

COMBACTE-CARE ECCMID 2016

Work Package 1A Update

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COMBACTE-CARE WP1A

	Academic	EFPIA
Leaders	Jesús Rodríguez-Baño (SAS) Hajo Grundmann (UMCG)	Seamus O'Brien (AZ)
Partners	George Daikos (NKUA) Mike Sharland (SGUL) Lul Raka (NIPKH) Jan Bayersman (UULM) Herman Goossens (UA) Marc Bonten (UMCU) Marlieke de Kraker (UNIGE)	Helen Steele (GSK) Anne Witschi (Basilea) Jon Goodall (AZ)



EURECA

(COMBACTE-CARE WP1A)

European prospective cohort study on Enterobacteriaceae
showing REsistance to CArbapenems



EURECA team (beyond partners)

- Sevilla
 - SAS-HUVM staff: Pilar Retamar, L. Eduardo López Cortés, Alvaro Pascual, Lorena López-Cerero
 - COMBACTE: Belén Gutiérrez-Gutiérrez (study coordinator), Jesús Sojo, Jose Bravo-Ferrer, María Paniagua, Zaira Palacios
 - Management Office and monitoring: Sophie Monteau, Almudena Serna, Eva López, Victoria García, Virginia Palomo
- Utrecht
 - Ron de Winter, Nienke Cuperus
 - eCRF: Joost Schostman, Chantal Hendricks
- London: Laura Folgori
- Antwerp: Tomi Kostyanev, Christine Lammens
- AZ: Fiona Aldridge



Some unanswered questions in CRE and CRAB

- Individual and group risk factors? → Target population for RCT
- Outcome determinants? → Design of RCT
- Best available treatment (BAT)? → Comparator in RCT
- Outcome impact and cost? → Medical and societal need



EURECA Objectives

Targeted infections:

- cIAI, pneumonia, cUTI, BSI due to CRE
- BSI due to CRAB
- To provide historical cohorts for comparison of efficacy of new drugs
- To identify the outcome predictors
 - Including best available therapy (BAT)
 - Impact of specific carbapenemases and carbapenem-MIC
- To identify the risk factors for CRE infection to inform the design of RCTs
- To assess the mortality, excess length of stay and cost associated to CRE infections



EURECA. Studies and designs

- Study 1. Prospective cohort studies
 - CRE: cIAI, cUTI, pneumonia and BSI
 - CRAB: BSI
- Study 2. Nested case-control-control study (only CRE)
 - Cases: CRE
 - Control 1: CSE (1:1)
 - Control 2: admitted (“non-infected”) patients (3:1)
- Study 3. Matched cohorts (only CRE)
 - Same as above
- Quality of data: monitoring



**CRE and CRAB
prospective cohorts**

201 CRAB

804 CRE

Study 1: Prospective Cohort Study
Outcome predictors

248 selected CRE

**Study 2: Nested
Cases- Control**
Risk Factors

+

**248 Matched CSE
(1:1)**

Control 1

+

**744 Non-infected
(3:1)**

Control 2

**Study 3: Matched
cohort Study**
-Cost
-Mortality
-Length of Stay

Matching criteria

- CSE: site, type of infection, hospital stay, ward
- Non-infected: site, hospital stay, hospital ward

EURECA. Outcome variables

- Study 1:
 - Primary
 - Mortality until day 30
 - Clinical response at day 21 (failure vs cure/improvement)
 - Secondary
 - Microbiological response at day 21
 - Hospital mortality, infection-related mortality until day 30
 - Length of hospital stay
 - Duration of antibiotic treatment
 - Recurrence, superinfection
 - Therapy-related adverse events

EURECA. Outcome variables

- Study 2:
 - Infection due to CRE
- Study 3
 - Mortality
 - Length of hospital stay, ICU stay and mechanical ventilation



Explanatory variables	Study 1	Study 2	Study 3
Selection criteria	<u>✓</u>	<u>✓</u>	<u>✓</u>
Demographics	<u>✓</u>	<u>✓</u>	<u>✓</u>
Epidemiological variables		<u>✓</u>	<u>✓</u>
Previous colonisation by CRE/antibiotics received		<u>✓</u>	<u>✓</u>
Hospital level-variables		<u>✓</u>	<u>✓</u>
Comorbidities	<u>✓</u>		
Acquisition	<u>✓</u>	<u>✓</u>	<u>✓</u>
Pitt score, SOFA and APACHE -II	<u>✓</u>	<u>✓</u>	<u>✓</u>
Invasive procedures		<u>✓</u>	<u>✓</u>
Type of infection	<u>✓</u>	<u>✓</u>	<u>✓</u>
Microbiological variables	<u>✓</u>	<u>✓</u>	<u>✓</u>
Other analytical results	<u>✓</u>		
Safety of drugs	<u>✓</u>		
Antimicrobial therapy	<u>✓</u>		
Non-antibiotic treatment (source control, support therapy)	<u>✓</u>		
Outcome	<u>✓</u>		
Length of hospital stay		<u>✓</u>	<u>✓</u>

EURECA. Statistical analyses

- Mortality, BAT: cox regression models
- Cure/improvement: multivariate logistic regression
- Length of stay: competing risk analysis
- Risk factors: multilevel analysis



EURECA

(COMBACTE-CARE WP1A/B)

European prospective cohort study on Enterobacteriaceae
showing REsistance to CARbapenems

1

STUDY PROTOCOL

Title	Prospective observational study to assess the risk factors, clinical management and outcomes of hospitalized patients with serious infections caused by carbapenem-resistant Enterobacteriaceae and <i>Acinetobacter baumannii</i>
Acronym	EURECA
Study sponsor	FISEVI (Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla), Hospital Universitario Virgen Macarena, Avda Dr Fedriani 3, 41009 Sevilla, Spain
Lead investigator	Jesús Rodríguez-Baño Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospitales Universitarios Virgen Macarena y Virgen del Rocío. Sevilla, Spain
Co-lead investigators	Hajo Grundmann. University Medical Center. Groningen, The Netherlands Helen Steel. GSK, UK. Seamus O'Brian. Therapeutic Area Clinical Director and Operations and Strategy lead for the Infection Global Medicines Unit. AstraZeneca
Study coordinator and coordinator-associates	Belén Gutiérrez-Gutiérrez, Jesús Sojo-Dorado, Álvaro Pascual Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospitales Universitarios Virgen Macarena y Virgen del Rocío. Sevilla, Spain
Partners	Jan Beyersmann. Institute of Statistics. Ulm University. Ulm, Germany Marlieke de Kraker. Geneva University hospital, Department of Infection prevention and control, Geneva, Switzerland. Mike Sharland. St George's, University of London. London, United Kingdom. George Daikos. First Department of Medicine, University of Athens, Laiko General Hospital. Athens, Greece.

3

WP1A. EURECA. Sites selection

- Site Selection Committee
- Feasibility tests (CLIN-NET, LAB-NET)
- Target countries/regions: Spain, Italy, Balkan countries, Greece, Turkey
- 50 European hospitals selected
- Criteria
 - Rate of CRE and CRAB
 - Lab capacity
 - Paediatric beds
 - Experience
- National/regional coordinators



Albania	University Hospital of Lung Diseases 'Shefqet Ndroqi'
Bulgaria	University Hospital for Emergency Medicine Pirogov
Croatia	University Hospital for Infectious Diseases, Zagreb
Greece	Agioi Anargyroi General Hospital of Athens
Greece	Attikon University General Hospital
Greece	Evangelismos General Hospital of Athens
Greece	General Hospital of Larissa
Greece	General University Hospital of Thessaloniki 'Ahepa'
Greece	Hippokration Hospital of Thessaloniki
Greece	Iaso General Hospital
Greece	Laiko General Hospital
Greece	University Hospital of Alexandroupolis
Greece	University Hospital of Larissa
Greece	University Hospital of Patras
Italy	Florence University Hospital
Italy	Hospital Luigi Sacco
Italy	IRCCS Fondazione Ca Granda Ospedale Maggiore Policlinico



Italy	Molinette Teaching Hospital
Italy	National Institute for Infectious Diseases Lazzaro Spallanzani
Italy	Policlinico S. Orsola Malpighi
Italy	Policlinico Universitario A. Gemelli
Italy	San Martino University Hospital
Italy	University of Milan-Bicocca, San Gerardo
Italy	University of Naples S.U.N./Monaldi Hospital
Kosovo	University Clinical Center of Kosovo
Montenegro	Clinical Center of Montenegro Podgorica
Romania	Clinical Hospital Of Infectious Diseases Of Iasi
Romania	Cluj Napoca Infectious disease Clinical Hospital
Romania	Elias university emergency hospital
Romania	Fundeni Clinical Hospital
Romania	Infectious and Tropical Diseases Hospital “Dr. Victor Babes”
Romania	Mures County Clinical Emergency Hospital
Romania	The National Institute of Infectious Diseases Matei Bals
Serbia	Clinical Centre of Serbia



Serbia	Clinical Centre of Svezdara
Serbia	Clinical Centre of Vojvodina
Serbia	Clinical center Nis
Serbia	Clinical center of “Dragisa Misovic”
Spain	Hospital Universitari de Bellvitge
Spain	Hospital Universitario 12 de Octubre
Spain	Hospital Universitario Carlos Haya Málaga
Spain	Hospital Universitario La Paz
Spain	Hospital Universitario Ramon y Cajal
Spain	Servicio Andaluz de Salud- Reina Sofia University Hospital
Spain	Hospital Puerta de Hierro
Turkey	Ankara University
Turkey	Hacettepe University School of Medicine
Turkey	Izmir Chest Diseases and Surgery Training and Research Hospital
Turkey	Marmara University School of medicine
Turkey	Uludag University

National/regional coordinators

Italy: Pierluigi Viale

Greece: George Daikos (partner)

Romania: Adriana Hristea

Turkey: Murat Akova

Serbia (1) and Montenegro: Biljana Carevic

Serbia (2): Gorana Dragovac

Albania, Bulgaria, Kosovo and Croatia: Lul Raka (partner)



WP1A. EURECA. Ethical issues

- Observational (no intervention)
- All data are anonymised
- Access-controlled web-based eCRF
- IRBs approval. Written informed consent if needed



IRBs approval and agreements

- IRBs approval
 - Protocol and IC translated to local languages
 - Already obtained for sites in Rumania, Kosovo and Spain - ongoing in the others
- Agreements
 - Translated to local languages
 - Signed in some Spanish sites
 - Ongoing in the rest of sites
- Webcast investigators training

WP1A. EURECA. eCRF

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Jesús Rodríguez Baño

Data collection overview

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Search filter:

Subject nr

Site

Sort by

Date of admission from

Date of admission to

First name

Last name

Local Patient ID

Subject	Screening	Day 0	Day 3	Day 7	Day 14	Day 21	Day 30	Antimicrobial therapy	Adverse events
T069								1	1
T068									
T067								1	1
T066								1	1
T055								1	1
T049								2	2
T048								1	1
T047								1	1
T046								1	1
T045									

Updates of pending controls

Site	status	Patient_Eur eca_id	Patient_gro up	Source_ of_infec tion	Type_of_aq uisition	Type_of_ser vice	Specific_ward	Match_for_ patient____en ter_Eureca =	Date_of_ho spitalization	Date_for _day_0	Days_from_admission_to _day_0	Deadline_to _include_co ntrols	CSE	Adm1	adm2	adm3
UMC Utrecht	Completed	T052	CRE	cUTI	Community	Medical	Nephrology		01/02/16	04/02/16	3		T055	T056	T057	T065
UMC Utrecht	Matched	T055	CSE	cUTI	Community	Medical		T052	14/02/16	17/02/16						
UMC Utrecht	Matched	T056	Admitted			Medical	Nephrology	T052	10/02/16	12/02/16						
UMC Utrecht	Matched	T057	Admitted			Medical	Nephrology	T052	07/02/16	09/02/16						
UMC Utrecht	Matched	T065	Admitted			Medical	Nephrology	T052								
UMC Utrecht	Does not need controls	T053	CRAB	BSI	Nosocomial	ICU	ICU		02/02/16	12/02/16						
UMC Utrecht	Need controls	T054	CRE	PN	Nosocomial	ICU	ICU-1		03/02/16	17/02/16	14	18/05/16	T061			
UMC Utrecht	Matched	T061	CSE	PN	Nosocomial	ICU		T054	27/02/16	09/02/16						
UMC Utrecht	In Search		Admitted			ICU	ICU-1				Required 13					
UMC Utrecht	In Search		Admitted			ICU	ICU-1				Required 13					
UMC Utrecht	In Search		Admitted			ICU	ICU-1				Required 13					
UMC Utrecht	Need controls	T058	CRE	BSI	Community	Pediatric ICU	Pediatric ICU-2		13/02/16	14/02/16	1	15/05/16	T060	T063		
UMC Utrecht	Matched	T060	CSE	BSI	Community	Pediatric ICU		T058	08/02/16	08/02/16						
UMC Utrecht	Matched	T063	Admitted		Community	Pediatric ICU	Pediatric ICU-2	T058	12/02/16	12/02/16						
UMC Utrecht	In Search		Admitted			Pediatric ICU	Pediatric ICU-2				Required 0					
UMC Utrecht	In Search		Admitted			Pediatric ICU	Pediatric ICU-2				Required 0					
UMC Utrecht	Does not need controls	T059	CRAB	BSI	Nosocomial	ICU	ICU		06/02/16	08/02/16						
UMC Utrecht	Does not need controls	T062	CRAB	BSI	Nosocomial	Surgery	Neurosurgery		03/02/16	11/02/16						
UMC Utrecht	Need controls	T064	CRE	IAI	Nosocomial	Surgery	Trauma		22/01/16	04/02/16	13	05/05/16				
UMC Utrecht	In Search		CSE	IAI	Nococomial	Surgery					Required from 10 to 12					
UMC Utrecht	In Search		Admitted			Surgery	Trauma				Required 12					
UMC Utrecht	In Search		Admitted			Surgery	Trauma				Required 12					
UMC Utrecht	In Search		Admitted			Surgery	Trauma				Required 12					



WP1A. Dissemination activities

Type	Title	Target audience
Presentation	Investigators meeting (Belgrade)	Participants
Manuscript	Palacios-Baena Z et al. Comprehensive clinical and epidemiological assessment of colonisation and infection due to carbapenemase-producing Enterobacteriaceae in Spain. J Infect. 2016 Feb;72(2):152-60.	Medical community
Meeting Abstract (ECCMID)	Predictive rule for mortality in bloodstream infections due to carbapenemase-producing Enterobacteriaceae. Gutiérrez-Gutiérrez et al. ECMID 2016	ID and CM specialists
Manuscript	Predictive rule for mortality in bloodstream infections due to carbapenemase-producing Enterobacteriaceae. Gutiérrez-Gutiérrez et al. Submitted.	Medical community
Presentation	EURECA overview. Conference and CLIN-Net National Coordinator Meeting. Grindelwald Switzerland	CLIN-Net Coordinators
Web	EURECA progress and start	Scientific community, public



Comprehensive clinical and epidemiological assessment of colonisation and infection due to carbapenemase-producing Enterobacteriaceae in Spain

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Laura Zamorano^k, Verónica Bautista^b, Adriana Ortega^b,
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and REIPI Group for CPE^q

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EURECA

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Thank you all for the hard work!!!