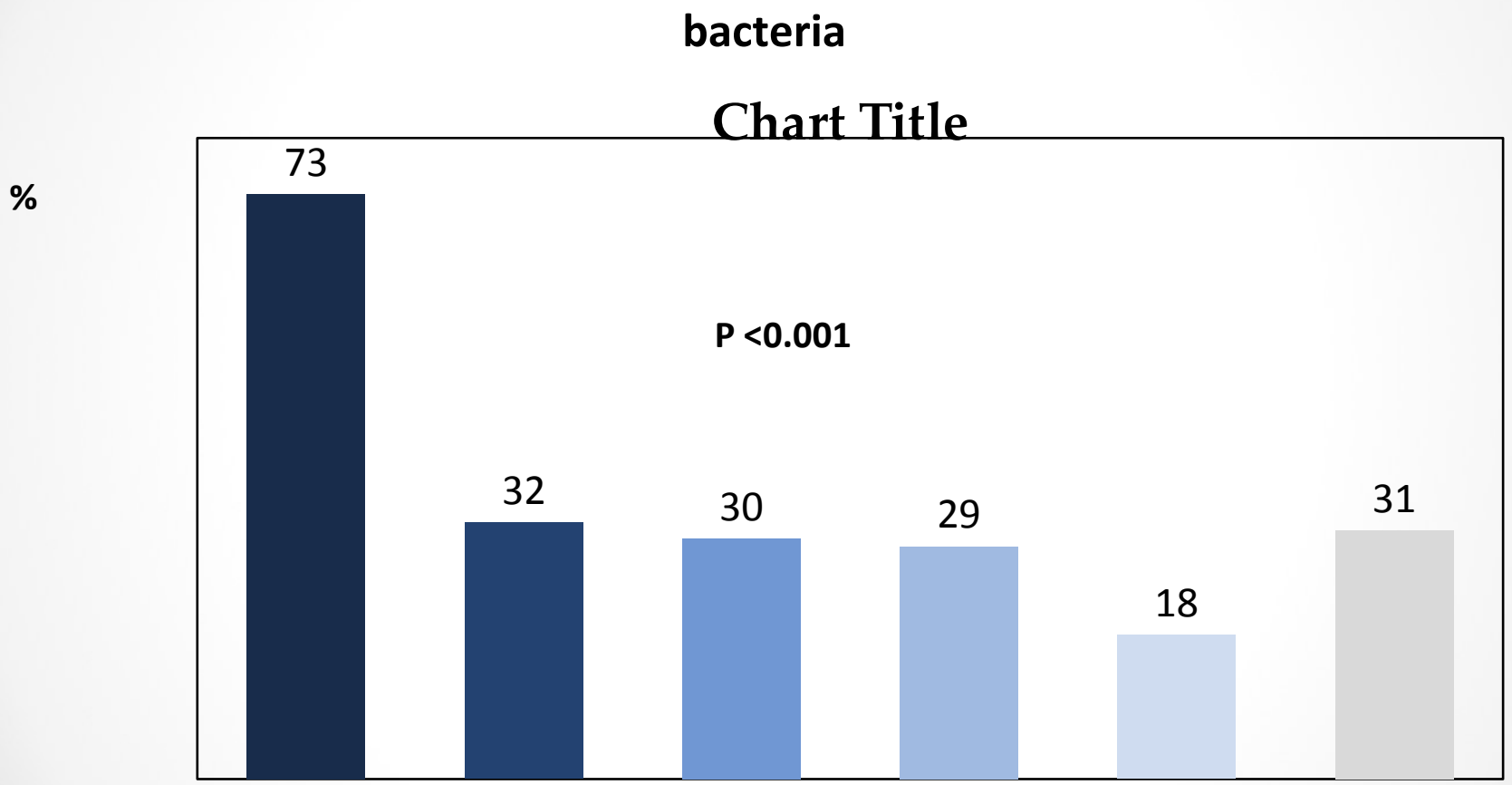


(data from S. Piano et al. "Global study" ; EASL : 2017)

"The Global Study": Types of MDR bacteria

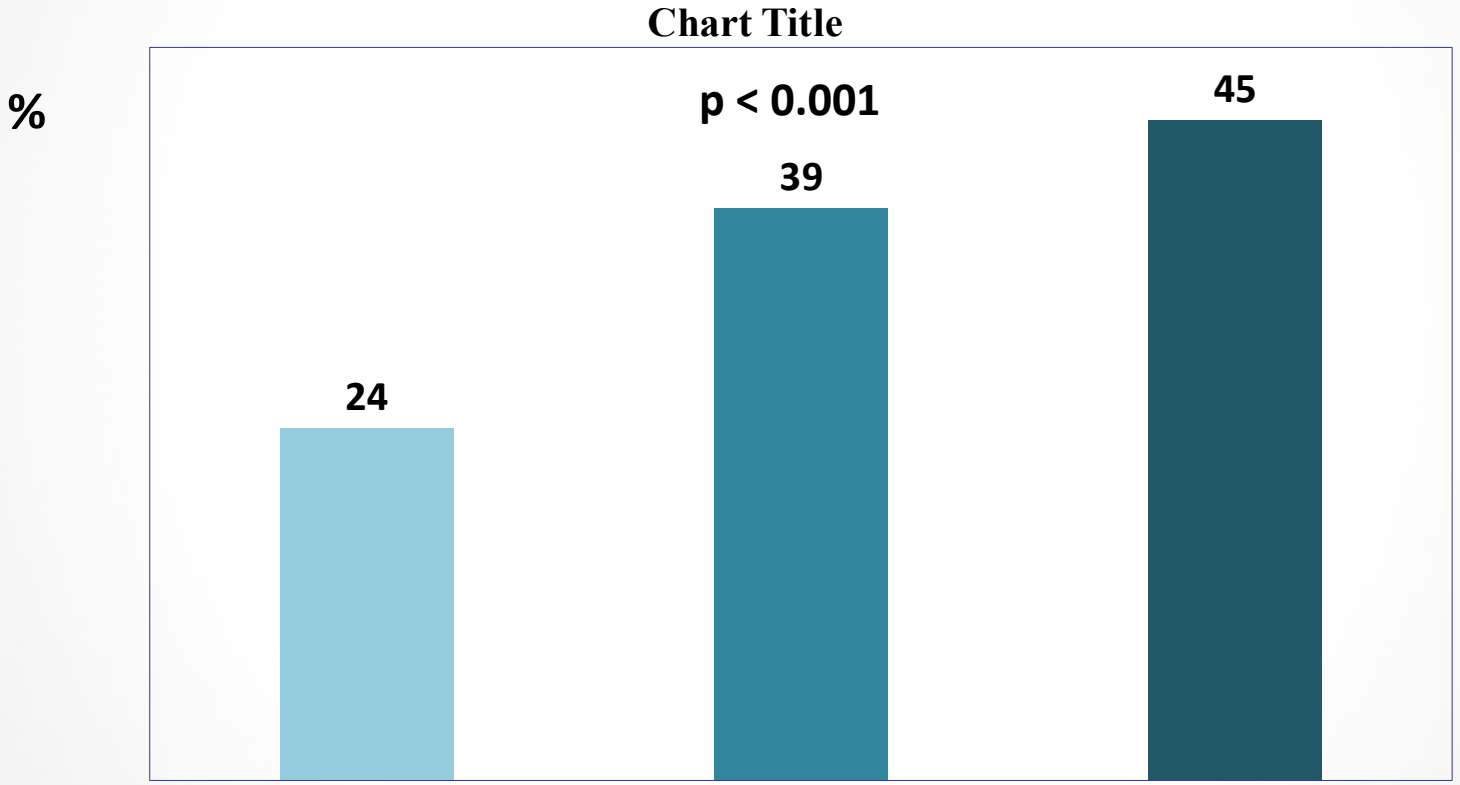


(data from S. Piano et al. "Global study" ; EASL : 2017)



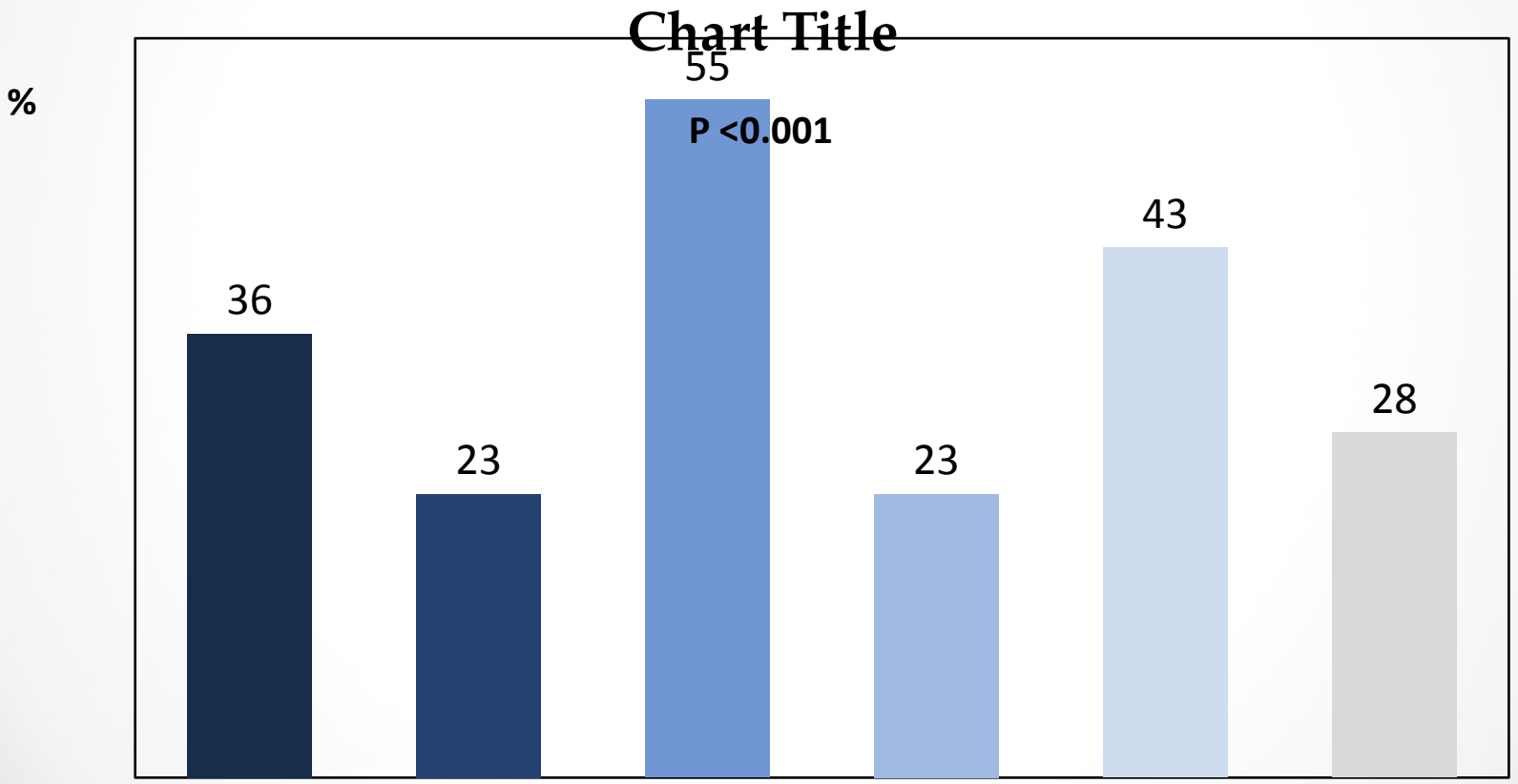
(data from S. Piano et al. "Global study" ; EASL : 2017)

Prevalence of MDR bacteria according to health care exposure



(data from S. Piano et al. "Global study" ; EASL : 2017)

"The Global Study": Prevalence of infections sustained by MDR bacteria according to the types of infection



(data from S. Piano et al. "Global study" ; EASL : 2017)

Agenda

- Epidemiology
- Risk factors and prevention

Risk factors for MDR bacteria in patients with positive cultures (N=740)

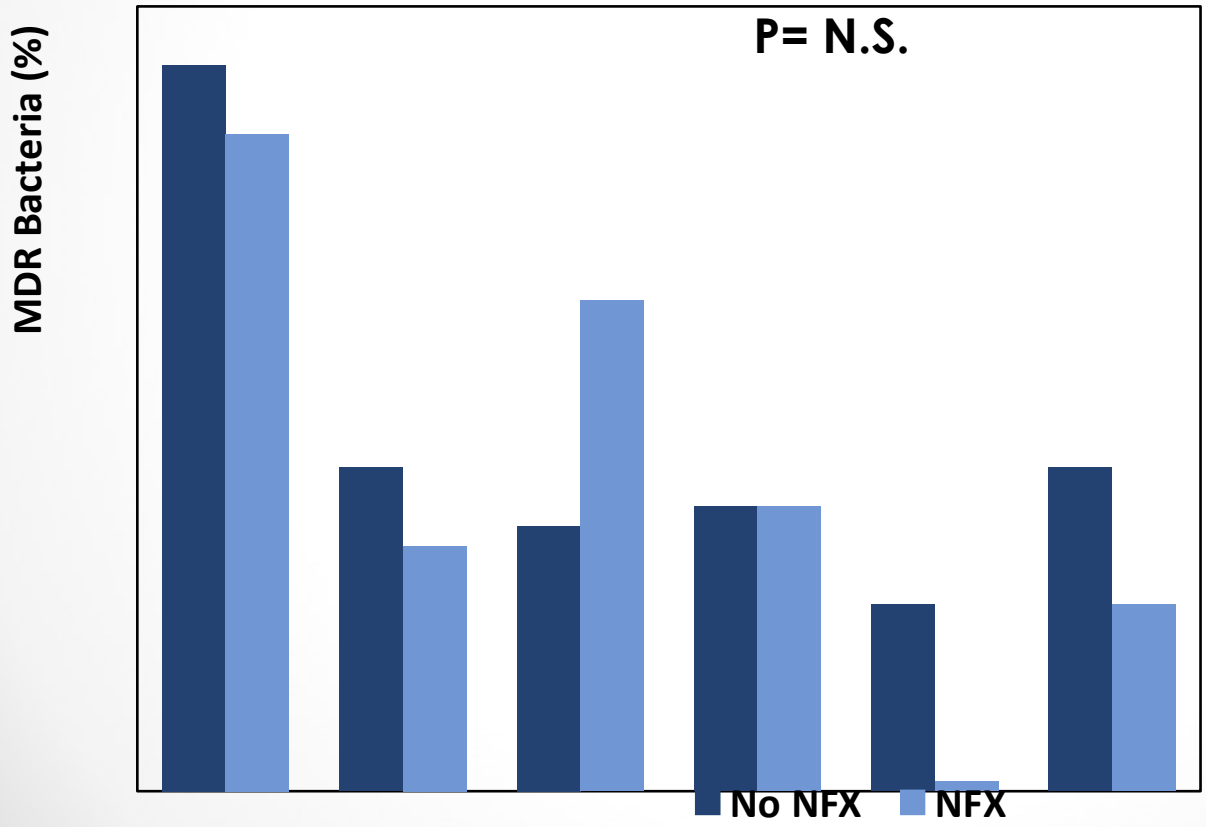
Variables	No MDR	MDR	P
Norfloxacin prophylaxis – n (%)	45 (9)	21 (8)	0.772
Treatment with rifaximin – n (%)	147 (30)	81 (32)	0.669
Isolation of MDR bacteria in the previous 6 months – n (%)	29 (6)	22 (9)	0.214
Use of antibiotics in the previous 3 months – n (%)	186 (38)	156 (62)	<0.001
Invasive procedures in the previous month – n (%)	188 (39)	143 (57)	<0.001
MELD score – m (SD)	20 (8)	22 (8)	0.023

(data from S. Piano et al. "Global study" ; EASL : 2017)

Probability of death according to the use of Norfloxacin or Placebo in patients with Child-Pugh Class C Cirrhosis

Courtesy of R. Moreau et al.(unpublished results).

MDR bacteria according to norfloxacin (NFX) prophylaxis in different countries (N=740)

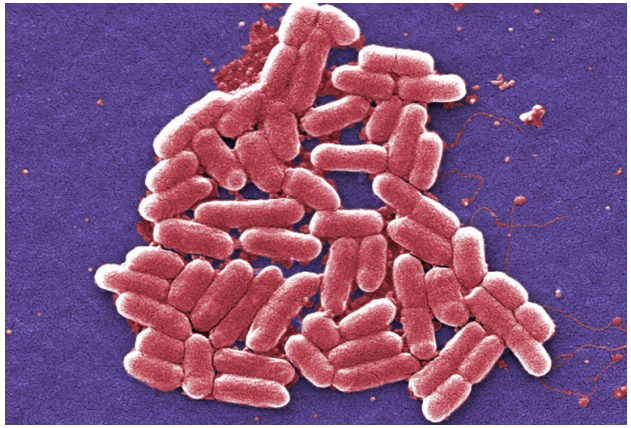


(data from S. Piano et al. "Global study" ; EASL : 2017)

The New York Times The New York Times | https://nyti.ms/1Wo9Yu7

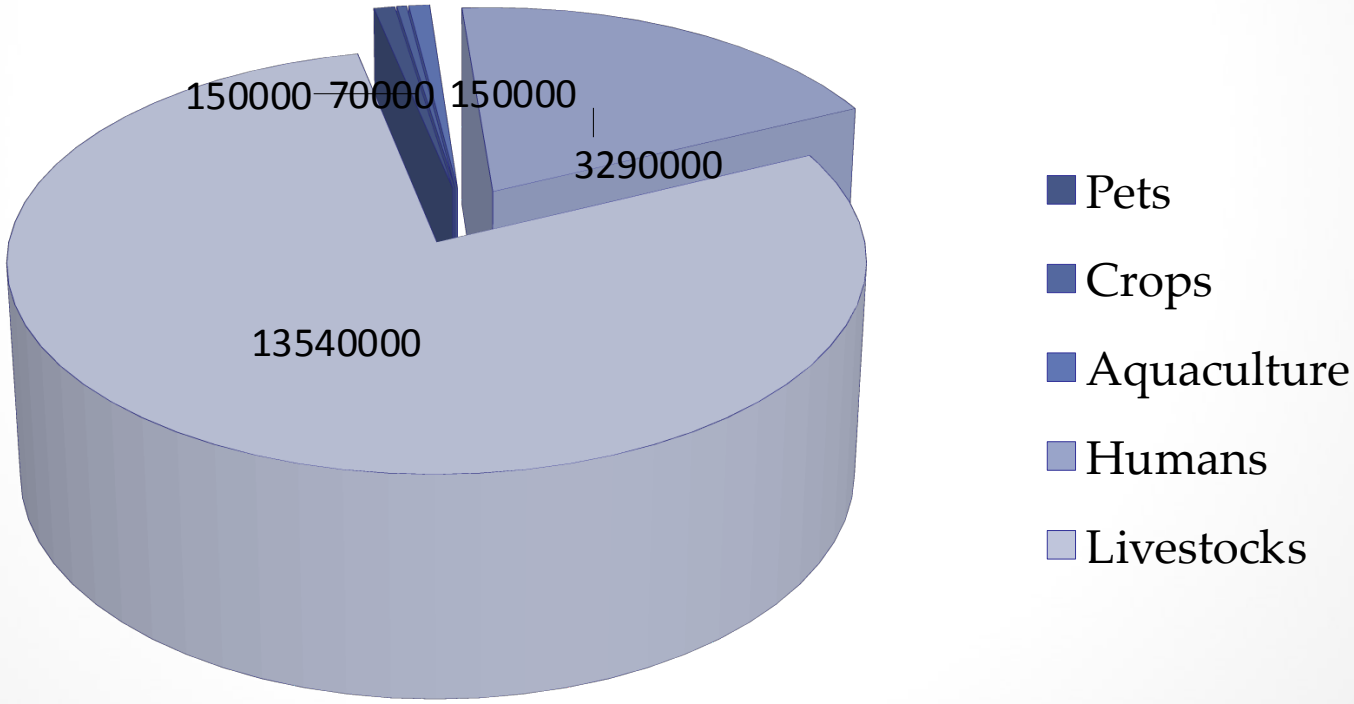
HEALTH

Infection Raises Specter of Superbugs Resistant to All Antibiotics



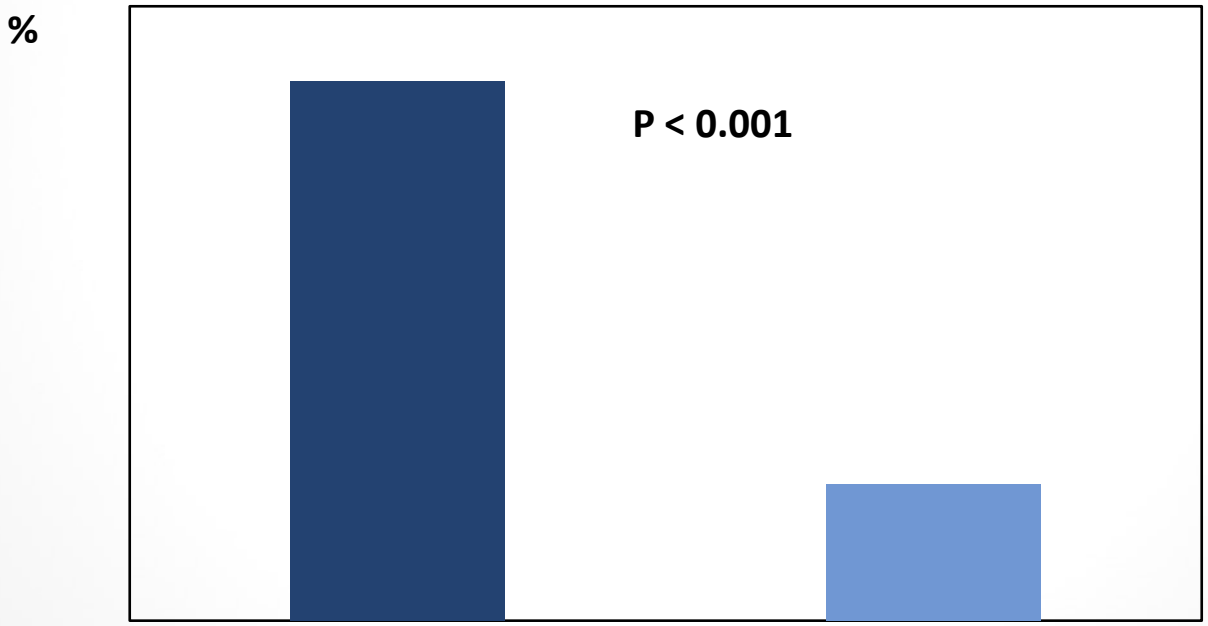
By SABRINA TAVERNISE and DENISE GRADY MAY 26, 2016

Estimated annual antibiotic use (Kg) in the United States



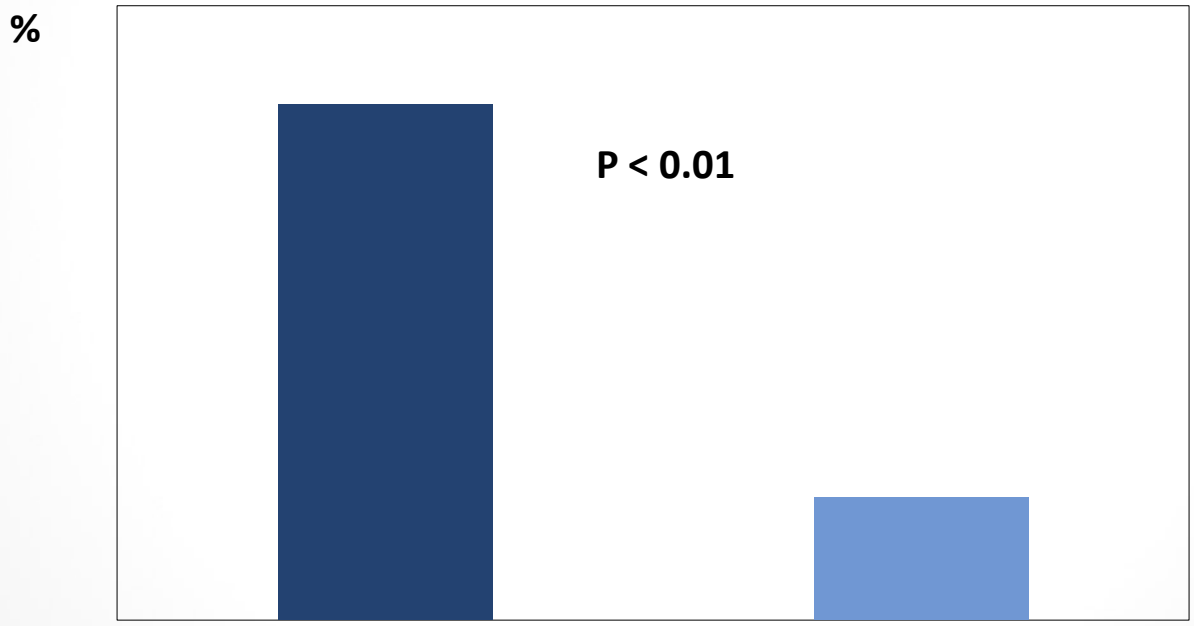
A. Hollis et al. NEJM 2013 ; 369 : 2474-2476

Isolation of ESBL + E.Coli in pigs from farms according to the use of 3rd generation cephalosporins



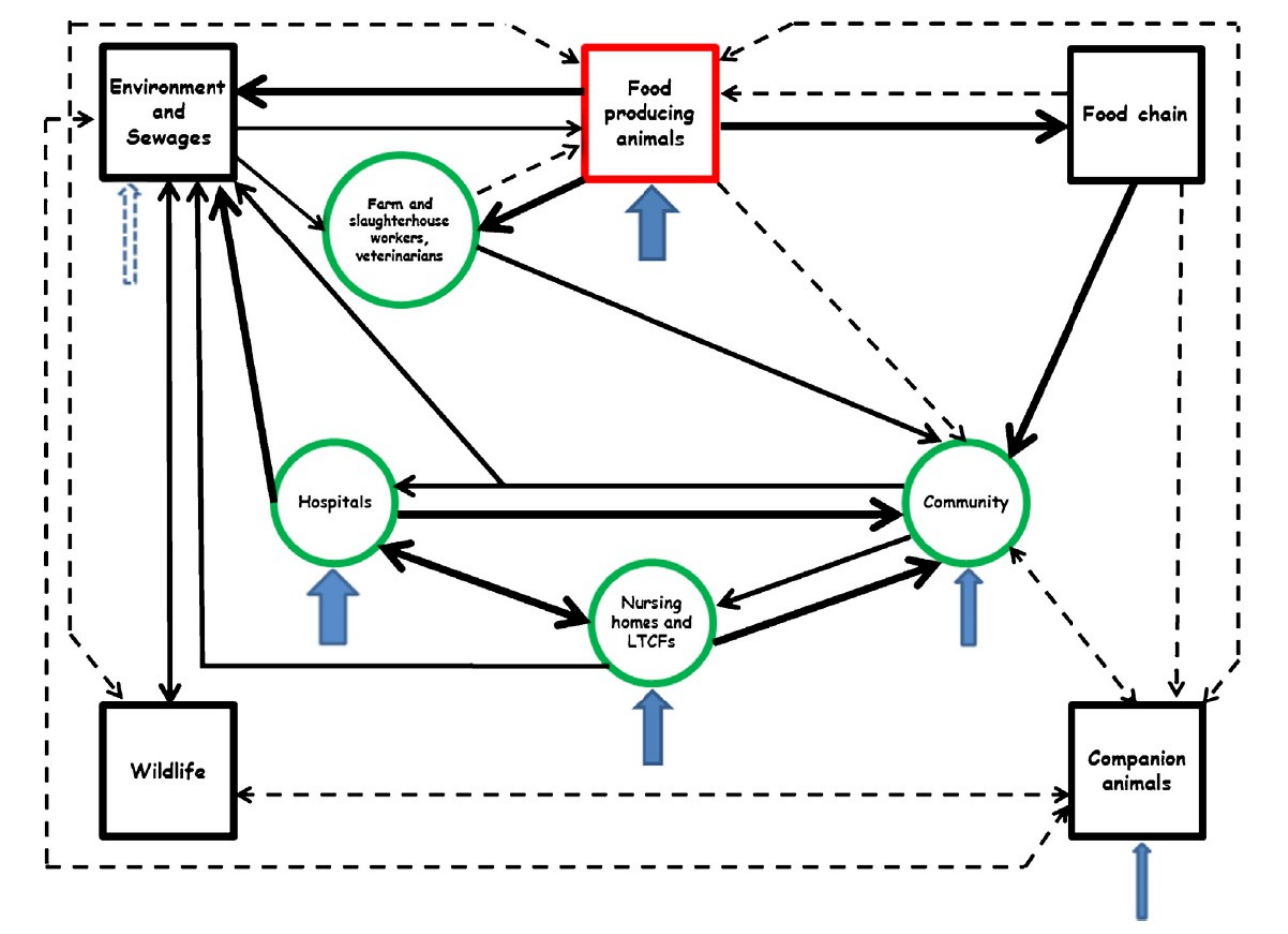
AM. Hammerum et al. J Antimicrob Chemother. 2014 ; 69 : 2650-2657.

Isolation of ESBL + E.Coli in farmers according to the isolation of ESBL+ E.Coli in pigs



AM. Hammerum et al. J Antimicrob Chemother. 2014 ; 69 : 2650-2657.

Settings contributing to the pool of antimicrobial resistance and transmission of MDR bacteria



S.N. Seiffert et al. / Drug Resistance Updates 2013 ; 16 : 22– 45.

Independent predictors of infections sustained by MDR bacteria

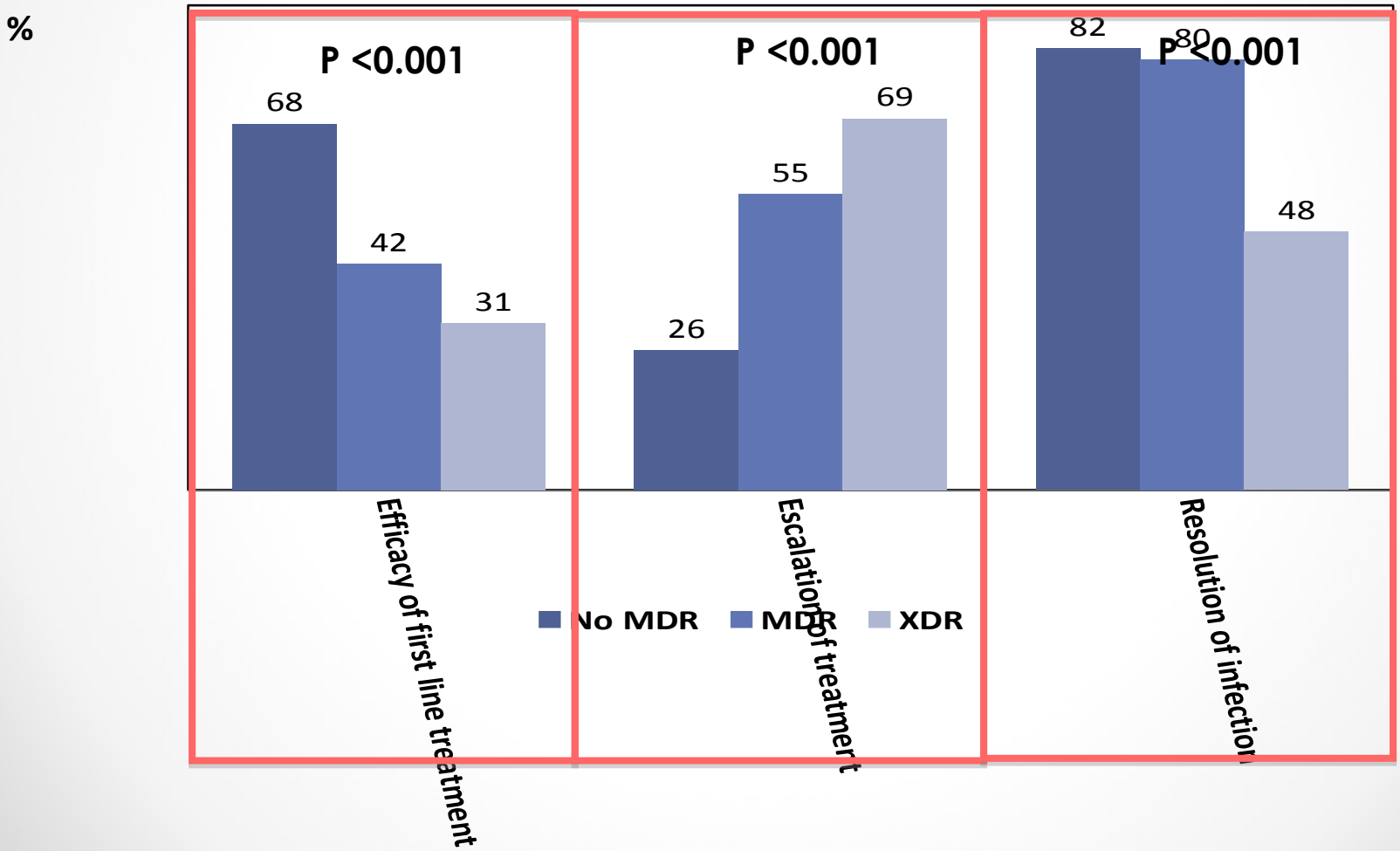
Variables	OR	95% CI	P
Geographic area			
South America	2.23	0.99 – 5.00	0.053
India	7.94	3.30 – 19.11	<0.001
Other Asian Countries	2.79	1.20 – 6.46	0.017
Type of infection			
UTI	2.48	1.59 – 3.87	<0.001
Pneumonia	3.20	1.83 – 5.59	<0.001
Cellulitis	2.92	1.41 – 6.07	0.004
Use of antibiotics in the previous 3 months	1.92	1.32 – 2.80	0.001
Health care exposure			
HCA	1.62	1.04 – 2.52	0.032
Nosocomial	2.65	1.75 – 4.01	<0.001

(data from S. Piano et al. "Global study" ; EASL : 2017)

Agenda

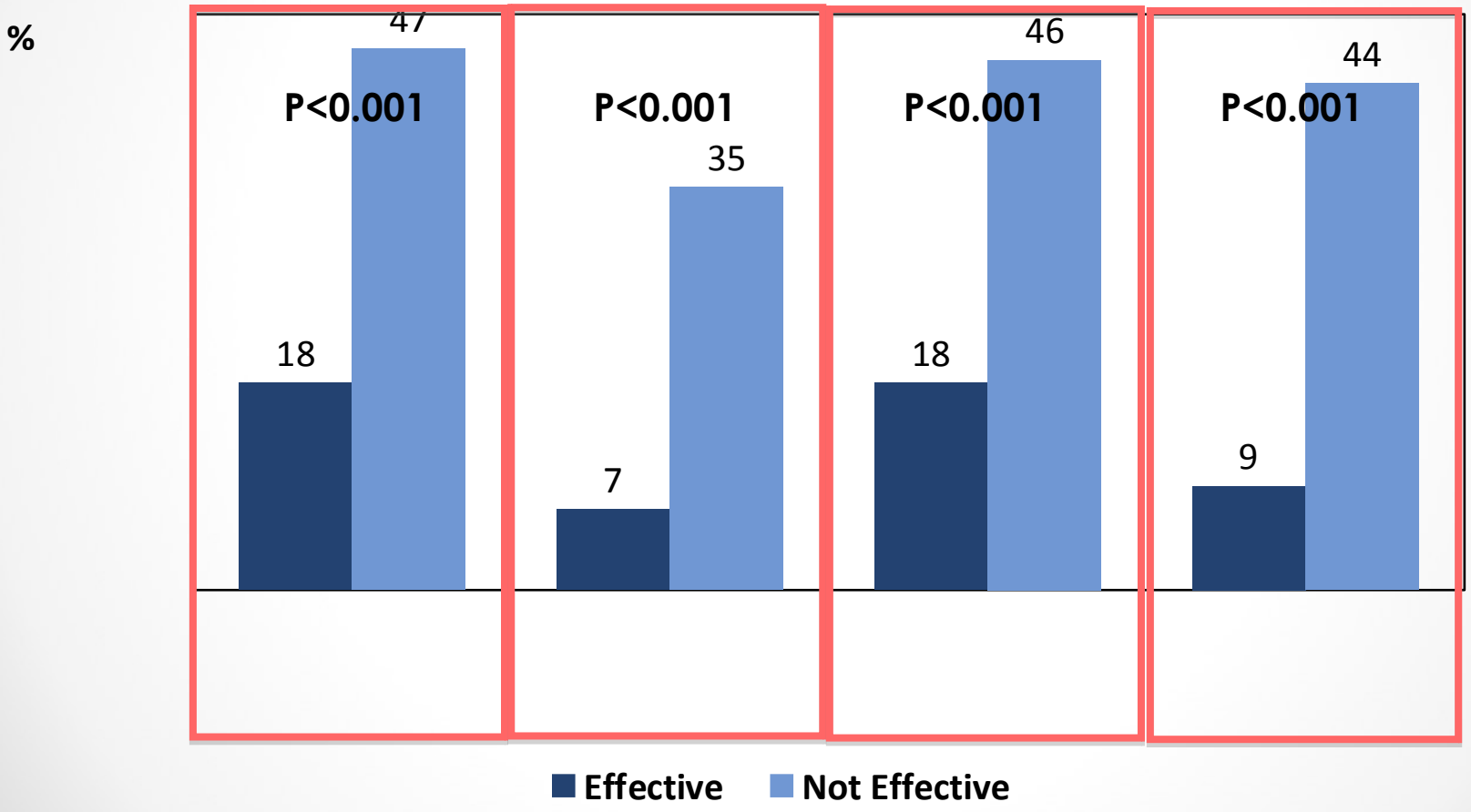
- Epidemiology
- Risk factors and prevention
- Impact on outcome

Events related to treatment according to MDR and XDR bacterial infection



(data from S. Piano et al. "Global study" ; EASL : 2017)

Events according to the efficacy of first line treatment

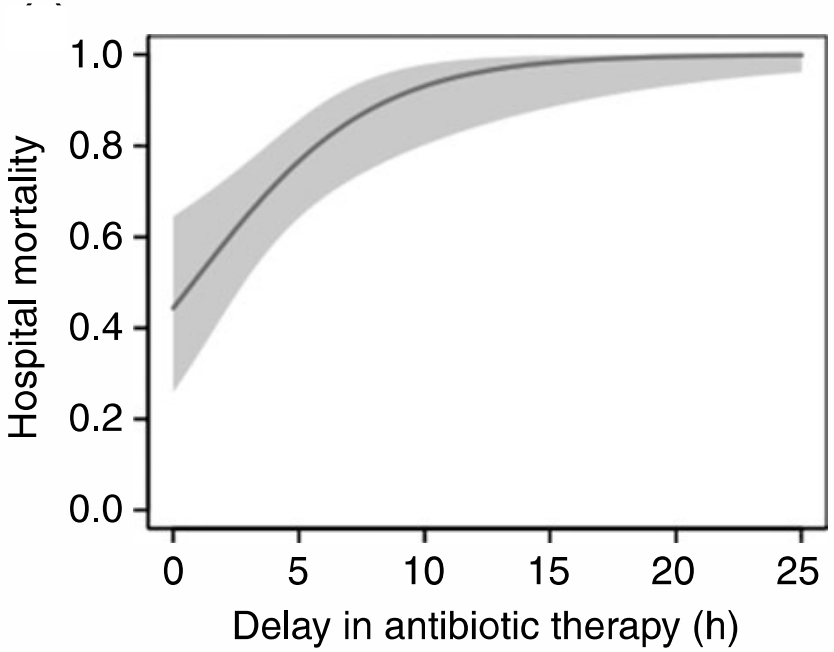


(data from S. Piano et al. "Global study" ; EASL : 2017)

Agenda

- Epidemiology
- Risk factors and prevention
- Impact on outcome
- Treatment/prevention

Effect of the delay in antimicrobial therapy on inhospital mortality in patients with SBP related septic shock



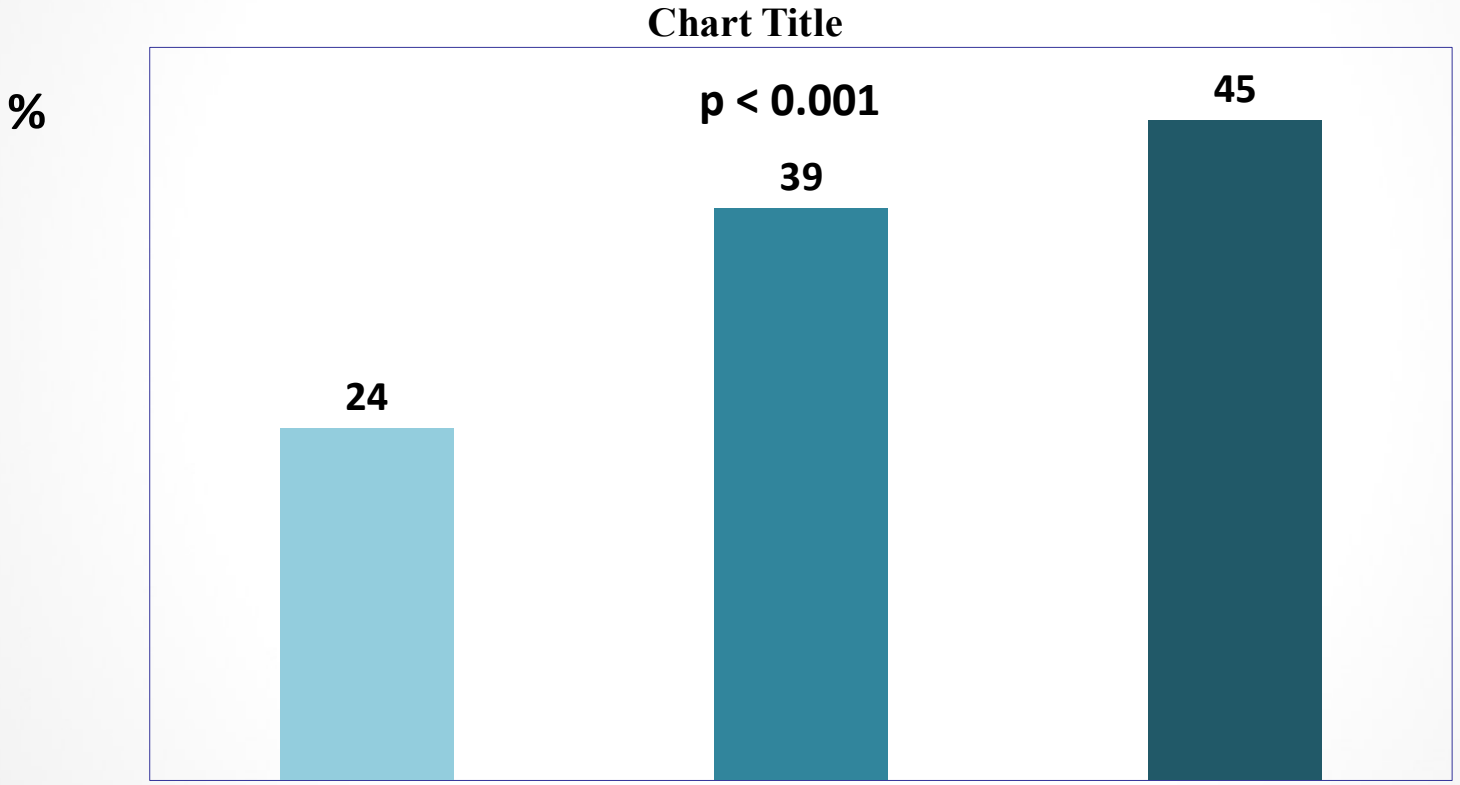
C. J. Karvellas et al. APT ; 2015 ; 41 : 747-757.

Classification of bacterial infections

- **Infections are defined as community-acquired** if they were diagnosed within 48-72 hours of admission without hospitalizations in the previous 6 months.
- **Infections are defined as Healthcare-associated** (HCA) if they were diagnosed within 48-72 hours of admission in patients with at least two days of hospitalization in the previous 6 months.
- **Infections are defined as nosocomial** if they were diagnosed beyond 48-72 hours of admission.

J.S. Bajaj et al. Hepatology 2012 : 56 : 2328-2335

Prevalence of MDR bacteria according to health care exposure



The quick SOFA score (qSOFA)

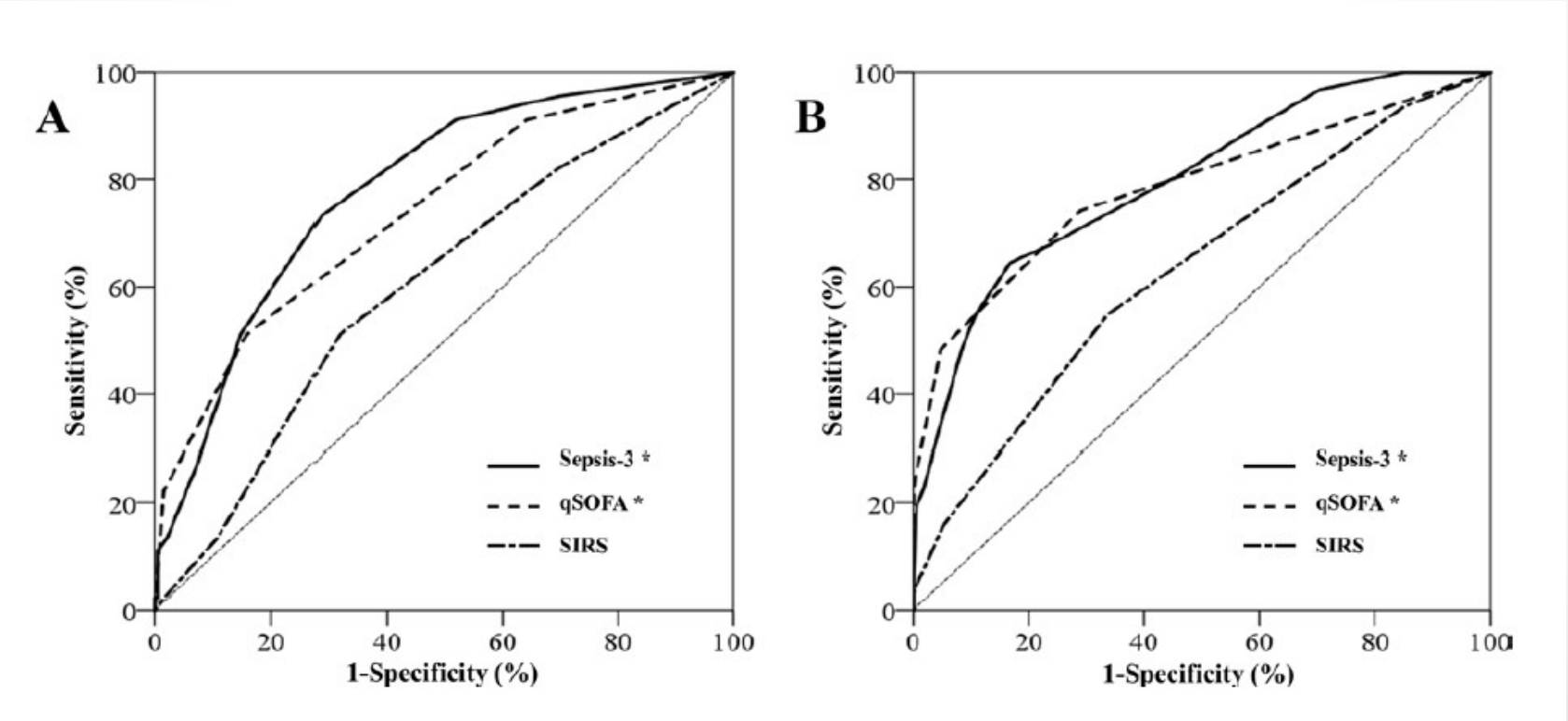
- or low blood pressure (SBP≤100 mmHg),
- or high respiratory rate (≥22 breaths per min),
- or altered mentation (Glasgow coma scale<15).

The Sepsis 3 criterium

Increase of Sequential Organ Failure Assessment (SOFA) ≥2 points from baseline consequent to infection

M. Singer et al. JAMA 2016 ; 315 : 801-810.

The quick SOFA and the Sepsis 3 versus SIRS



S. Piano et al. Gut. 2017 ; [Epub ahead of print]

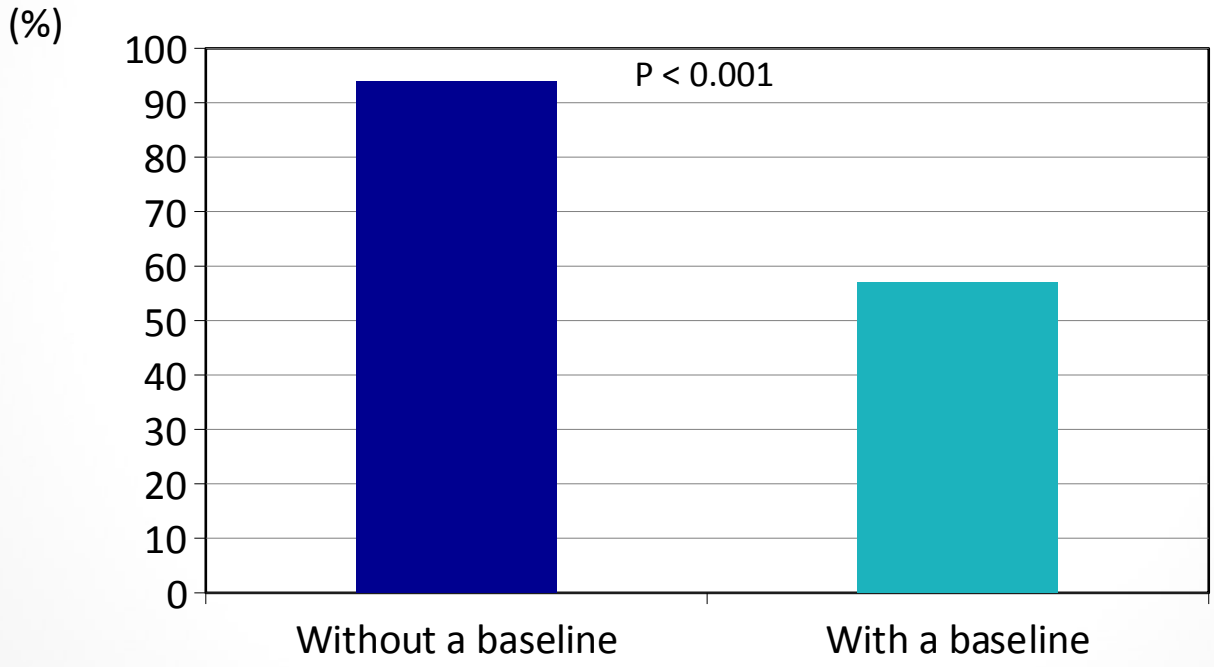
Definition of organ failure: the Clif-SOFA score

Table 1. The Chronic Liver Failure (CLIF)-Sequential Organ Failure Assessment (SOFA) Score

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dL)	<1.2	≥1.2 - ≤2.0	≥2.0 - <6.0	≥6.0 - <12.0	≥12.0[a]
Kidney (Creatinine, mg/dL)	<1.2	≥1.2 - <2.0	≥2.0 - <3.5[b] or use of renal-replacement therapy	≥3.5 - <5.0	≥5.0
Cerebral (HE grade)	No HE	I	II	III[c]	IV
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets≤20x10^9/L[d]
Circulation (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin[e]	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs PaO/FiO2:	>400	>300 - ≤400	>200 - ≤300	>100 - ≤200	≤100
or SpO2/FiO2	>512	>357 - ≤512	>214 - ≤357	>8 - ≤214[f]	≤89

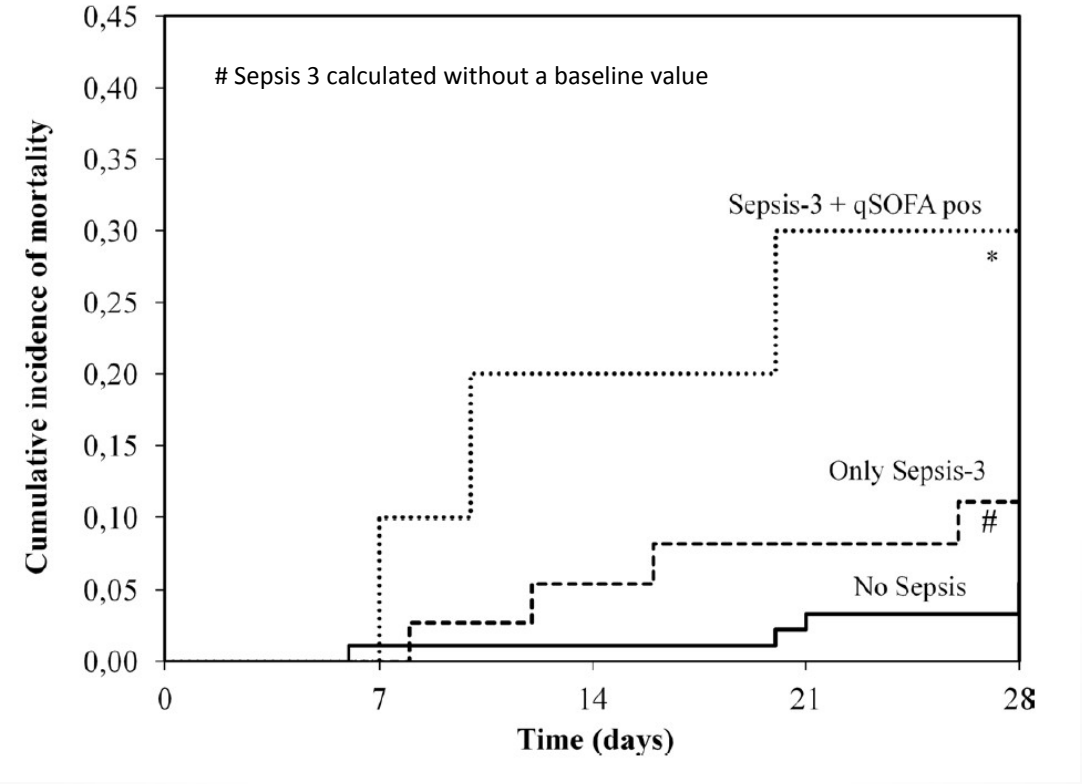
R. Moreau et al. (Canonic study) Gastroenterology 2013 ; 144 : 1426-1437

Positivity of Sepsis 3 in patients with cirrhosis and bacterial infections



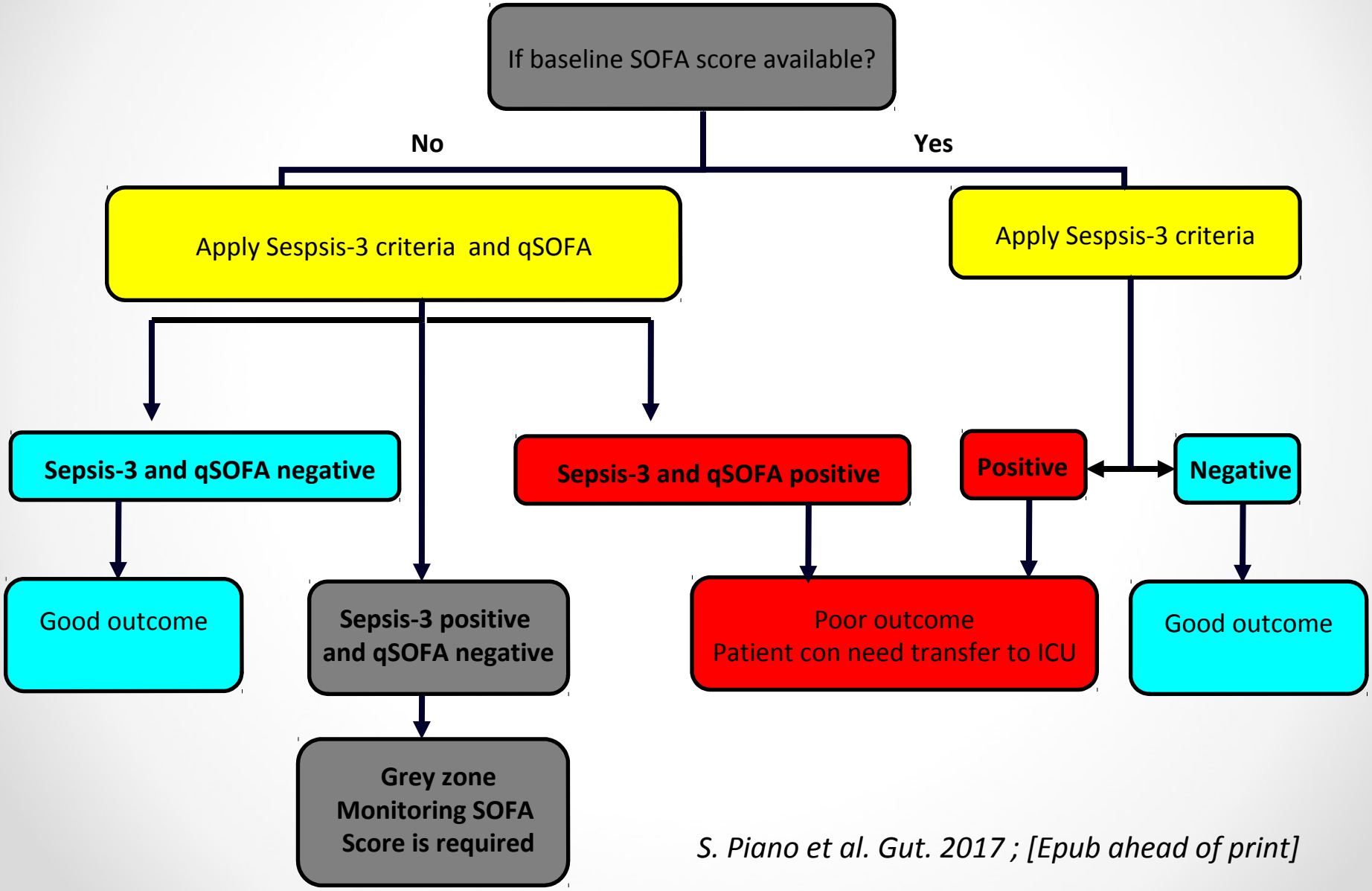
S. Piano et al. Gut. 2017 ; [Epub ahead of print]

The quick SOFA and the Sepsis 3 versus SIRS

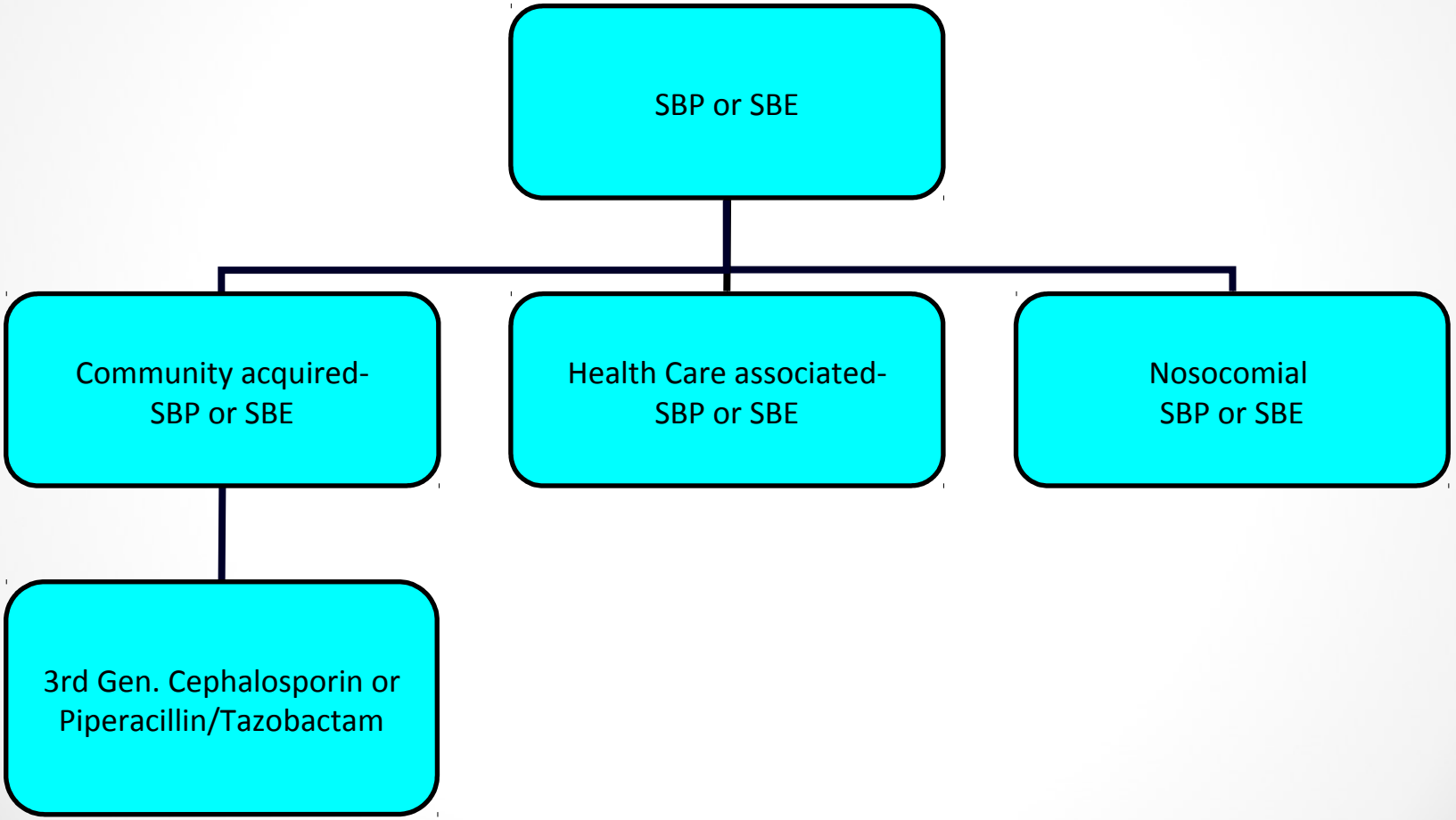


S. Piano et al. Gut. 2017 ; [Epub ahead of print]

Algorithm for the application of qSOFA and Sepsis-3 criteria in patients with cirrhosis and bacterial infections

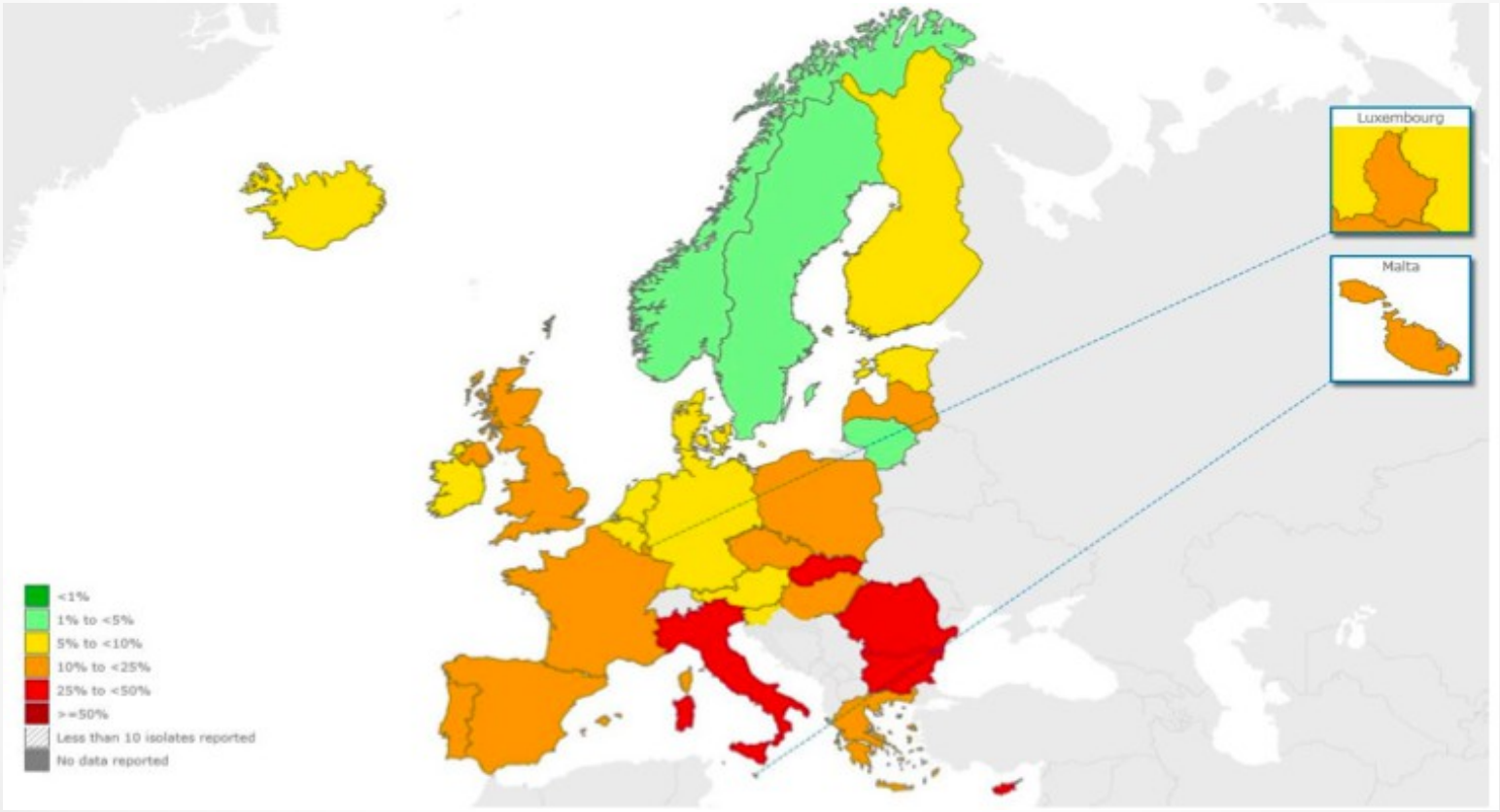


S. Piano et al. Gut. 2017 ; [Epub ahead of print]

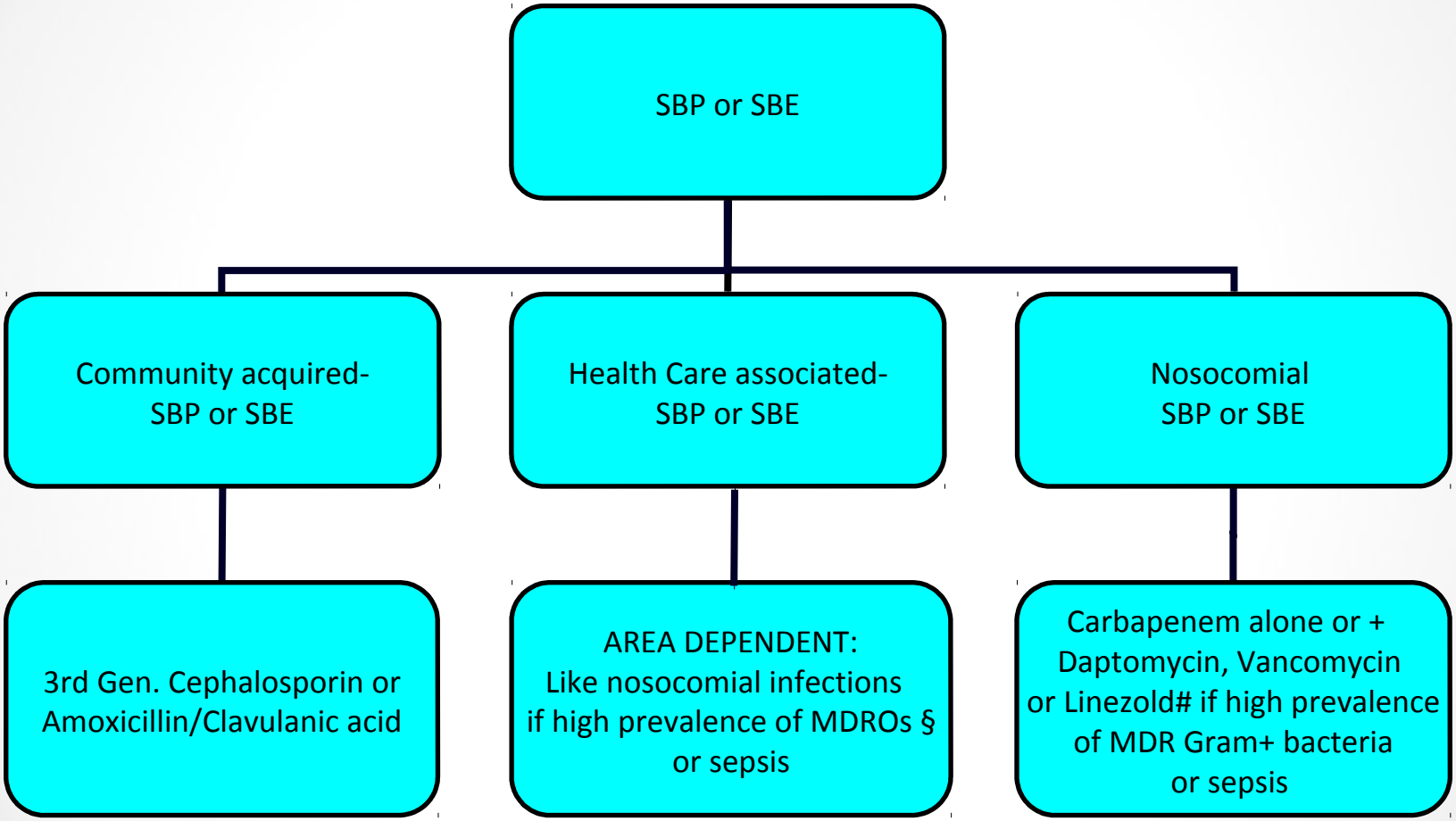


Adapted from R. Jalan et al. J. Hepatol. 2014 : 60 : 1310-1324

Escherichia coli: percentage (%) of invasive isolates with resistance to 3° generation cephalosporins by country



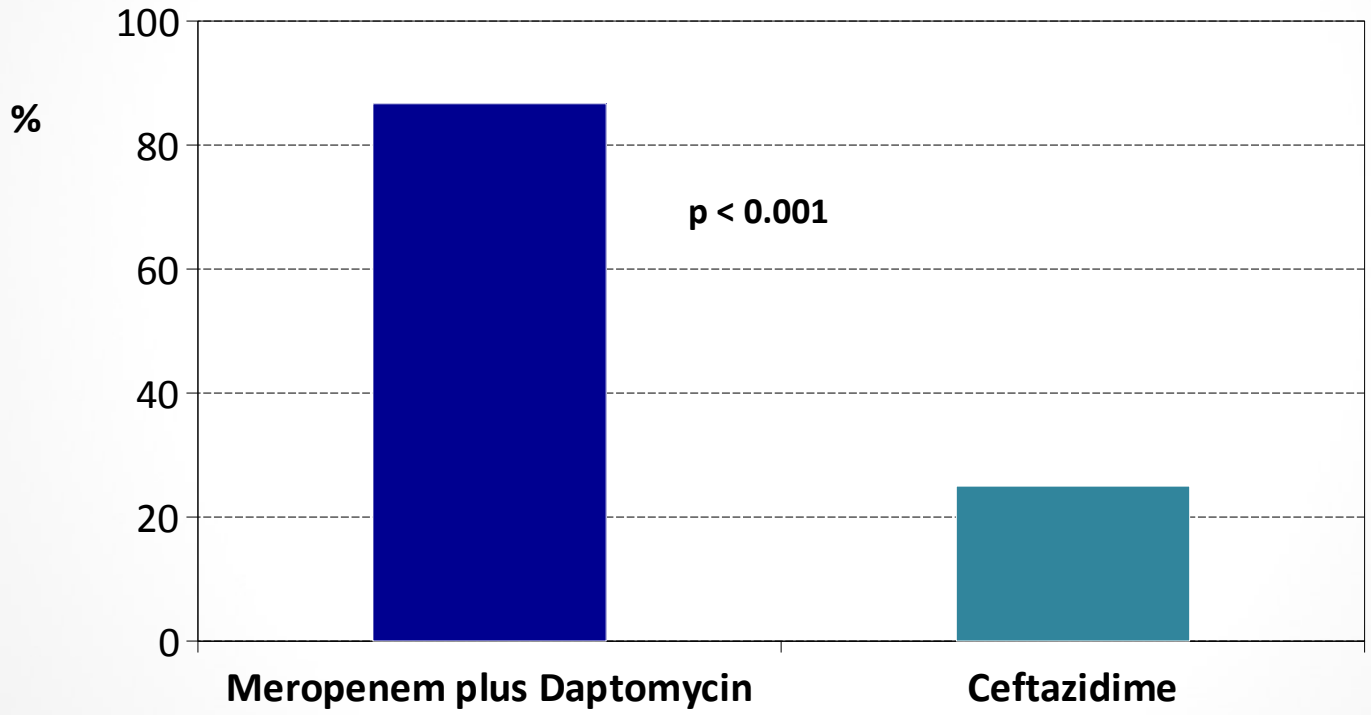
European Centre for Disease Prevention and Control, Report , 2014



§ piperacillin/tazobactam in areas with low prevalence of MDROs

***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).**

Response to first line antibiotic treatment according to the assigned group



S. Piano et al. Hepatology 2016 ; 63 : 1299-309.

Meropenem plus daptomycin for nosocomila SBP

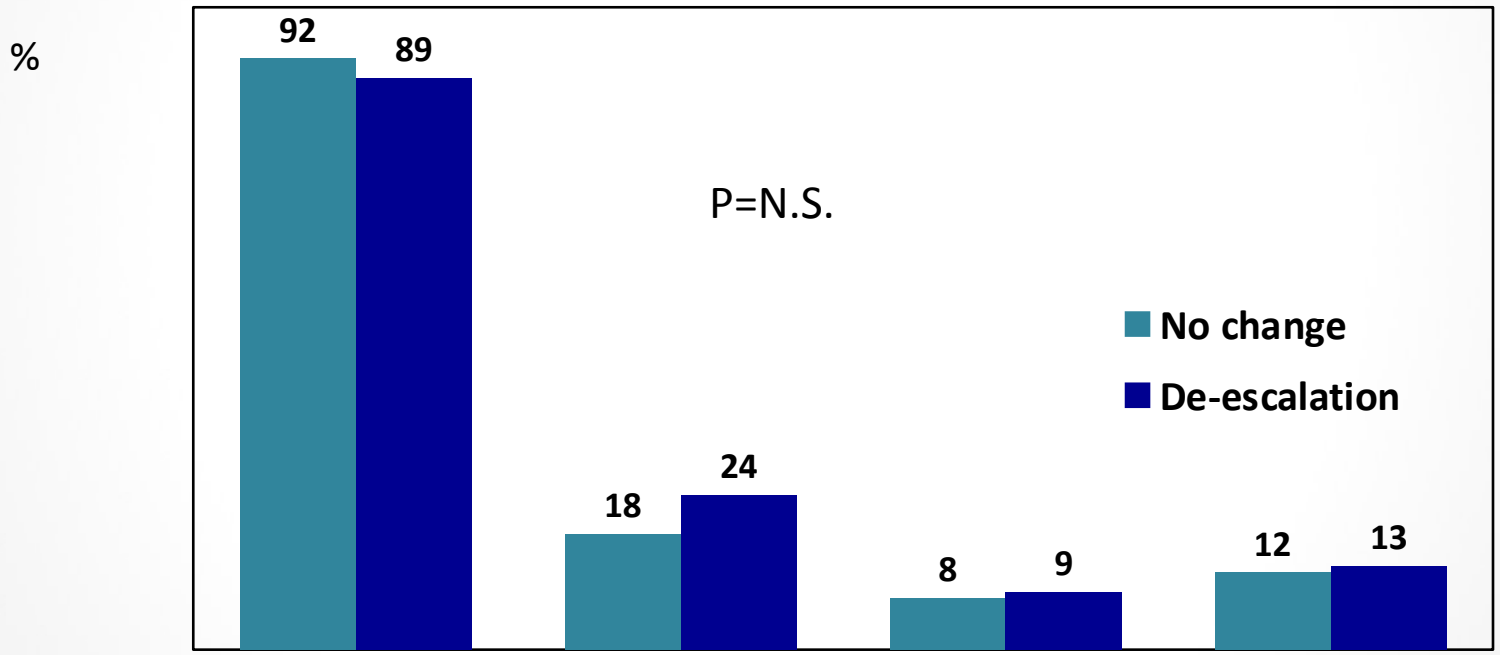
S. Piano et al. Hepatology 2016 ; 63 : 1299-309.

Independent predictors of in-hospital mortality (Including results of cultures and response to first line treatment)

Variables	OR	95% CI	P
Age	1.02	1.01 – 1.04	0.001
MELD	1.08	1.05 – 1.11	<0.001
ACLF	1.59	1.02 – 2.47	0.042
CRP	1.27	1.08 – 1.48	0.003
Ineffective first line treatment	7.15	4.88 – 10.47	<0.001

(data from S. Piano et al. "Global study" ; EASL : 2017)

Impact of the de-escalation of antibiotic treatment on outcomes



The ICA Global Study 2016

Summary on bacterial infections

- MDR bacteria are very common in patients with cirrhosis in particular in Asia (in India also XDR bacteria are very common)
- Previous treatment with antibiotics, health-care exposure are risk factors for MDR bacteria
- Norfloxacin prophylaxis does not seem to be a risk factor for MDR bacterial infections
- Nosocomial infections, pneumonia, XDR and MDR bacterial infections are more difficult to be treated.
- Efficacy of the first line treatment is the strongest predictor of survival in patients with cirrhosis and bacterial infections
- De-escalation of antibiotics is safe and should be implemented to minimize the risk of the development of further resistance.