The EUROBACT-2 cohort study

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!!! Many thanks to A. Tabah !!!

CONTENT

- Eurobact-2 database
- Original study
- The role of centre and country factors
- Liver disease
- Conclusions/perspectives

EUROBACT-2 DATABASE

WHY «**2**»?

Intensive Care Med (2012) 38:1930–1945
DOI 10.1007/s00134-012-2695-9

SPECIAL ARTICLE

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Despoina Koulenti
Kevin Laupland
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Claude Martin
Jordi Rello
Georges Dimopoulos
Jean-François Timsit

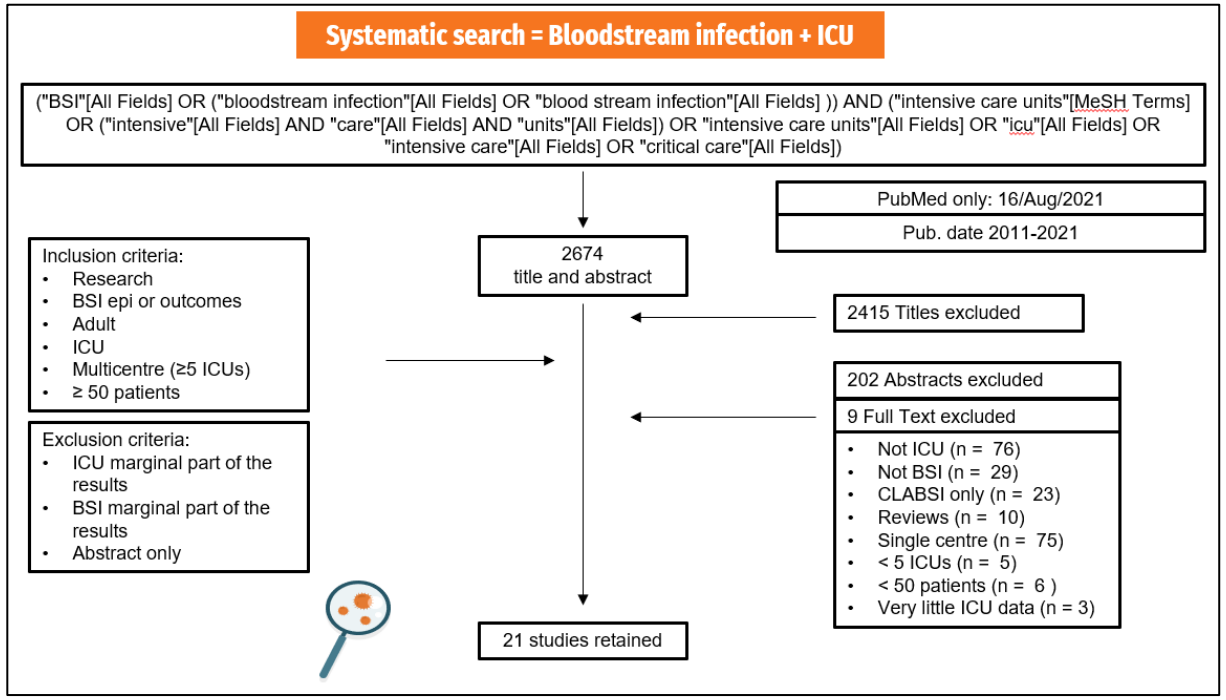
Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study

Eurobact "1" (in 2009): 162 intensive care units (ICUs) in 24 countries, 1,156 patients

A. Tabah et al. Intensive Care Med (2012) 38:1930–1945

EUROBACT-2 DATABASE

RESEARCH GAP:



Author	Date	size	Population	
prospective studies				
Vincent	2020	1239	ICU patients (n=BSI)	EPIC 3 - large pp study
Adrie	2017	571	HA-BSI	Outcomerea db - detailed epidemio and pat
Delle Rose	2015	324	ICU-BSI	5 Italian ICUs - Incidence 13.2% - mortality 4
Valles	2011	726	BSI (all, ICU)	27 spanish hospitals, 726 BSI present on ICU
Kett	2011	99	candidemia / Epic2	An ancillary EPIC 2 that shows higher mortal
Retrospective cohort studies				
Benetazzo	2020	307	ESBL-E BSI	Retrospective cohort of 307 ESBL-E BSI - 70%
Garnacho	2020	294	Candidemia	Spain Retrospective cohort 9 ICUs in Spain, 5
Chen	2017	152	VRE HA-BSI	Taiwan, 4 years of VRE BSI in 9 hospitals, 15
Ernogul	2016	831	HA-BSI GNB	831 gram neg HA BSI in 17 Turkish ICUs - 4
Puig	2014	164	Candida ICU-BSI	Candida ICU-BSI in 29 ICUs - 168 episodes in
Koupetori	2014	754	Mix Ward / ICU	46 hospitals in greece - comparing BSI admit
Walaszek	2018	184	HAI (n=BSI)	7 Polish ICUs - incidence of HA-BSI 7.2% - re
Administrative health records				
Wang	2020	14234	HA-BSI	Taiwan DB nationwide cohort - 14,234 HA-B
Epidemiological reports (no patient or treatment data)				
Robinueau	2018	1952	BSI	121 hospitals in france -1 month surveillanc
Meyer	2013	5970	HA-BSI	Epidemio of Candidemia in 682 ICUs in germ
ECDC	2017	5298	ICU-BSI	ECDC report 2017
Kim	2020	2248	Candidemia	Korea - 11 year epidemiological report of ca
RCT Data				
Daneman	2018	100	Pilot RCT - BSI in ICU	Pilot trial for the balance trial 100 pts with
Wittekamp	2018	199	Cluster RCT SDD (HA-BSI)	Cluster RCT of SOD/SDD in 15 ICUs (8665 pa
Other				
Braga	2018	60	Infection (little BSI data	Point prevalence study in brazil 28 Hospitals
Lecronier	2018	151	Port removals in ICU (BSI)	5 ICUs - 151 patients with implantable port

Evidence & population gaps: No large-scale data with detailed characteristics HA-BSI in the ICU

Many thanks to A. Tabah

EUROBACT-2 DATABASE

Methods: Prospective international cohort study

	Inclusion criteria	
	HA-BSI	BSI acquired > 48h after hospital admission
	In the ICU	• Ward-acquired and transfer to ICU directly for the management of the BSI • ICU acquired
	Adult patients	Age ≥ 18
	Exclusion criteria	
Strictly	Contaminants	
	Community acquired	
	Outcome measure	
	Day-28 mortality	

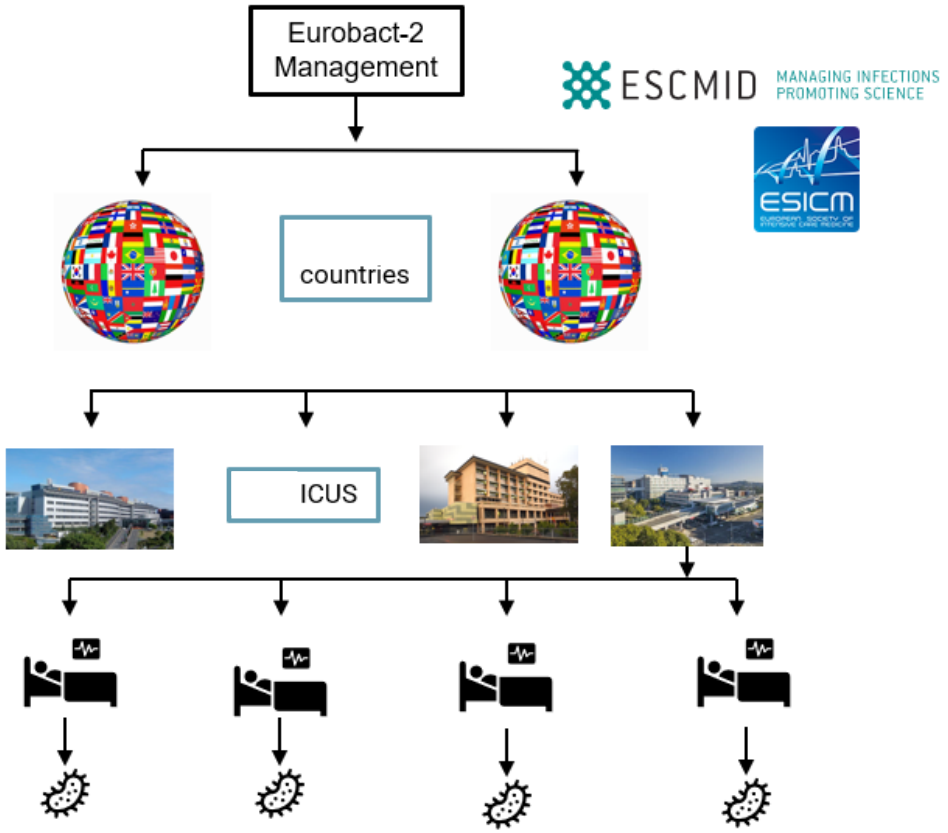
Flexible 3-months inclusion for ICUs

Many thanks to A. Tabah

EUROBACT-2 DATABASE

The Eurobact-2 network

- Partnership with OUTCOMEREA
- Endorsement by scientific societies
  - ESICM + ESCMID
  - Engagement local societies (country) and other groups
- National coordinators



Many thanks to A. Tabah

EUROBACT-2 DATABASE

FUNDING & ETHICS & GOVERNANCE

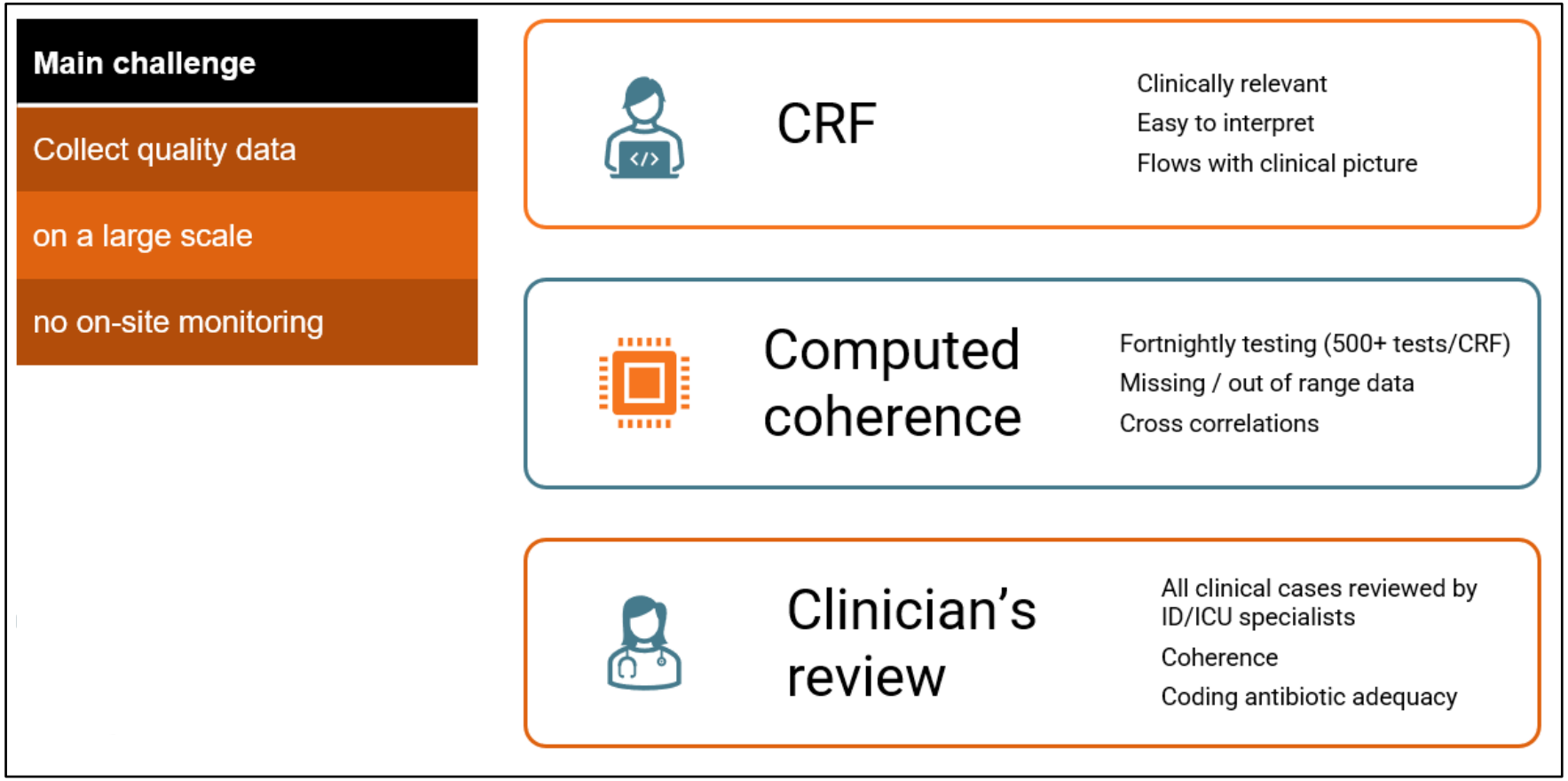
ESICM: Euro 25,000
ESCMID: Euro 35,000
Administration
eCRF and online database
Initial data management and analysis
Redcliffe Hospital Private Practice Trust Fund: A$9600
Study extension (COVID-19)
Norva Dahlia foundation: A$5000
Per patient payment in Australia (99 inclusions)

Initial Ethical approval with waiver of consent
RBWH HREC: LNR/2019/QRBW/48376
At each site
Ethics
Governance
Data transfer agreements
Investigator(s) agreement
Protocol registration
clinicaltrials.org: NCT03937245

Many thanks to A. Tabah

EUROBACT-2 DATABASE

CHALLENGES



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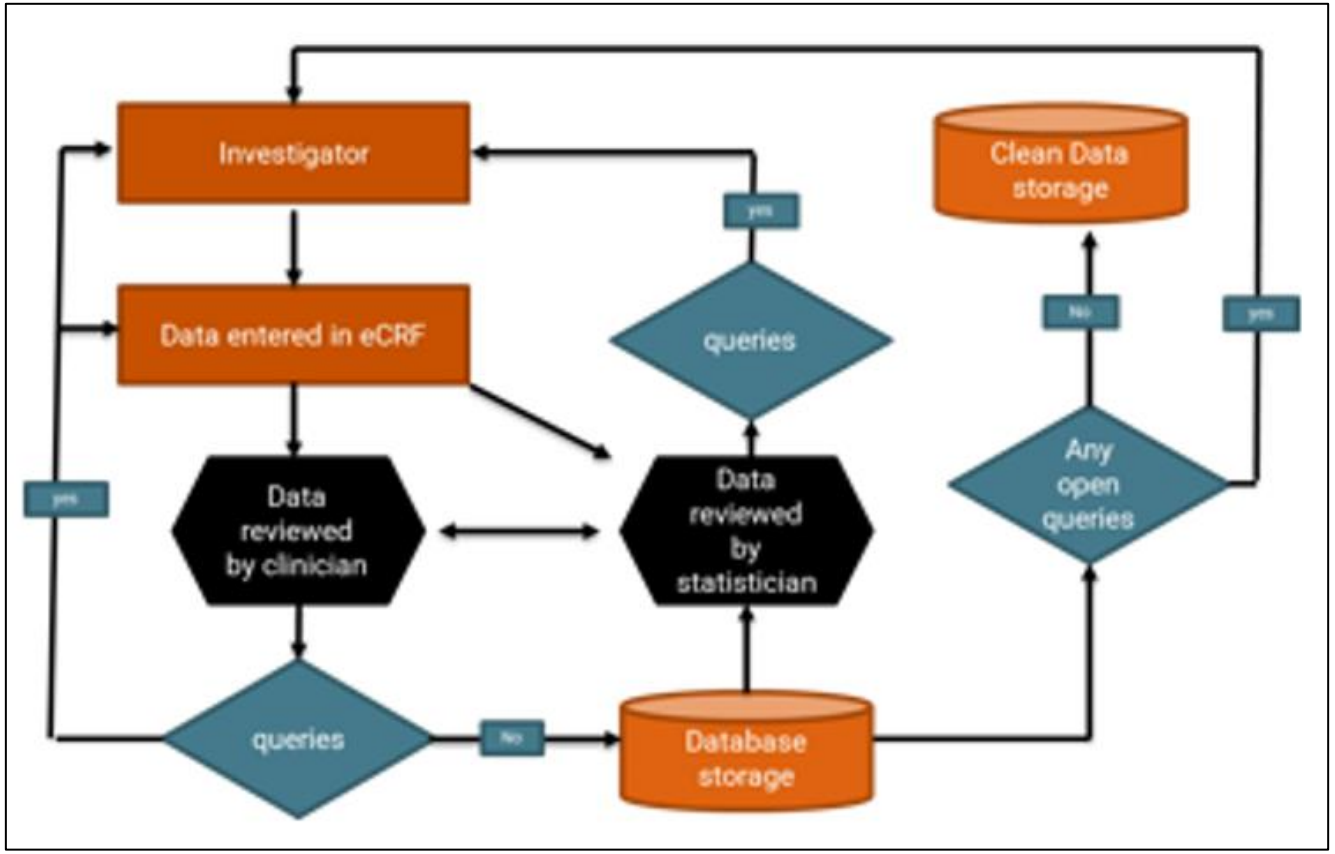
EUROBACT-2 DATABASE

CHALLENGES



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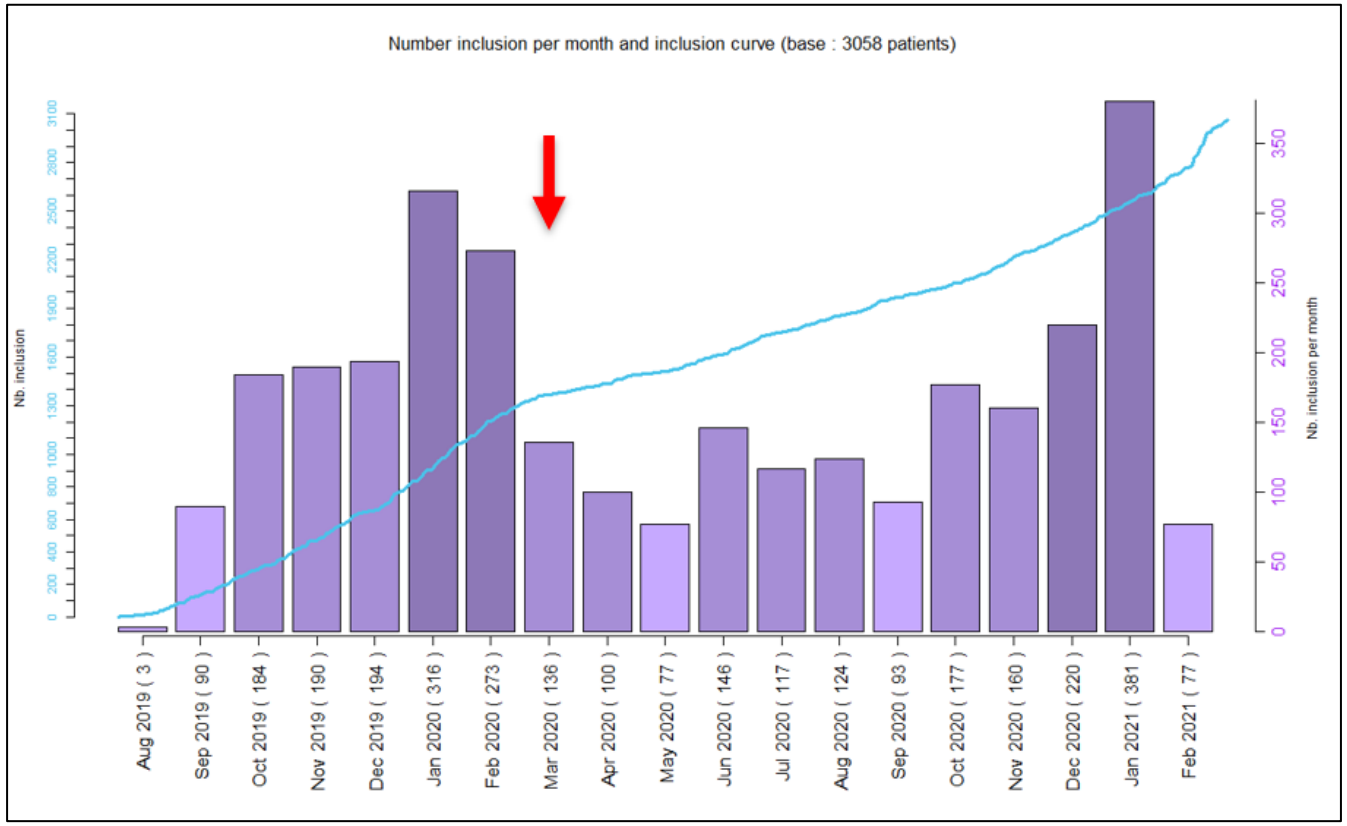
EUROBACT-2 DATABASE

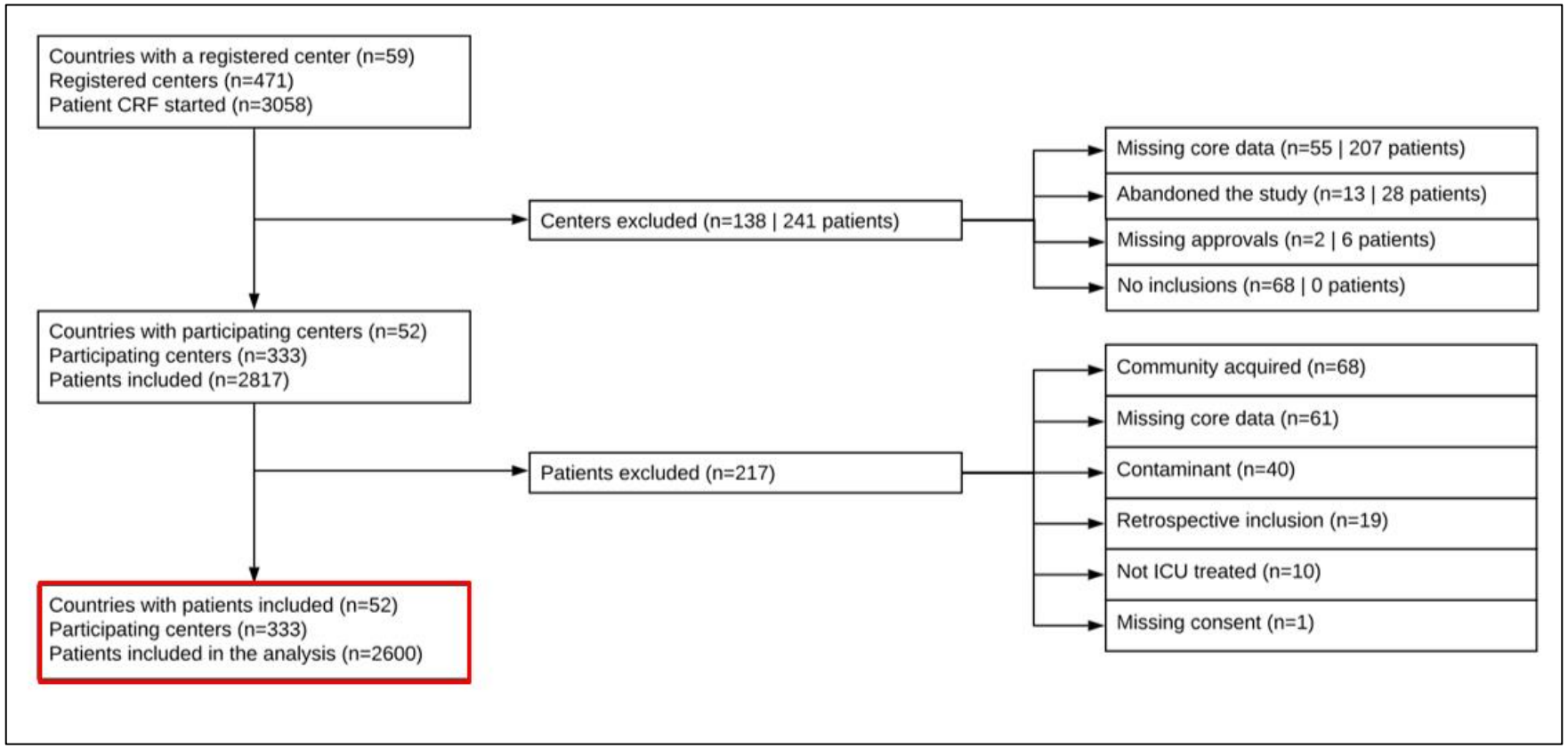
CHALLENGES – INCLUSIONS & COVID-19



Many thanks to A. Tabah

EUROBACT-2 DATABASE

FINALLY…



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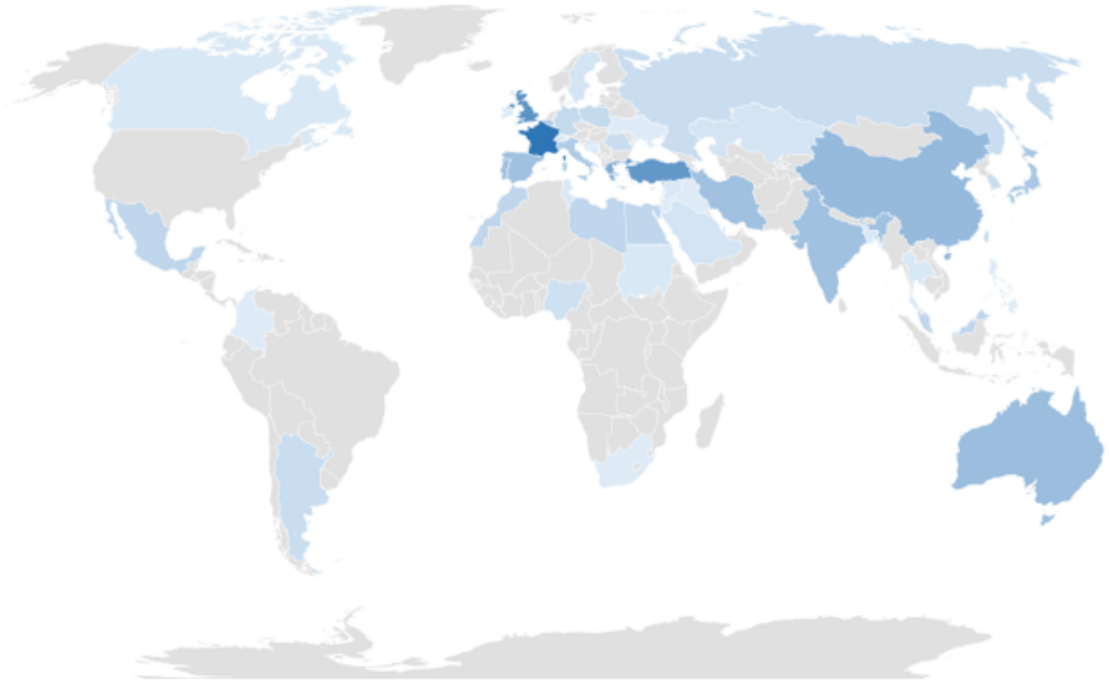
FINALLY…



Many thanks to A. Tabah

EUROBACT-2 DATABASE

FINALLY…

- Several meetings with the core team…
- Several research questions developed…
- Core paper & several ancillary analyses planned… [role of centre & sub-analysis of cirrhotic patients]

CONTENT

- Eurobact-2 database
- Original study
- The role of centre and country factors
- Liver disease
- Conclusions/perspectives

ORIGINAL STUDY

SOME DATA

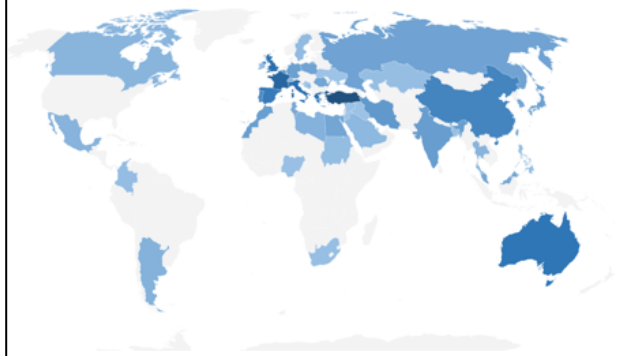
Intensive Care Med (2023) 49:178–190
https://doi.org/10.1007/s00134-022

ORIGINAL

Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care unit patients: the EUROBACT-2 international cohort study

Alexis Tabah[1,2,3,4*], Niccolò Buetti[5,6], Quentin Staiquly[7], Stéphane Ruckly[6,7], Murat Akova[8], Abdullah Tarik Aslan[9], Marc Leone[10], Andrew Conway Morris[11,12,13], Matteo Bassetti[14], Kostoula Arvaniti[15], [21,22], Pedro Povoa[23,24,25], Liesbet De Bus[26], , Khalid Abidi[33], Hendrik Bracht[34], ois Barbier[38], Jean-François Timsit[39,40]on nd the OUTCOMEREA Network

333 participating Centers



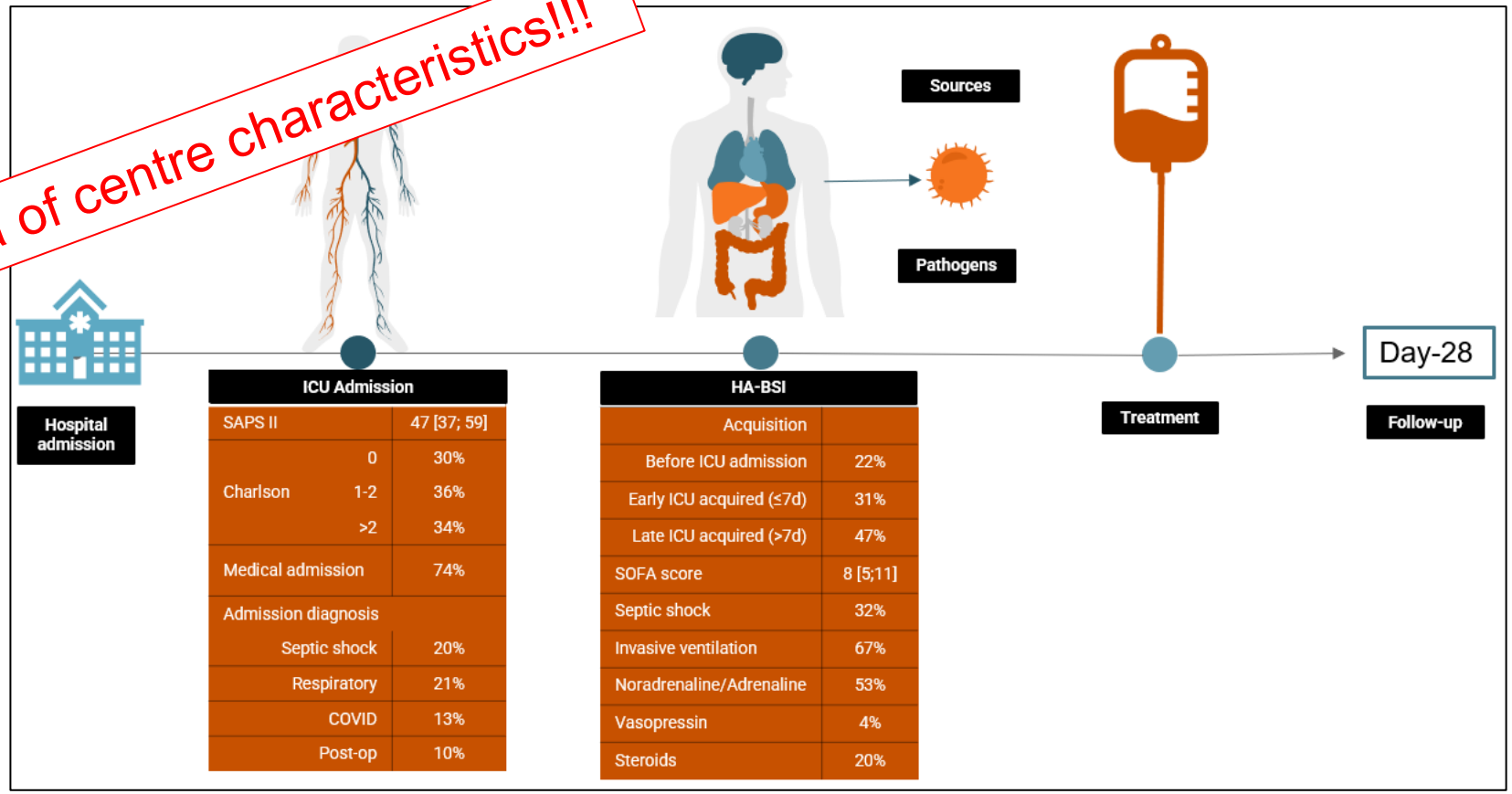
Academic status	82% teaching hospitals
Type of ICUs	84% mixed Medical/surgical
Closed model	75%
ICU Beds / Ventilation	14 [10; 21]
Nurse / patient ratio	2 [1.3; 2.9]

Tabah A, Buetti N *et al.*, Intensive Care Med. 2023 Feb;49(2):178-190

ORIGINAL STUDY

SOME DATA

And a lot of data of centre characteristics!!!



ICU Admission		
SAPS II		47 [37; 59]
Charlson	0	30%
	1-2	36%
	>2	34%
Medical admission		74%
Admission diagnosis		
	Septic shock	20%
	Respiratory	21%
	COVID	13%
	Post-op	10%

HA-BSI	
Acquisition	
Before ICU admission	22%
Early ICU acquired (≤7d)	31%
Late ICU acquired (>7d)	47%
SOFA score	8 [5;11]
Septic shock	32%
Invasive ventilation	67%
Noradrenaline/Adrenaline	53%
Vasopressin	4%
Steroids	20%

Tabah A, Buetti N *et al.*, Intensive Care Med. 2023 Feb;49(2):178-190

ORIGINAL STUDY

SOME DATA

- Mostly **ICU-acquired BSI**
- Mostly **Gram-negative**
- Sources: **respiratory tract and intravascular catheters**
- Adequacy **24h approximately 50%**

Table 3 Patient characteristics at diagnosis of hospital-acquired bloodstream infection and day-28 mortality

Characteristics	All patients (*N* = 2600)	Dead on D28 (*n* = 966)	Alive on D28 (*n* = 1634)	OR [95% CI]	*p* value
Time from ICU admission to HA-BSI					
Acquired prior to ICU admission	558 (21.5)	188 (19.5)	370 (22.6)	1.03 [0.82; 1.29]	0.017
Early ICU-acquired (≤ 7 days)	810 (31.2)	327 (33.9)	483 (29.6)	1.32 [1.08; 1.6]	
Late ICU-acquired (> 7 days)	1232 (47.4)	451 (46.7)	781 (47.8)	1	
Gram-negative bacteria[a]	1623 (62.4)	608 (62.9)	1015 (62.1)	0.98 [0.82; 1.17]	0.823
DTR Gram-negative	350 (13.5)	185 (19.2)	165 (10.1)	1.71 [1.33; 2.21]	< 0.001
Gram-positive bacteria[a]	859 (33)	312 (32.3)	547 (33.5)	0.98 [0.82; 1.17]	0.821
Resistant Gram-positive (MRSA, MRSE or VRE)	323 (12.4)	112 (11.6)	211 (12.9)	0.86 [0.66; 1.11]	0.248
Fungus[a]	227 (8.7)	102 (10.6)	125 (7.6)	1.39 [1.04; 1.86]	0.026
Strict anaerobe bacteria[a]	57 (2.2)	15 (1.6)	42 (2.6)	0.76 [0.41; 1.41]	0.382
Polymicrobial blood culture	290 (11.2)	106 (11)	184 (11.3)	1 [0.77; 1.32]	0.973
Source of HA-BSI					
Intravascular catheter	686 (26.4)	239 (24.7)	447 (27.4)	1	0.027
Intra-abdominal	392 (15.1)	145 (15)	247 (15.1)	1.33 [1; 1.76]	
Other	217 (8.3)	69 (7.1)	148 (9.1)	1.01 [0.71; 1.44]	
Primary	425 (16.3)	169 (17.5)	256 (15.7)	1.26 [0.96; 1.65]	
Respiratory	694 (26.7)	288 (29.8)	406 (24.8)	1.39 [1.09; 1.77]	
Urinary	186 (7.2)	56 (5.8)	130 (8)	0.9 [0.62; 1.3]	
More than 1 possible source of infection	853 (32.8)	322 (33.3)	531 (32.5)	1.14 [0.94; 1.37]	0.191
Time to adequate antimicrobial therapy					
≤ 24 h, *n* (%)	1339 (51.5)	463 (47.9)	876 (53.6)	1	< 0.001

Tabah A, Buetti N *et al.*, Intensive Care Med. 2023 Feb;49(2):178-190

ORIGINAL STUDY

SOME DATA

- *K. pneumoniae*: >1/4 resistant to carbapenems
- *E. coli*: emergency of carbapenem resistance
- *Acinetobacter* spp: almost 85% resistant to carbapenems

Table 4 Characteristics of the pathogens in the initial blood culture in EUROBACT-2 and comparison with EUROBACT-1 and EPIC III studies

Pathogens	EUROBACT-2 *n* = 2927 (%)	EUROBACT-1 (*n* = 1317)*	EPIC III BSI (*n* = 1239)**
Gram-negative bacteria	1726 (59)	759 (57.6)	515 (44.6)
Klebsiella spp.	482 (27.9)	156 (20.1)	144 (28)
Carbapenem resistant	182 (37.8)	59 (37.8)	86 (59.7)
DTR*	133 (27.6)	.	.
PDR*	11 (2.3)	3 (1.9)	.
Escherichia coli	272 (15.8)	98(12.9)	116 (22.5)
Carbapenem resistant	20 (7.4)	1(1)	32 (27.6)
DTR*	9 (3.3)	.	.
PDR*	0 (0)	0(0)	.
Enterobacter spp.	141 (8.2)	88 (11.6)	.
Carbapenem resistant	31 (22)	5 (5.7)	.
DTR*	8 (5.7)	.	.
PDR*	0 (0)	0(0)	.
Pseudomonas spp.	247 (14.3)	150 (19.7)	67 (13)
Carbapenem resistant	82 (33.2)	56 (37.3)	10 (14.9)
DTR*	25 (10.1)	.	.
PDR*	4 (1.6)	0(0)	.
Acinetobacter spp.	350 (20.3)	160 (21.1)	68 (13.2)
Carbapenem resistant	296 (84.6)	110 (68.7)	53 (77.9)
DTR*	176 (50.3)	.	.
PDR*	8 (2.3)	1 (0.6)	.

Tabah A, Buetti N *et al.*, Intensive Care Med. 2023 Feb;49(2):178-190

ORIGINAL STUDY

SOME DATA

- By day-28:
  - 966 (**37.1**%) patients had died
    - 91% in the ICU
    - 9% after ICU discharge
- Death was preceded by a decision to withhold or withdraw life-sustaining treatment for 268 (27.7%).

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- Original study
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THE ROLE OF CENTRE & COUNTRY

INTRODUCTION

- **Initial adequate therapy** and **mortality** represent ones of the most important process and outcome indicators
- International cohorts → focus mostly on individual patient factors
  - the role of different structural indicators or centre-/country-based factors → disregarded in the literature
- Associations between these structural indicators and the adequacy of antimicrobial therapy or mortality remain unknown due to the paucity of standardized multicontinental data.

Niederman MS et al., Critical care, 2021;25(1):307. Klompas Met al., JAMA. 2023;329(7):535-6. Vincent JL et al. JAMA. 2020;323(15):1478-87.

THE ROLE OF CENTRE & COUNTRY

OBJECTIVE:

- To evaluate the associations between centre-/country-based factors and two important process and outcome indicators:
  - **Adequacy of antimicrobial therapy within the first 24 hours.**
  - **28-day mortality**

  - Using the EUROBACT-2 database!

THE ROLE OF CENTRE & COUNTRY

METHODS - POPULATION:

- Centers: included a minimum of ten consecutive HABSI patients or recruited patients for a period >2 months
  - [flexible start of the inclusion period was allowed]
- Adult patients with a first episode of HABSI treated in ICU

THE ROLE OF CENTRE & COUNTRY

METHODS - DEFINITIONS:

- Data on hospital and centre characteristics were stratified into the following subgroups:
  - Structure of the ICU **[1]**
  - Organization of the microbiology laboratory and infectious diseases **[2]**
  - Aggregated ICU antimicrobial resistance (AMR)-related factors **[3]**
- Country data from WHO Tripartite Antimicrobial Resistance (AMR) Country Self-Assessment Survey (TrACSS) **[4]**

- **Indicators**:
  - *Process indicator:* adequate antimicrobial therapy within the first 24 hours
  - *Outcome indicator*: 28-day mortality
- Patients were **followed for up** to 28 days or until hospital discharge.

TRACSS, available from: https://amrcountryprogress.org/#/ response-overview, last accessed September 6 2023. Patel J et al., LID, 2023;23(6):706-18.

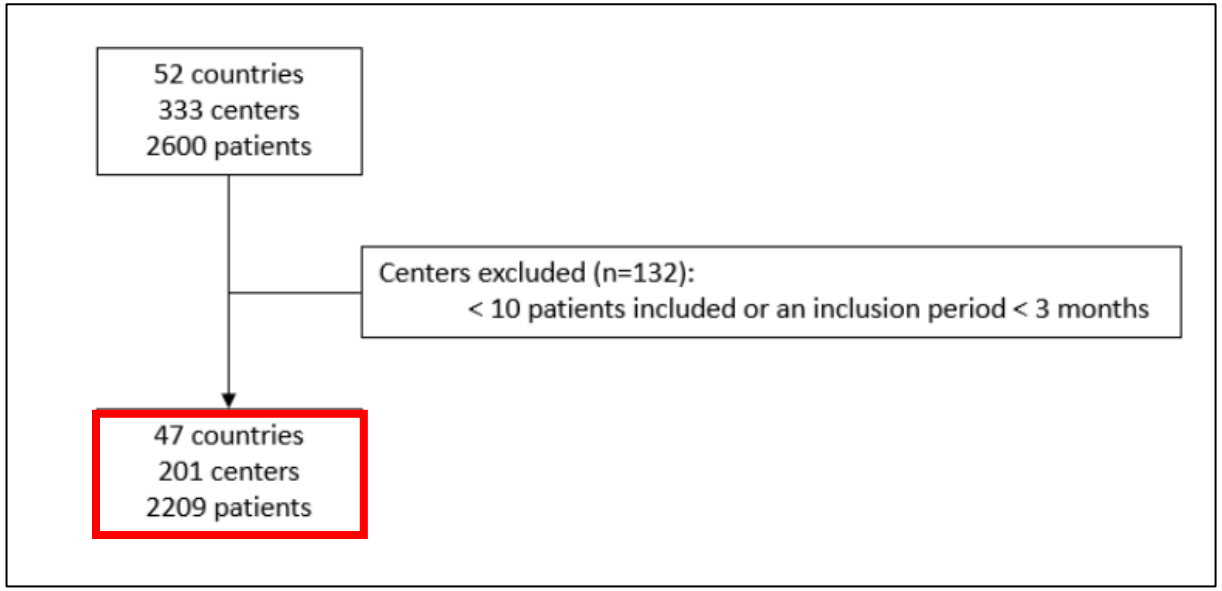
THE ROLE OF CENTRE & COUNTRY

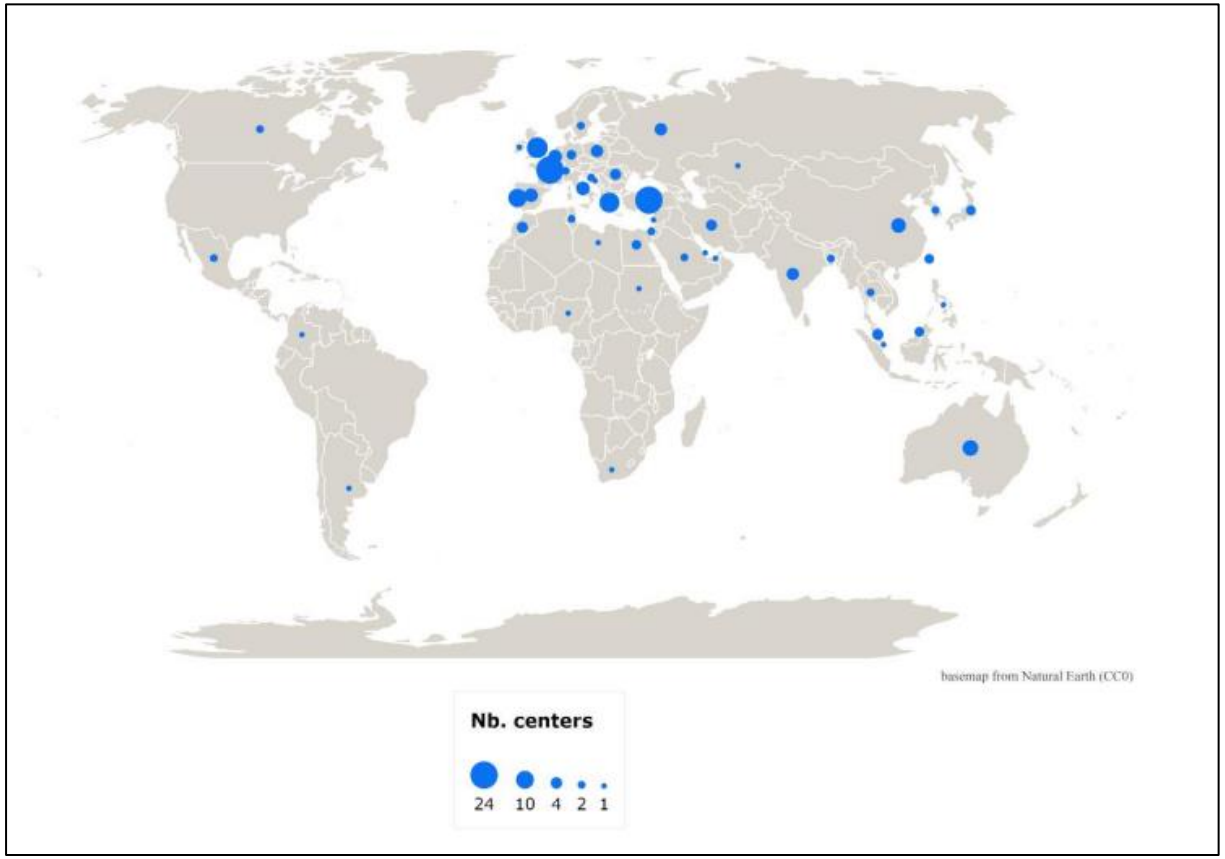
METHODS - STATISTICS:

1) **Descriptive statistics** for the different subgroups (for the 2 indicators)
2) To identify factors with the two indicators → **logistic mixed model** for each subgroup
    - Random effect for center
    - Univariable and multivariable models
    - Presence of septic shock (and SOFA for the indicator “28-day mortality”) was forced into multivariable models

THE ROLE OF CENTRE & COUNTRY

RESULTS:





THE ROLE OF CENTRE & COUNTRY [1]

RESULTS – STRUCTURE OF THE ICU

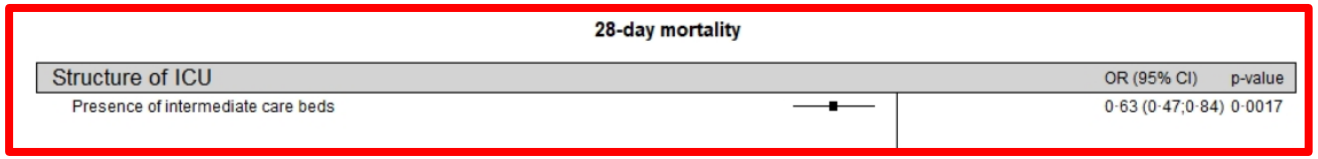
- Funding, type of ICU, structure of the ICU, number of beds per nurse, number of beds per doctor, number of senior doctors, number of junior or in training doctors, number of ventilator beds, presence of intermediate care beds, recruitment in surgery/trauma or burn wards, 24 hours coverage by senior level doctors, presence of general surgery team and operating theatre 24/7

THE ROLE OF CENTRE & COUNTRY [1]

RESULTS – STRUCTURE OF THE ICU

eTable 1: Structure of ICU and univariable/multivariable models for adequate therapy within the first 24h

	Univariate		Multivariable	
	OR (95% CI)	*p-value*	OR (95% CI)	*p-value*
Teaching hospital	0.77 (0.54 – 1.1)	0.15		
Funding		0.92		
Public	1			
Private	1.09 (0.7 – 1.69)			
Mixed	1.06 (0.58 – 1.91)			
Type of ICU		0.68		
Medical	1			
Surgical	0.95 (0.5 – 1.81)			
Mixed	0.85 (0.57 – 1.27)			
Structure of the ICU		0.08		
Closed-ICU	1			
Open-ICU	0.76 (0.55 – 1.04)			
Number of beds per nurse		0.66		
<1.6	1			
[1.6-2.25[	0.98 (0.68 – 1.4)			
[2.25-2.8[	0.8 (0.54 – 1.16)			
≥2.8	0.94 (0.65 – 1.34)			
Number of beds per doctor		0.22		
<1.9	1			
[2-2.8[	1.15 (0.79 – 1.67)			
[2.8-4.1[	1.11 (0.78 – 1.59)			
≥4.1	0.8 (0.55 – 1.15)			
Number of junior or in training doctors		0.86		
<2	1			
[2-4[	1.06 (0.7 – 1.58)			
[4-6[	1.12 (0.72 – 1.74)			
≥6	0.96 (0.63 – 1.46)			
Number of senior doctors		0.10		
<2	1			
[2-3[	1.14 (0.75 – 1.73)			
[3-5[	1.33 (0.87 – 2.04)			
≥5	1.59 (1.05 – 2.42)			
Presence of intermediate care beds	0.68 (0.53 – 0.87)	<0.01	0.63 (0.47 – 0.84)	<0.01
Number of beds in ICU		0.09		
<12	1			
[12-20[	0.76 (0.53 – 1.11)			
[20-28[	0.63 (0.43 – 0.91)			
≥28	0.7 (0.48 – 1.01)			
Recruitment: General or paediatric wards	1.61 (0.91 – 2.86)	0.10		
Recruitment: Cardiac-surgery, coronary-care or post-operative, neuro-surgical or trauma wards	0.74 (0.54 – 1.01)	0.06		
Recruitment: Burn wards	0.93 (0.67 – 1.3)	0.69		
24-hour medical coverage by senior level doctors	0.69 (0.42 – 1.11)	0.12		
24-hour medical coverage by junior or in training doctors	0.89 (0.61 – 1.29)	0.53		
General surgery team and operating theatre available 24/7	0.28 (0.06 – 1.23)	0.09		
Septic Shock at HABSI (SOFA>=2 and Lactate >=2 and Vasopressor=1)**			2.04 (1.64 – 2.55)	<0.01
SOFA without cardio points at HABSI**			1.24 (1.20 – 1.28)	<0.01



Any factors associated with **adequate therapy** within the first 24h

Presence of IMC beds associated with decreased **mortality**

THE ROLE OF CENTRE & COUNTRY [2]

RESULTS – MICROBIOLOGY LAB & ID ORGANIZATION

- Availability of ID specialists or clinical microbiologists, availability of clinical pharmacists, selection of empirical treatment, therapy drug monitoring [TDM], timing of blood culture incubation, monitoring and reporting of positive blood cultures, antimicrobial testing and reporting of susceptibility data

THE ROLE OF CENTRE & COUNTRY [2]

RESULTS – MICROBIOLOGY LAB & ID ORGANIZATION

eTable 3: Organization of the microbiology laboratory and infectious diseases and univariable/multivariable models for adequate therapy within the first 24h

Variable	Univariate OR (95% CI)	*p-value*	Multivariable OR (95% CI)	*p-value*
TDM for aminoglycosides		<0.01		<0.01
not available	1		1	
available at least once a week	1.53 (1.08 – 2.16)			
available every day within few hours	0.74 (0.39 – 1.41)			
available every day	1.26 (0.77 – 2.06)			

Organization of the microbiology laboratory and infectious diseases	OR (95% CI)	p-value
Therapeutic Drug Monitoring for aminoglycosides		0·0006
TDM is not available	ref.	
TDM is available at least once a week	1·22 (0·76;1·95)	
Available everyday	1·48 (1·03;2·14)	
Available everyday within few hours	1·79 (1·34;2·38)	

Aminoglycoside TDM everyday within few hours associated with increased adequacy of antmicrobial therapy within 24h

eTable 4: Organization of the microbiology laboratory and infectious diseases and univariable/multivariable models for 28-day mortality

Variable	Univariate OR (95% CI)	*p-value*	Multivariable OR (95% CI)	*p-value*
Consultation of infectious diseases specialists or clinical microbiologists		0.69		
24/7	1.28 (0.71 – 2.28)			
TDM for aminoglycosides		<0.01		0.01
not available	1		1	
available every day within few hours	0.66 (0.49 – 0.89)			
available every day	0.59 (0.41 – 0.87)			

Organization of the microbiology laboratory and infectious diseases	OR (95% CI)	p-value
Therapeutic Drug Monitoring for aminoglycosides		0·012
TDM is not available	ref.	
TDM is available at least once a week	0·83 (0·49;1·40)	
available everyday	0·72 (0·47;1·09)	
available everyday within few hours	0·57 (0·41;0·80)	
Consultation of clinical pharmacists		0·049
Never	ref.	
Business	0·75 (0·53;1·06)	
24h/7	0·67 (0·47;0·95)	

TDM for aminoglycoside available everyday or **within few hours** and **24/7 consultation of clinical pharmacists**

THE ROLE OF CENTRE & COUNTRY [3]

RESULTS – ICU AMR RELATED FACTORS

- Selective oropharyngeal and/or digestive tract decontamination, surveillance culture and screening of multidrug-resistant microorganism, percentage of MRSA, percentage of VRE, percentage of Enterobacterales producing ESBL, percentage of Enterobacterales producing carbapenemase (CPE) at the ICU level

THE ROLE OF CENTRE & COUNTRY [3]

RESULTS – ICU AMR RELATED FACTORS

Variable	Univariate OR (95% CI)	*p-value*	Multivariable OR (95% CI)	*p-value*
Selective oropharyngeal and/or digestive tract decontamination (miss=32)		0.05		
Never	1			
In a selected group of patients	0.88 (0.59 – 1.32)			
In All ICU patients	0.91 (0.66 – 1.26)			
Surveillance cultures and screening for multidrug resistant organism carriage		0.69		
Never/Only when clinically indicated	1			
For all (most) patients, on admission	1.07 (0.75 – 1.53)			
For all (most) patients, on admission and at least once weekly during the ICU stay	1.45 (1.09 – 1.93)			
Percentage of *Enterococcus* spp. Isolates resistant to vancomycin in the ICU		0.09		0.04
less than 10%	1		1	
10 to 24.9%	1.67 (1.06 – 2.62)		1.67 (1.00 – 2.80)	
25 to 100%	0.67 (0.38 – 1.19)		0.67 (0.38 – 1.19)	
Unknown	1.37 (0.91 – 2.08)		1.37 (0.91 – 2.08)	
Percentage of Enterobacteriales isolates producing carbapenemases in the ICU		0.05		
less than 10%	1			
10 to 24.9%	1.45 (0.98 – 2.15)			
25 to 100%	1.52 (1.07 – 2.14)			
Unknown	1.24 (0.86 – 1.77)			

ICU AMR-related factors	OR (95% CI)	p-value
Surveillance cultures and screening for multidrug resistant organism carriage		0·028
Never/Only when clinically indicated	ref.	
For all (most) patients, on admission	1·07 (0·75;1·53)	
For all (most) patients, on admission and at least once weekly during the ICU stay	1·45 (1·09;1·93)	

ICU AMR-related factors	OR (95% CI)	p-value
Percentage of Enterococcus spp. isolates resistant to vancomycin in the ICU		0·040
Less than 10%	ref.	
10 to 24·9%	1·67 (1·00;2·80)	
25 to 100%	0·67 (0·38;1·19)	
Unknown	1·37 (0·91;2·08)	

Surveillance MDR cultures every week were associated with an increased probability of adequate antmicrobial therapy within 24h

Percentage of VRE 10-25% were associated with high 28-day mortality

THE ROLE OF CENTRE & COUNTRY [4]

RESULTS – COUNTRY FACTORS

- Geographical region, income categories, Organisation for Economic Co-operation and Development [OECD] membership, Human development index [HDI], and current health expenditure).
- Country data from WHO Tripartite Antimicrobial Resistance (AMR) Country Self-Assessment Survey (TrACSS) were extracted
  - National action plan on AMR, Training and professional education on AMR, National monitoring system for consumption and rational use of antimicrobials, National surveillance system for AMR, policies for optimizing antimicrobial use

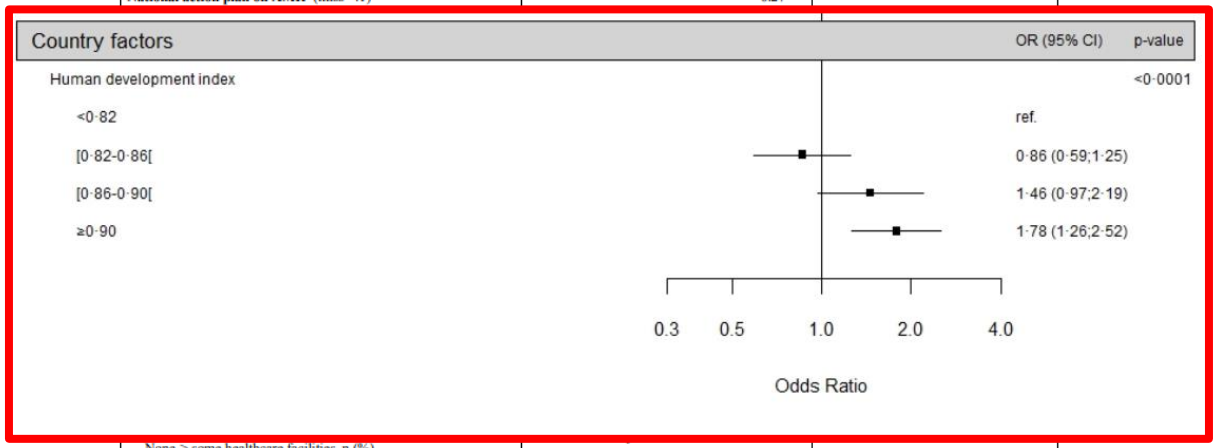
TRACSS, available from: https://amrcountryprogress.org/#/ response-overview, last accessed September 6 2023. Patel J et al., LID, 2023;23(6):706-18.

THE ROLE OF CENTRE & COUNTRY

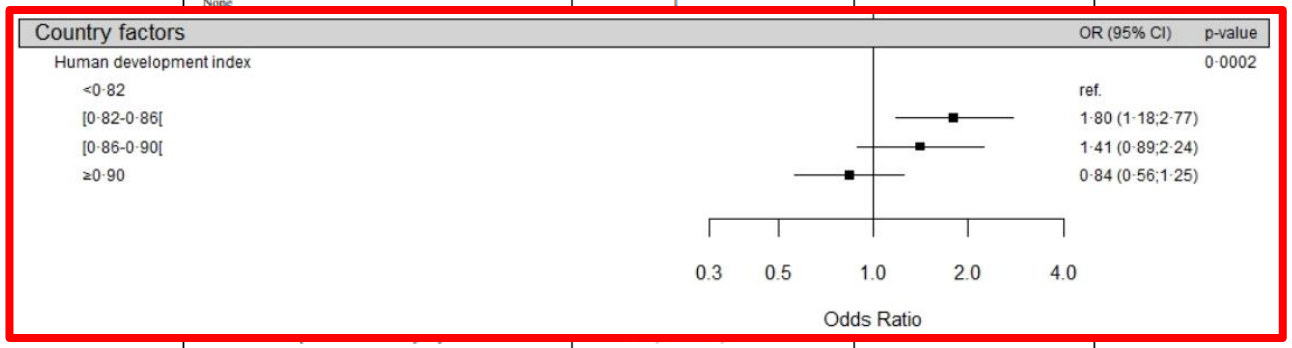
[4]

RESULTS – COUNTRY FACTORS

Variable	Univariate OR (95% CI)	*p-value*	Multivariable OR (95% CI)	*p-value*
OECD member	1.22 (0.92 – 1.63)	0.17		
National action plan on AMR[1] (miss=41)		0.27		
None-> some healthcare facilities, n (%)				
In most healthcare/guidelines implemented for all majors, n (%)	1.26 (0.98 – 1.64)			
Region		0.64		
America	1.48 (0.46 – 4.74)			
East Asia and Pacific	1.93 (0.78 – 4.77)			
≥0.90	1.77 (1.25 – 2.51)		1.78 (1.26 – 2.52)	
Septic Shock at HABSI (SOFA>=2 and Lactate >=2 and Vasopressor=1)**			1.29 (1.06 – 1.56)	0.01



Variable	Univariate OR (95% CI)	*p-value*	Multivariable OR (95% CI)	*p-value*
OECD member	0.89 (0.67 – 1.18)	0.41		
National action plan on AMR[1] (miss=41)		0.03		
Not implemented	1			
Developed and implemented	0.75 (0.58 – 0.97)			
Training and professional education[1] (miss=77)		<0.01		
Never/In some pre-service training and continuing professional development	1			
In all relevant pre-service training and continuing professional development	0.62 (0.48 – 0.81)			
National monitoring system for consumption and rational use of antimicrobials[1] (miss=41)		0.18		
None	1			
Policies for optimizing antimicrobial use[1]		<0.01		
None-> some healthcare facilities, n (%)				
In most healthcare/guidelines implemented for all majors, n (%)	0.7 (0.54 – 0.91)			
Region		0.43		
America	0.60 (0.19 – 1.89)			
East Asia and Pacific	0.54 (0.22 – 1.31)			
Septic Shock at HABSI (SOFA>=2 and Lactate >=2 and Vasopressor=1)**			2.04 (1.64 – 2.55)	<0.01
SOFA without cardio points at HABSI**			1.23 (1.19 – 1.27)	<0.01



Increasing values of HDI were associated with an increased probability of adequate antmicrobial therapy within 24h

Decreasing values of HDI were associated with an increased probability of 28-day mortality

THE ROLE OF CENTRE & COUNTRY

DISCUSSION

- Using a large multicontinental prospective cohort, we provided a detailed description of the organization of ICUs, microbiology laboratories, and antimicrobial stewardship processes worldwide.
- Several factors related to the centre and country were associated with the adequacy of antimicrobial therapy and mortality in critically ill patients with HABSI.
- Such an in-depth analysis on centre- and country-specific factors has never been performed.

THE ROLE OF CENTRE & COUNTRY

DISCUSSION

- **Aminoglycoside TDM** → an increased probability of adequate antimicrobial therapy within the first 24 hours and with decreased mortality:
  - TDM → optimize antibiotic dosing in an attempt to improve the achievement of pharmacokinetic/pharmacodynamic targets and outcomes of severe infections in critically ill patient

  HOWEVER:
  - TDM →simply represent a proxy measure for access to a highly functional laboratory system in a mature healthcare setting with multiple other protective factors?

- **Clinical pharmacists** → decreased 28-day mortality
  - optimal drug choice, avoiding interactions, and improving delivery with pharmacodynamic/pharmacokinetic optimization → provide safe and effective care to ICU patients with severe infections?

Wong G *et al.,* BMC Infect Dis. 2014;14:288. van Lent-Evers NA *et al.,* Ther Drug Monit. 1999;21(1):63-73.
Lee H *et al.*, Critical care medicine, 2019;47(9):1243-50.

THE ROLE OF CENTRE & COUNTRY

DISCUSSION

- **Screening for MDR carriage** → increased probability of adequate therapy within the first 24h
  - Importance not only for IPC purposes but for therapeutic outcomes?

- **IMC beds presence**→ decreased 28-day mortality
  - large cohort → the benefits of IMC beds in term of prognosis for severely ill patients

- **Country factors (HDI)** → associated with both indicators
  - HDI includes long and healthy life expectancy, education, and a decent standard of living measured by Gross National Income per capita
  - policy-mediated large-scale improvements → impact on process and outcome indicators in patients with severe infections

Vincent JL and Rubenfeld GD, Critical care, 2015;19(1):89. Capuzzo M *et al*., Critical care, 2014;18(5):551. WHO. Human development index (HDI) definition. Available from: https://www.who.int/data/nutrition/nlis/info/human-development-index. Last accessed 26 September 2023.

CONTENT

- Eurobact-2 database
- Original study
- The role of centre and country factors
- Liver disease
- Conclusions/perspectives

LIVER DISEASE

INTRODUCTION

- Patients with cirrhosis are especially susceptible to infections, yet there is a knowledge gap in critically ill cirrhotic patients.
- Epidemiological knowledge about the microorganisms responsible for HABSI in cirrhotic patients, their sources and the patient's outcome in the ICU are scarce.
- No large comparison of the characteristics of these patients with a non-cirrhotic group has previously been performed.

OBJECTIVES

Describe the differences in the epidemiology of HABSI, with particular attention to *E. faecium* infections, between cirrhotic and non-cirrhotic patients in terms of patients' characteristics, source of infection, microorganism distribution and mortality.

Bajaj JS et al., Am J Gastroenterol 2019;3:1091–100. Johnson AL *et al.*, available from: https://doi.org/10.1136/bmjgast-2021-000695. Hoenigl M *et al.*, PLoS One 2014;9:4–9.

LIVER DISEASE

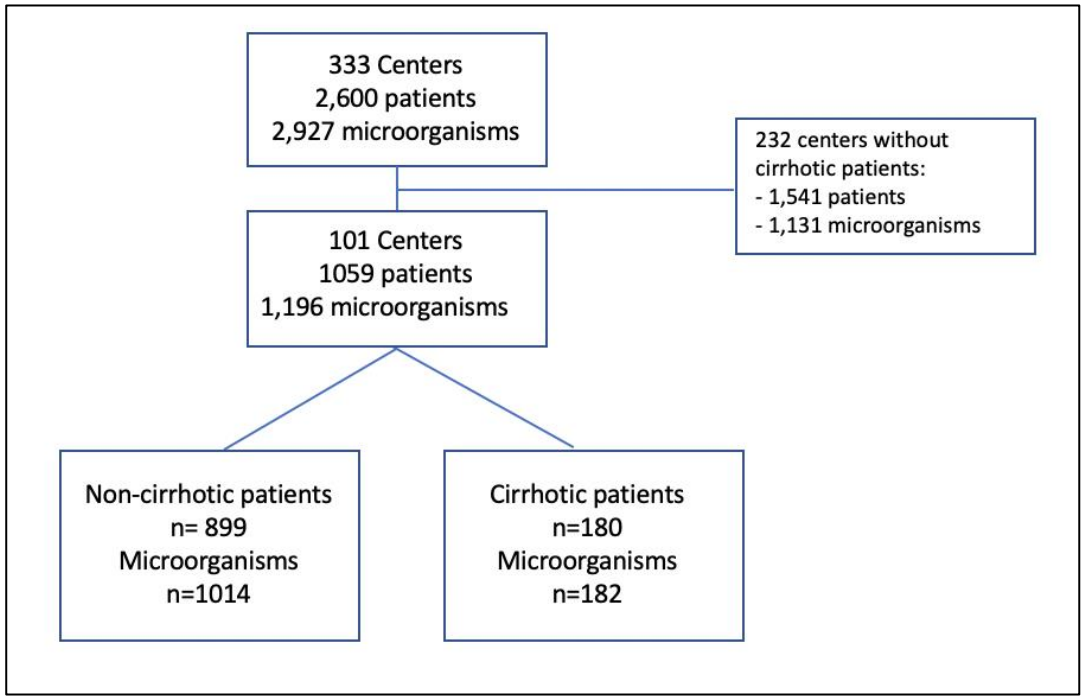
METHODS

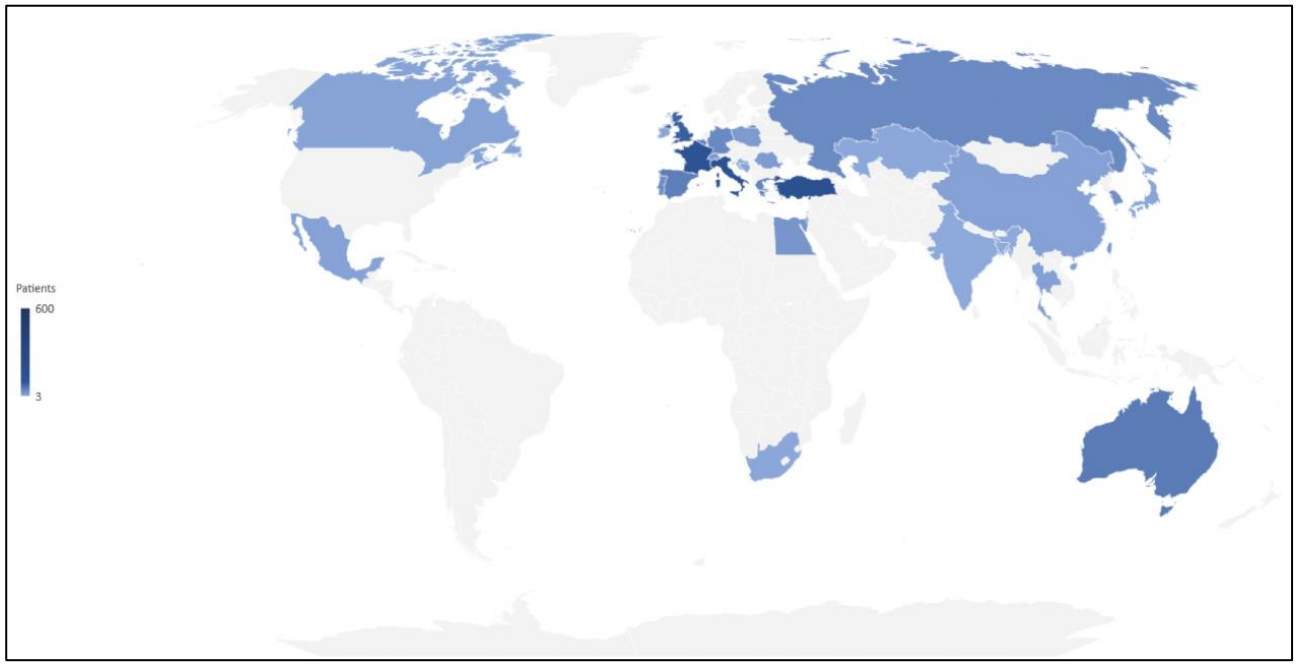
- Inclusion: centers that included both patients with and without cirrhosis
- Statistics:
  - Descriptive analysis of patients' characteristics on admission according to the presence of cirrhosis
  - Descriptive analysis of the distribution of HABSI microorganisms
  - Multivariable mixed logistic regression
    - Association between *E. faecium* and cirrhosis
  - Multivariable frailty Cox model with a random effect for center
    - Association between cirrhosis and mortality

LIVER DISEASE

RESULTS

- ICU & Patient selection





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LIVER DISEASE

RESULTS

Cirrhotic

- ↑↑↑ **ward acquisition**

- ↑↑↑ **abdominal sources**

Table 2. Characteristics of HABSI and sources of infection

N= 1059	Non-cirrhotic patients n= 899	Cirrhotic patients n =160	*p* value
Time to HABSI (days), median (IQR)	14 (8-26)	15 (8-25)	0.6
Site of acquisition, n(%)			0.03
-Ward	215 (23.9%)	51 (31.9%)	
-ICU	684 (75.1%)	109 (68.1%)	
Supposed source of the HABSI, n (%)			<0.01
-primary	110 (12.2%)	19 (11.9%)	
-catheter related	170 (18.9%)	24 (15%)	
-pulmonary	207 (23%)	23 (14.4%)	
-abdominal	169 (18.8%)	57 (35.6%)	
-urinary tract	105 (11.7%)	16 (10%)	
-cutaneous or soft tissue	63 (7%)	10 (6.3%)	
-others*	75 (8.3%)	11 6.9%)	
Source control, n (%)			0.6
-not required	381 (42.4%)	75 (46.9%)	
-required and complete	426 (47.4%)	71 (44.4%)	
-required but unsuccessful	92 (10.2%)	14 (8.8%)	
Appropriate antibiotic in the first 24 hours, n (%)	459 (51.1%)	78 (48.7%)	0.6

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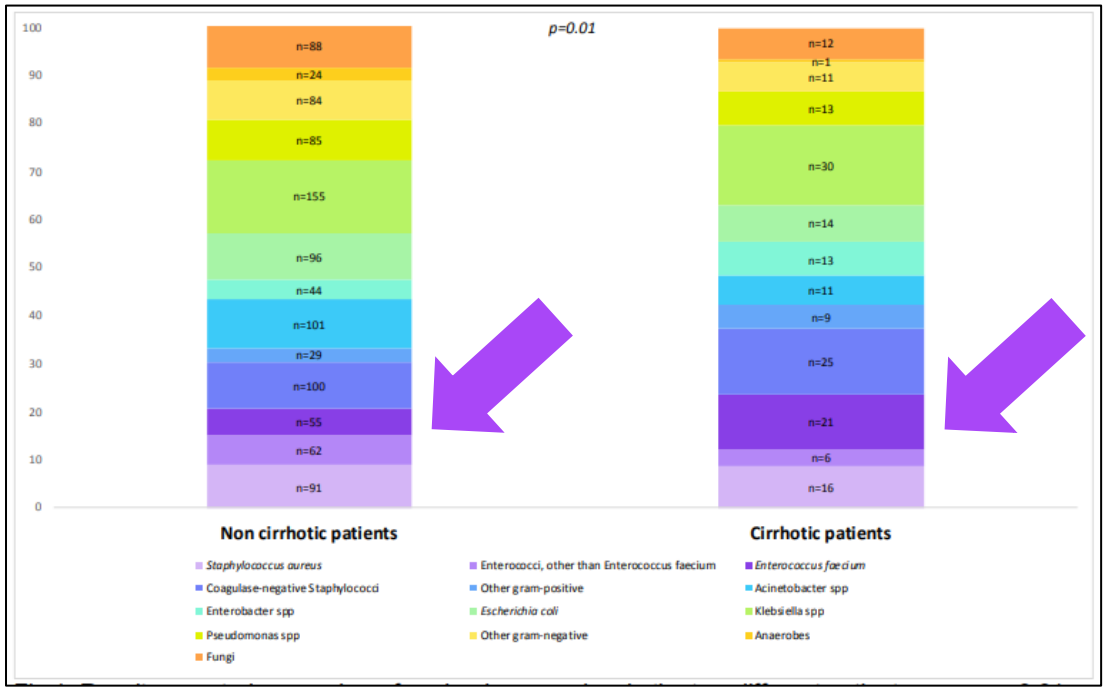
LIVER DISEASE

RESULTS

- Distribution of microorganisms



42.3% of HABSIs in cirrhotic patients were Gram-positive compared to 33.2% in non-cirrhotic patients (p=0.02)

E. faecium HABSI was found more often in cirrhotic patients than in non-cirrhotic patients (11.5 % *vs* 4.5%, p<0.01)

No differences were found for fungal infections (8.7% vs 6.6%, p=0.4)

No difference in antimicrobial resistance between patients with and without cirrhosis

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LIVER DISEASE

RESULTS

- Cirrhosis increased the risk of *E. faecium* HA-BSI

n=1059	*E. faecium* BSI, Odds ratio (CI 95%)	*p* value
Cirrhosis	**2.5 (1.3-4.5)**	**<0.01**
Reason for ICU admission:		
-Cardio-vascular disease	Ref.	
-Respiratory failure	1.5 (0.5-4.4)	0.4
-Neurological disease	0.3 (0.06-1.8)	0.2
-Abdominal disease	1.5 (0.5-5.2)	0.5
-Post-surgical treatment	0.9 (0.3-3.1)	0.9
-Renal failure	1.2 (0.1-11)	0.9
-Septic Shock	0.7 (0.2-2)	0.5
-COVID-19	3.2 (1.1-10)	0.04
-other*	0.7 (0.1-3.1)	0.6
Source of infection:		
-Primary	Ref.	
-Intravascular catheter related	0.6 (0.3-1.5)	0.3
-Pulmonary	0.2 (0.1-0.6)	<0.01
-Abdominal	0.4 (0.1-1.3)	0.5
-Urinary	0.4 (0.1-1.3)	0.1
-Skin	0.9 (0.3-3)	0.9
-Other**	0.6 (0.2-2)	0.4
BSI acquired before ICU admission	0.6 (0.3-1.3)	0.2
Antibiotics in the last 7 days	1.9 (0.9-3.9)	0.056
Delay between hospital admission and BSI	0.9 (0.9-1.1)	0.7

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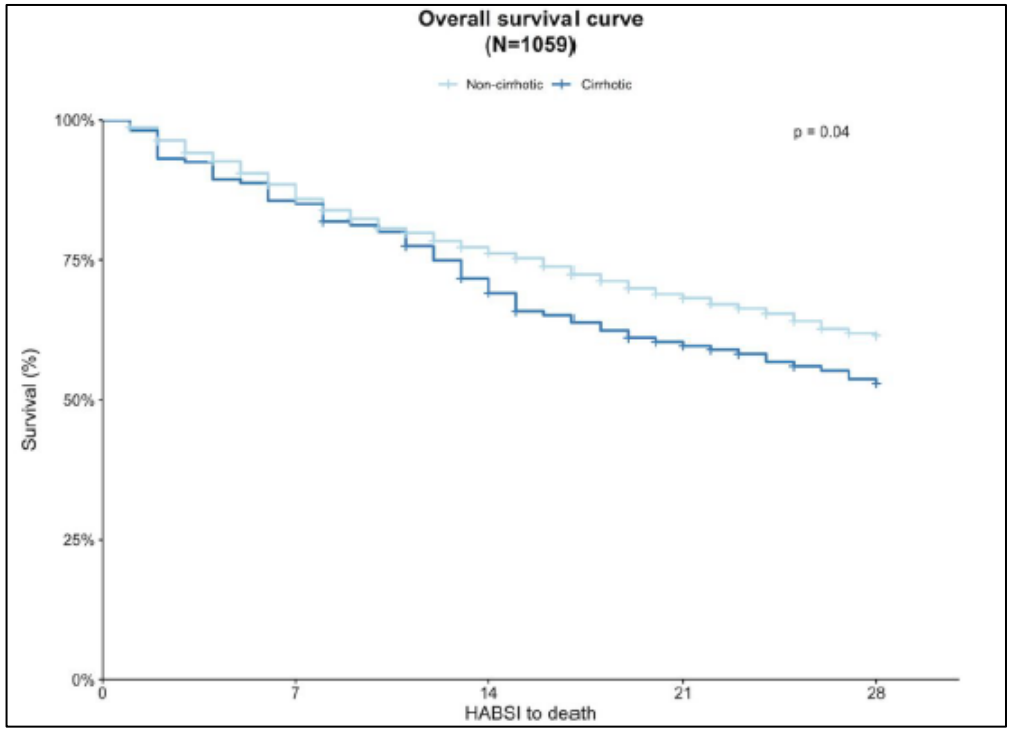
LIVER DISEASE

RESULTS

- Mortality increased for cirrhotic patients

Table E7. Multivariable frailty Cox model for the association cirrhosis and mortality

n=1057	Mortality, HR (95% CI)	p
Cirrhosis	**1.3 (1.01-1.7)**	**0.045**
Difficult-to-treat gram negative bacteria	1.8 (1.3-2.4)	<0.01
No consultation by a clinical pharmacist	0.9 (0.7-1.3)	0.9
Source control:		
-not required	1	<0.01
-required and complete	0.6 (0.5-0.8)	<0.01
-required but not achieved	2 (1.5-2.7)	<0.01
SAPS II on ICU admission	1.02 (1.01-1.03)	<0.01
Reason for ICU admission: COVID-19	2.2 (1.6-3)	<0.01



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LIVER DISEASE

DISCUSSION

- HABSI patients with liver cirrhosis had higher mortality than those without cirrhosis.
- HABSI in cirrhotic patients were more frequently due to Gram-positive bacteria, especially *E. faecium*, than in non-cirrhotic patients.
  - Abdominal? Repeated prophylactic antibiotic treatments?
  - *E. faecium* → >10% of HABSI in cirrhotic patients – empirical therapy?
- No difference regarding antimicrobial resistance was observed between the two groups
  - *Klebsiella* spp and *E coli* resistant to 3rd gen cephalosporins → almost fifty percent of all HABSI without differences between cirrhotic and non-cirrhotic patients.
- No significant difference in the incidence of fungal HABSI between cirrhotic and non-cirrhotic patients.

CONTENT

- Eurobact-2 database
- Original study
- The role of centre and country factors
- Liver disease
- Conclusions/perspectives

CONCLUSIONS

- Importance of large prospective cohort studies
  - Plan possible research questions at time of study design
  - Data quality: essential
  - Global picture (core paper)
  - Several analyses on specific populations (comorbidity, microorganism,…)
- Other not mentioned projects:
  - COVID-19 vs non-COVID-19 (Crit Care publication)
  - Turkey cohort study (JAC publication)
- Ongoing projects:
  - Elderly population (2x abstracts ECCMID 2024)
  - Methodological paper on adequacy of therapy in the first 24h
  - Bitherapy
  - Immunosuppressed patients
  - Patients with withdrawn/withdrawal
  - Source control
  - *Acinetobacter* spp HABSI
- Intravascular catheter HABSI population, Fungal HABSI, VRE

AND AND AND AND……

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Sub-Saharan Africa

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<u>**North America**</u>

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<u>**South Asia**</u>

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