Monza: un’esperienza vincente?

Milano, 14 Maggio 2020

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Disclosures

- AG received speaker’s honoraria and fees for attending advisory boards from ViiV Healthcare, Gilead, Janssen-Cilag, Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer and Novartis and received research grants from ViiV, Bristol-Myers Squibb, and Gilead.

Sometimes, late in the 60's, an authoritative American politician declared *'It's time to close the books on infectious diseases, declare the war against pestilence won, and shift national resources to such chronic problems as cancer and heart disease'*

William H. Stewart, the Surgeon General

Quali patogeni?

POLMONITI ALL'INGRESSO IN ICU (Dati GiViTI 2017)

POLMONITI NOSOCOMIALI ALL'INGRESSO IN ICU con microrganismi isolati: 779*				
	n° isolati	% su isolati tot	n° MDR	% su gruppo
Numero totale di microrganismi isolati	1026		339	43.5
Gram +	243	**31.2**	99	40.7
Staphylococcus aureus [MRSA]	136	17.5	74	54.4
Streptococcus pneumoniae [resistente alla penicillina]	41	5.3	4	9.8
Gram -	503	**64.6**	257	51.1
Pseudomonas aeruginosa [MDR CARBA-R]	132	16.9	37	28.0
Klebsiella spp [ESBL/CARBA-R]	134	17.2	68/42	50.7/31.6
Escherichia coli [ESBL/CARBA-R]	96	12.3	32/1	33.3/1.0
Acinetobacter [CARBA-R]	87	11.2	73	83.9

* Pazienti con **polmonite all'ingresso in ICU provenienti da ospedale o altra TI** (microrganismi isolati nel 57.8% dei casi)

GiViTI, Rapporto Progetto PROSAFE - Petalo INFEZIONI 2018

Quali patogeni?

CONFRONTO RESISTENZE 2005 - 2017

	POLMONITI NOSOCOMIALI ALL'INGRESSO IN ICU (2017)		INFEZIONI DURANTE LA DEGENZA IN ICU (2005)
	% su isolati tot	% MDR su gruppo	% MDR su gruppo
Totale microrganismi		43.5	26.8
Gram +	**31.2**	40.7	
Staphylococcus aureus	17.5	54.4 [MRSA]	13.0 [MRSA]
Gram -	**64.6**	51.1	
Pseudomonas aeruginosa	16.9	28.0 [MDR CARBA-R]	8.9 [MDR]
Klebsiella spp	17.2	50.7/31.6 [ESBL/CARBA-R]	6.0 [ESBL]
Escherichia coli	12.3	33.3/1.0 [ESBL/CARBA-R]	
Acinetobacter	11.2	83.9 [CARBA-R]	2.7 [CARBA-R]

Le infezioni in Terapia Intensiva. Rapporto del progetto di sorveglianza del GiViTI, anno 2005

GiViTI, Rapporto Progetto PROSAFE - Petalo INFEZIONI 2018

Global challenges...the need for innovation

PATHOGENS AND IMMUNITY

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RESEARCH ARTICLE

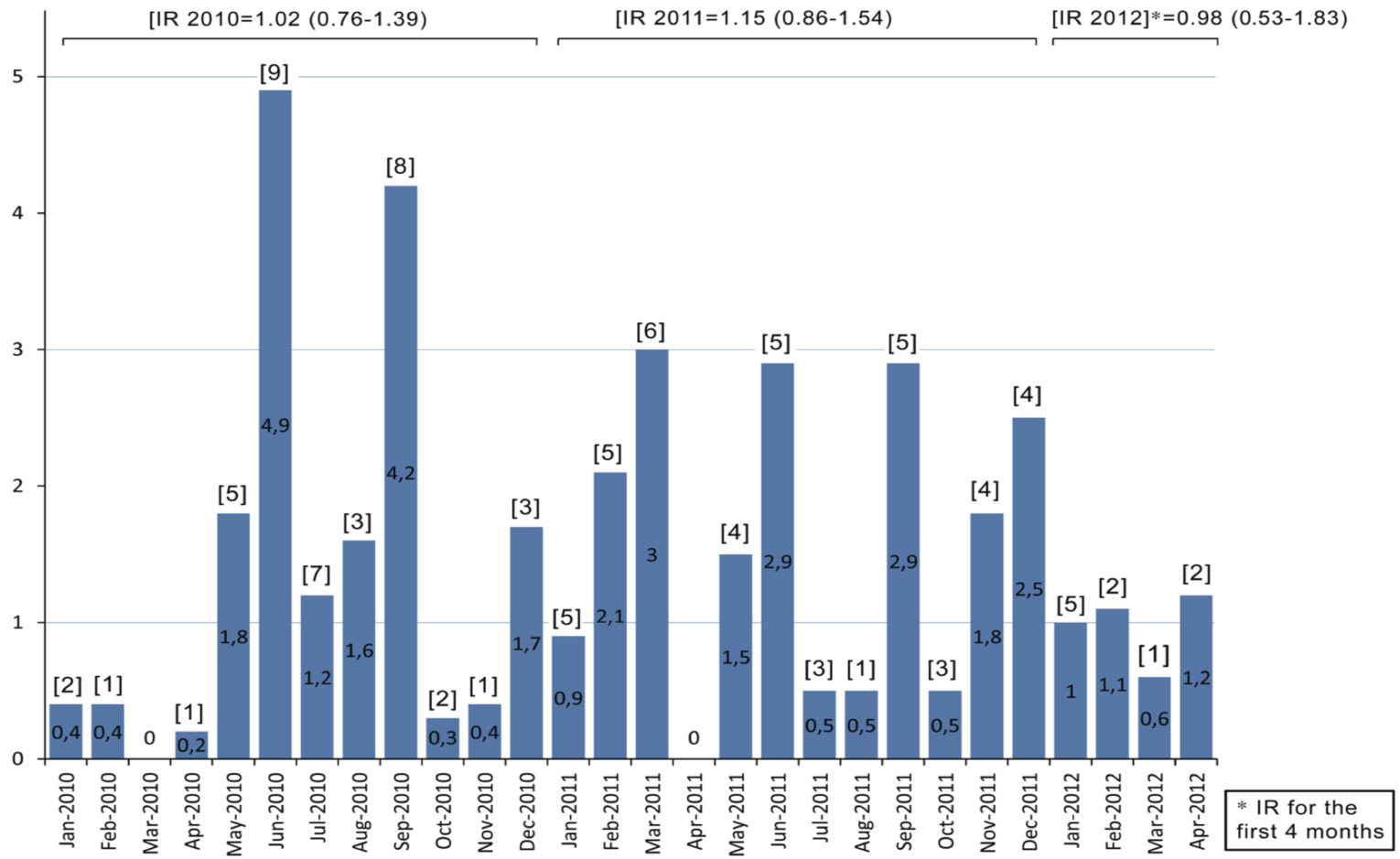
Published January 9, 2017

CLINICAL USEFULNESS OF *KLEBSIELLA PNEUMONIAE* CARBAPENEMASE-PRODUCING *K. PNEUMONIAE* GENOTYPING: THE EXPERIENCE OF A SINGLE-CENTER EPIDEMIC

AUTHORS

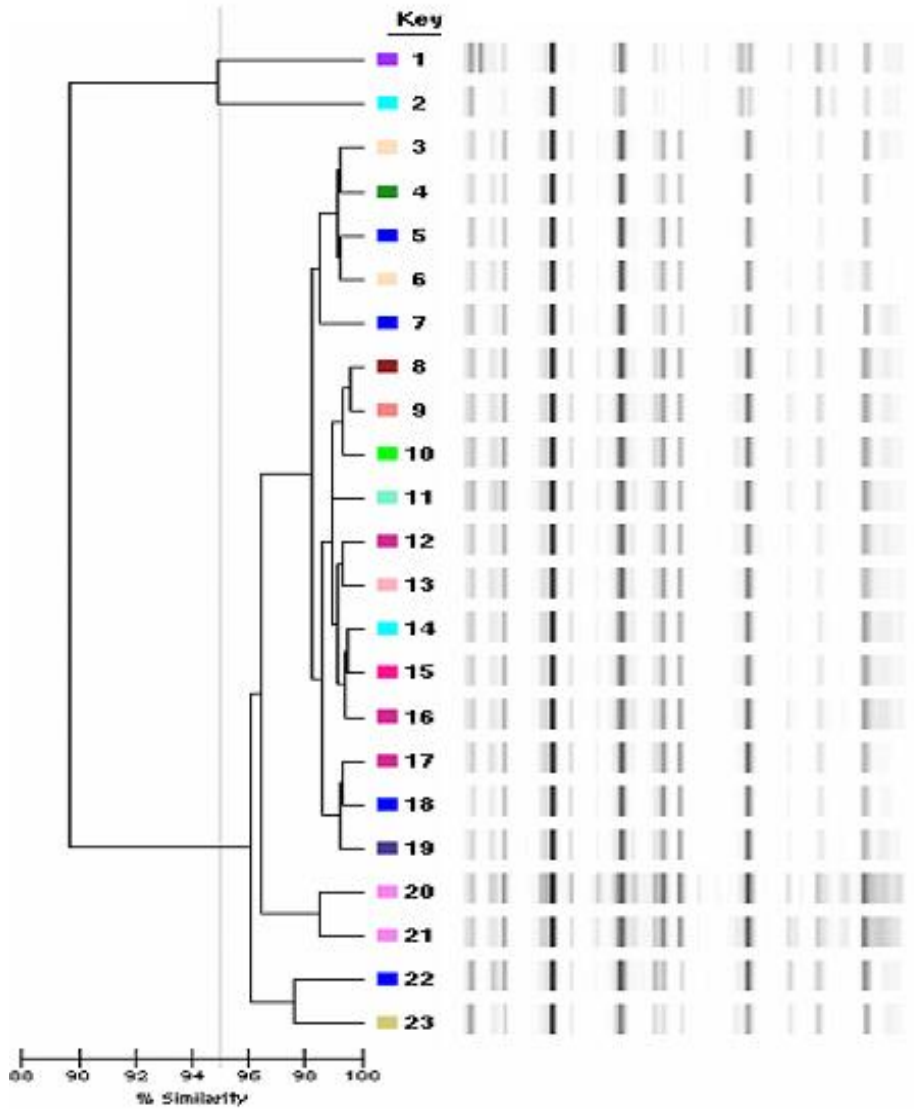
Marianna Rossi[1], Liliane Chatenoud[2], Egidio Franco Viganò[3], Anna Maria Peri[1], Laura Alagna[1], Simone Bramati[3], Monica Manenti[3], Monica Raggi[3], Annalisa Cavallero[3], Luca Bisi[1], Sebastiano Leone[1], Guglielmo Marco Migliorino[1], Alessandra Bandera[1], Andrea Gori[1]

Where we come from and who we are?



Rossi M et al. Pathogens and Immunity 2017

Ricerca clinica in ambito epidemiologico



Clone A

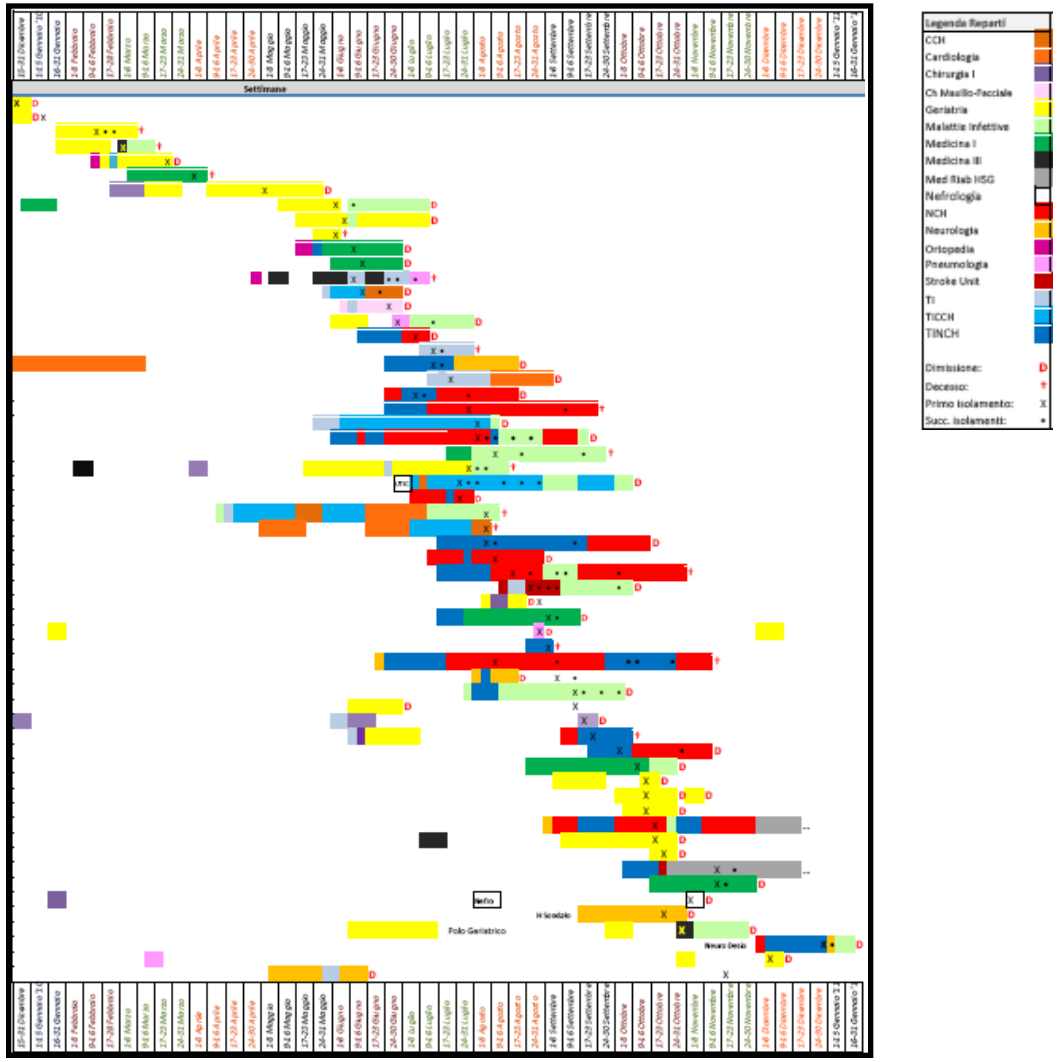
Clone C

Clone E

Clone F/L

Rossi M et al. Pathogens and Immunity 2017

Diffusione di KPC nei reparti di degenza



Caso indice: Reparto di Geriatria

Rapida diffusione a tutti i Reparti dell'Ospedale

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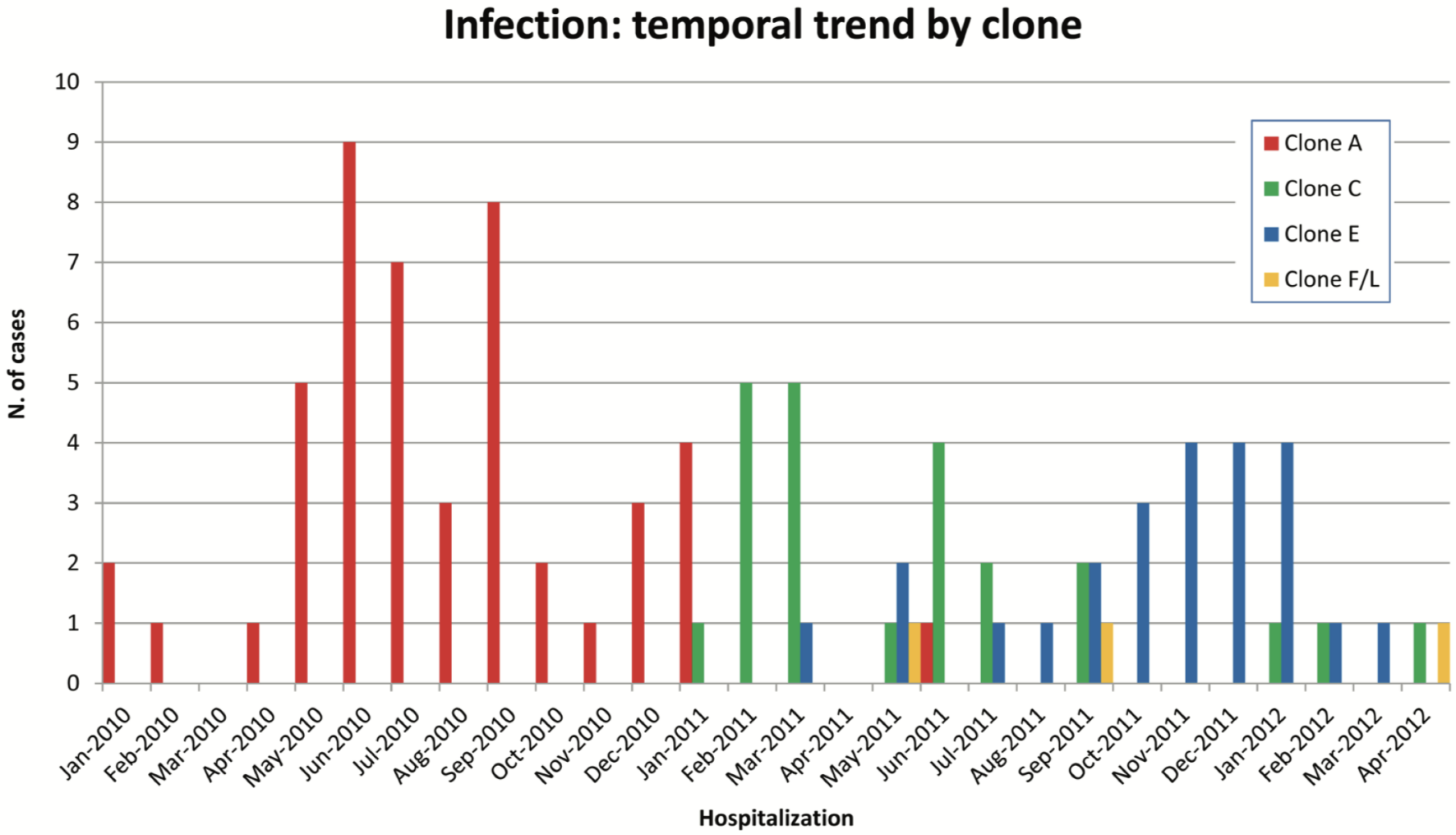
Where we come from and who we are?



Rossi M et al. Pathogens and Immunity 2017

Network KPC study

- Cohort study supported by the Italian Ministry of Health (RF-2011-02351728)
- 15 participating hospitals from Lombardy region, North Italy
- 8/15 800-bed public teaching institutions with about 25.000 admissions/year

Lombardy Region

10.000.000 inhabitants (16.5% of the Italian population)

Rossi M et al. ESCMID 2018

Network KPC study: study setting

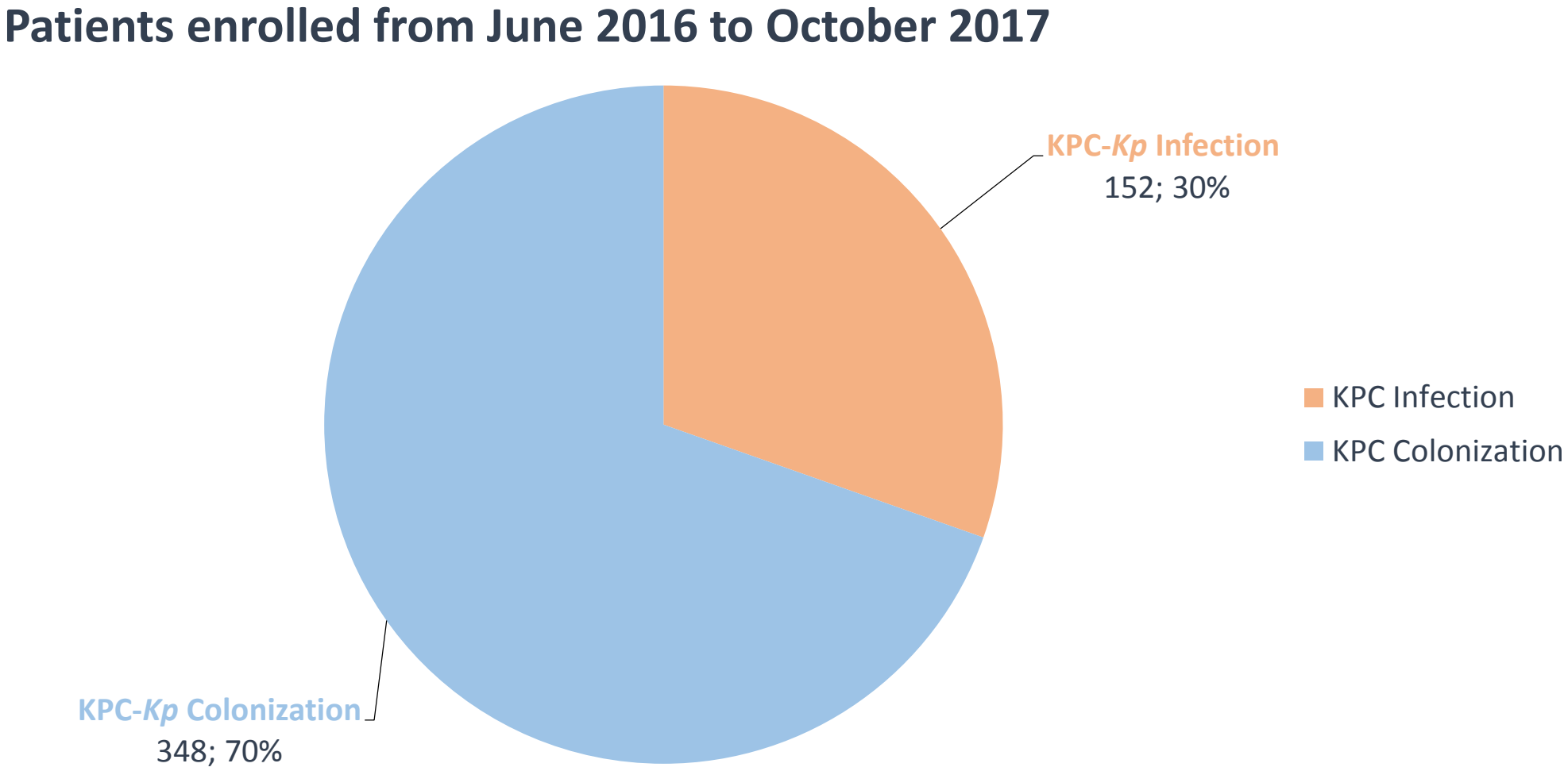
Inclusion criteria:
All KPC-*Kp* infected or colonized adult patients

Enrollment period:
10 – 24 consecutive months

Expected Sample Size:
About 1200 patients

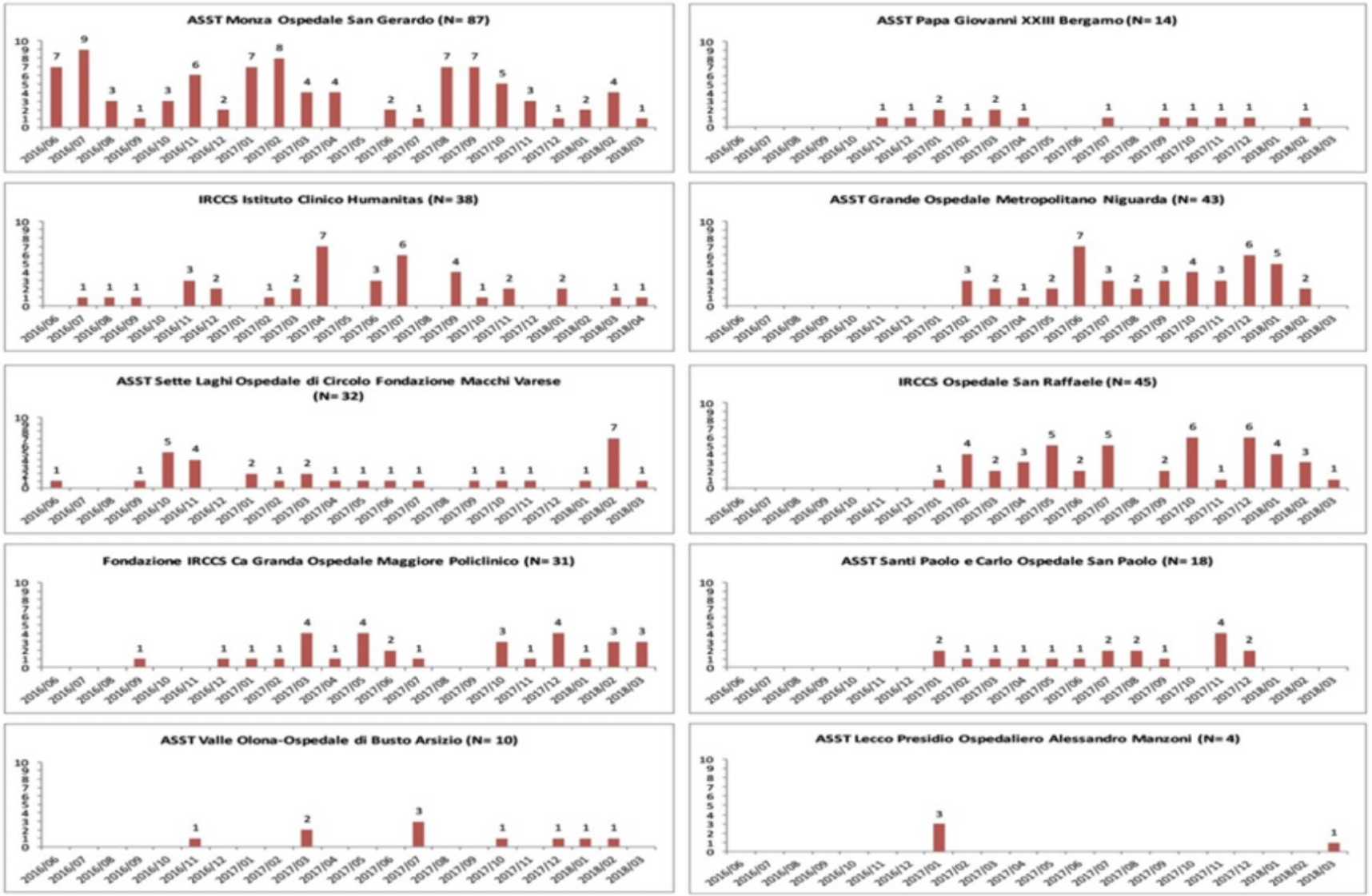
Rossi M et al. ESCMID 2018

KPC-*Kp* Infected and Colonized Patients

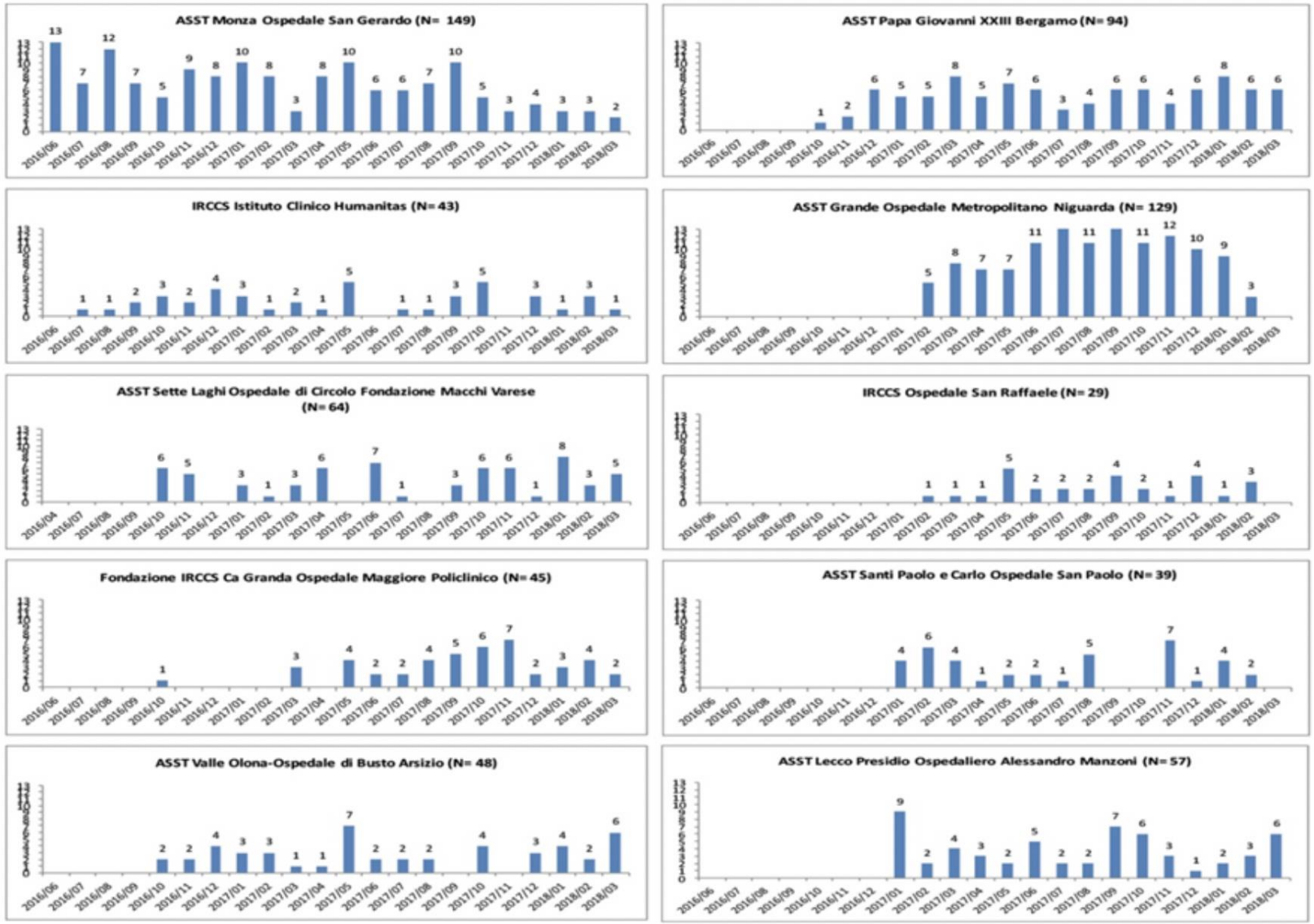


Rossi M et al. ESCMID 2018

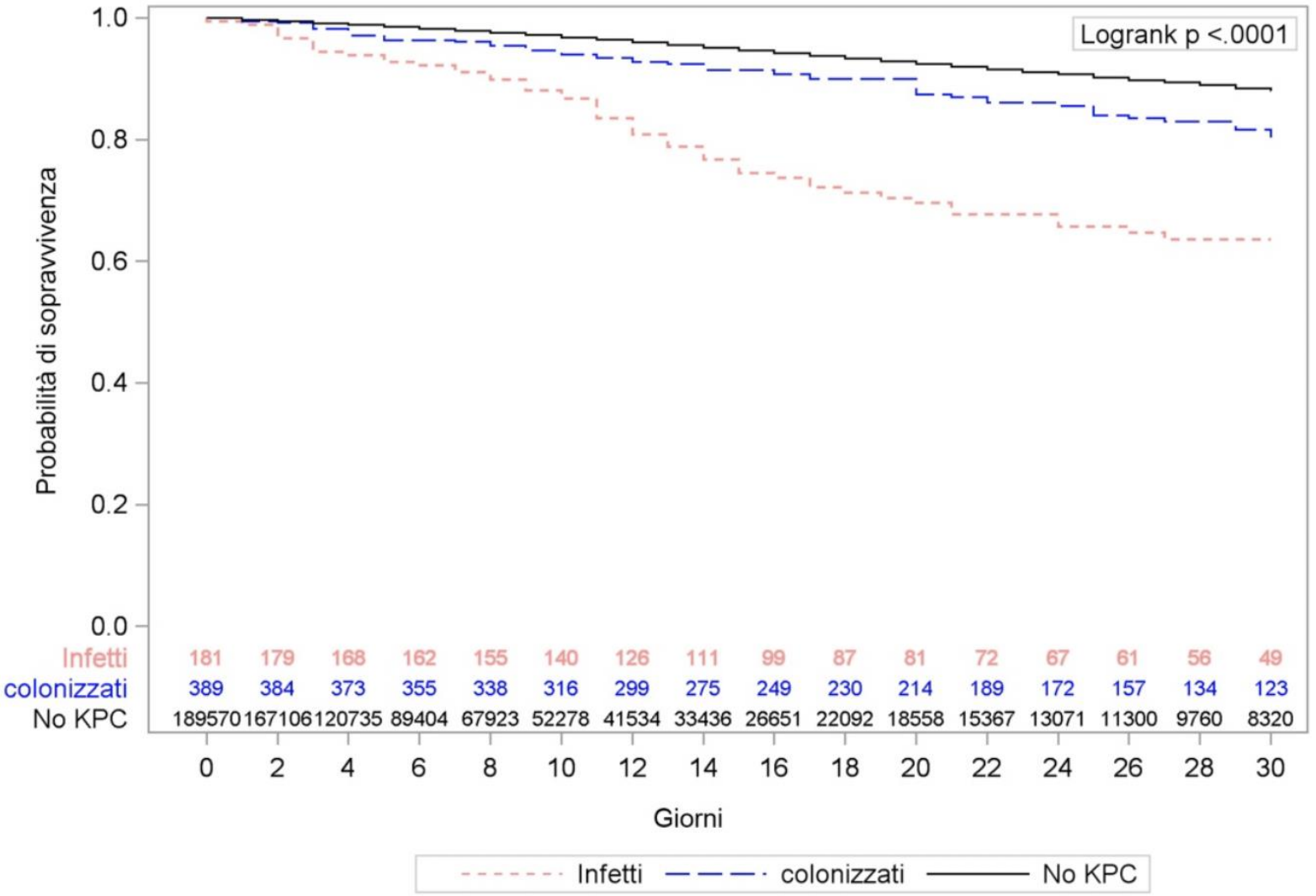
Distribuzione di frequenza dei pazienti infetti per centro e mese di isolamento



Distribuzione di frequenza dei pazienti colonizzati per centro e mese di isolamento



Mortalità a 30 giorni nei pazienti con infezione da KPC-*Kp*, colonizzati da KPC-*Kp* e pazienti non-KPC-*Kp*



Rossi M et al. ESCMID 2018

Critical Care Medicine
Society of Critical Care Medicine

Gastrointestinal colonization with multidrug-resistant Gram-negative bacteria during extracorporeal membrane oxygenation: effect on the risk of subsequent infections and impact on patient outcome

Authors

Giacomo Grasselli[1,2], MD; Vittorio Scaravilli[1], MD; Laura Alagna[3], MD; Michela Bombino[4], MD; Stefano De Falco[2], MD, Alessandra Bandera[2,3], MD; Chiara Abbruzzese[1], MD; Nicolò Patroniti[6], MD; Andrea Gori[2,3], MD; Antonio Pesenti[1,2], MD.

Conclusions

In patients undergoing ECMO for respiratory and/or circulatory failure, colonization by MDR G- bacteria is frequent and associated with more the tenfold odds for subsequent infection. Those infections are associated to an increased risk of death.

Patients population flowchart

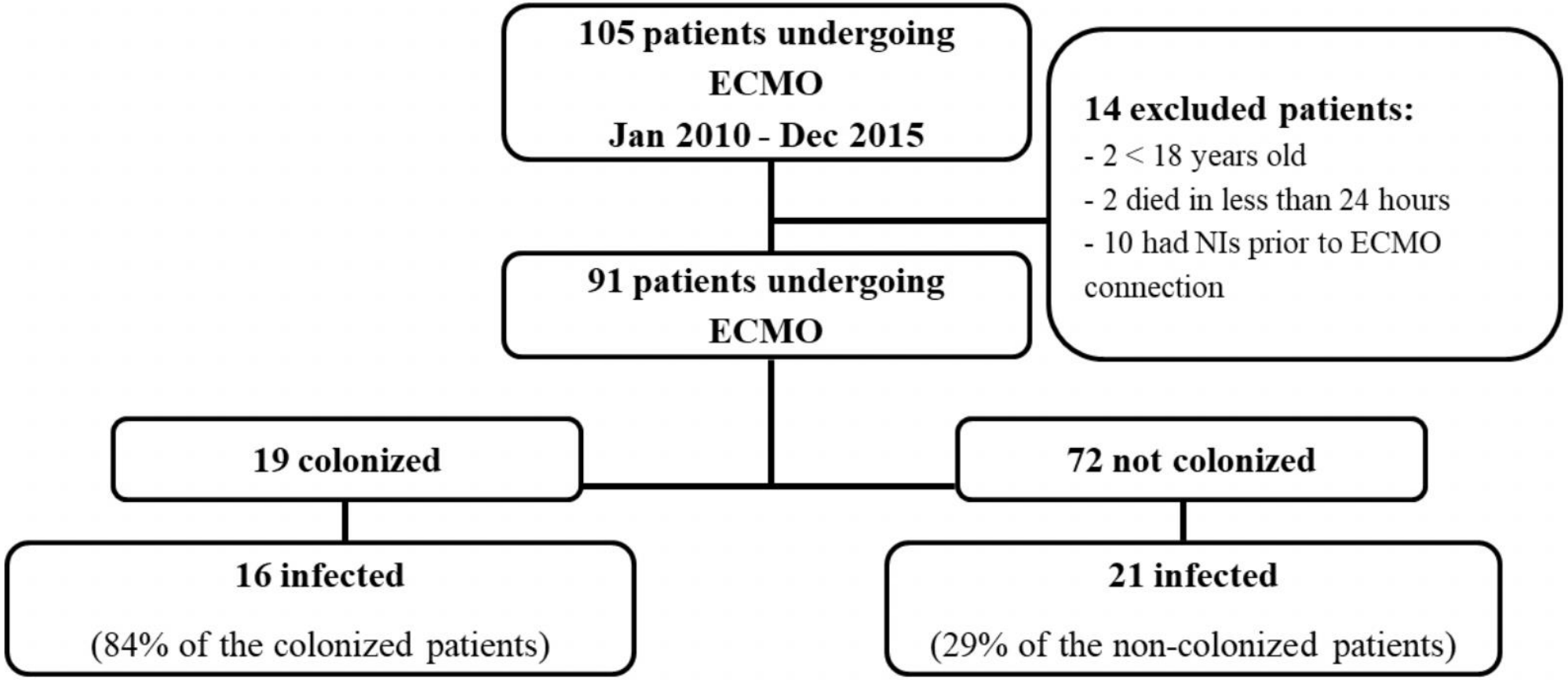
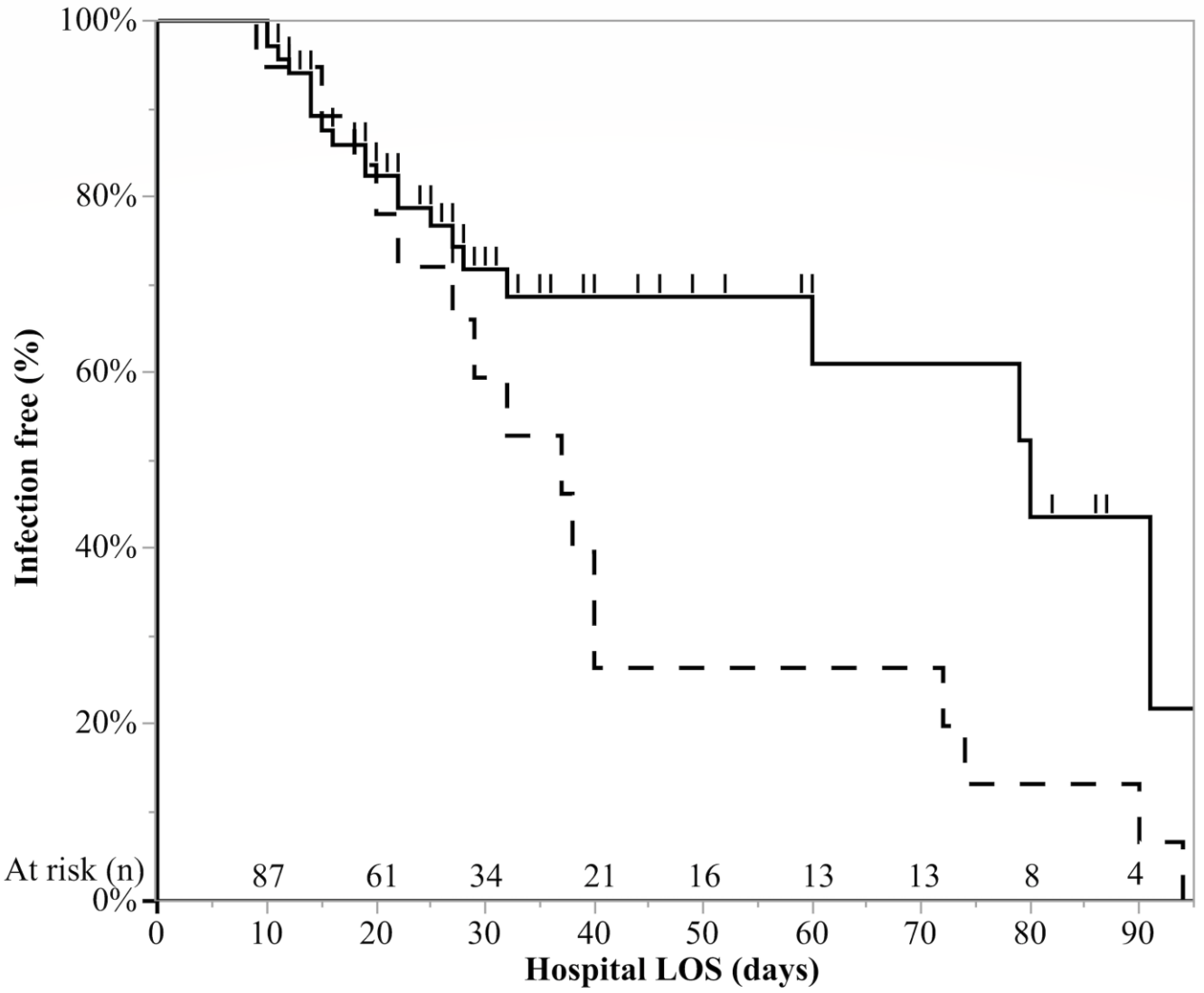


Figure S1. Patients population flowchart. ARDS, acute respiratory distress syndrome; ECMO,

Probability of being infection-free. Colonized patients vs non-colonized patients



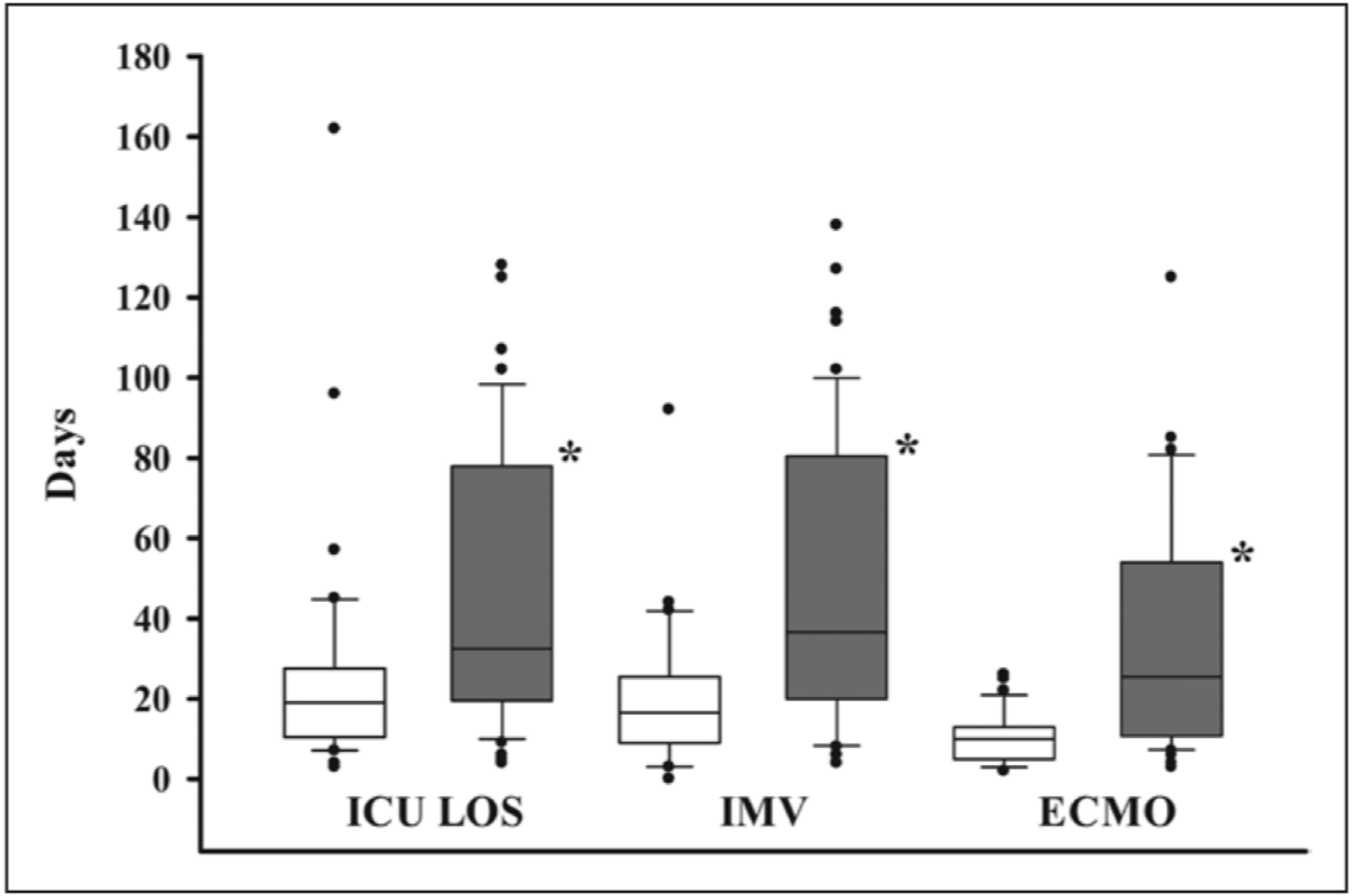
Nosocomial Infections During Extracorporeal Membrane Oxygenation: Incidence, Etiology, and Impact on Patients' Outcome

Giacomo Grasselli, MD[1]; Vittorio Scaravilli, MD[1]; Stefano Di Bella, MD[2]; Stefano Biffi, MD[3]; Michela Bombino, MD[4]; Nicolò Patroniti, MD[3,4]; Luca Bisi, MD[5]; Anna Maria Peri, MD[5]; Antonio Pesenti, MD[1,6]; Andrea Gori, MD[3,5]; Laura Alagna, MD[5]

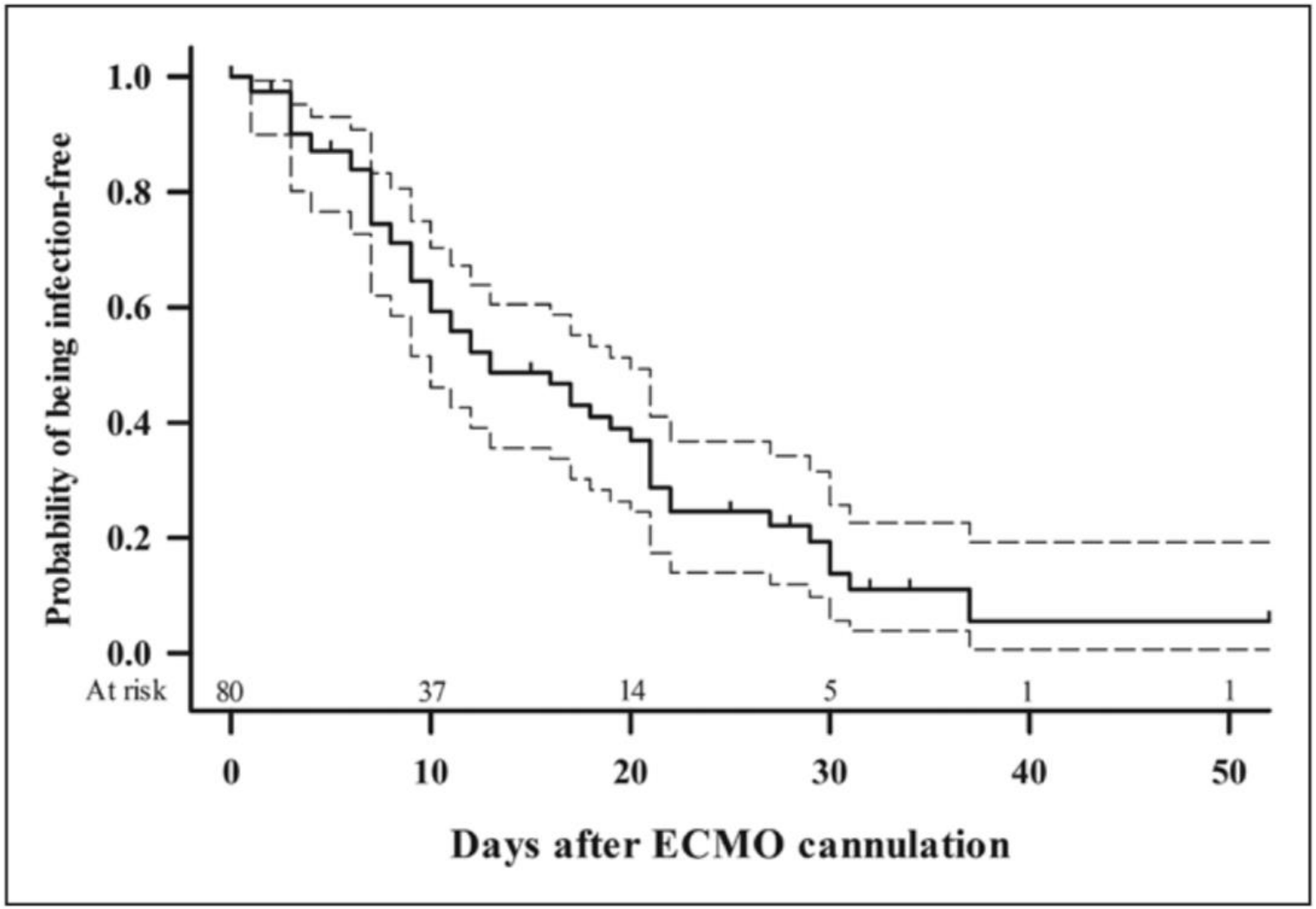
Conclusions: Infections (especially ventilator-associated pneumonia) during extracorporeal membrane oxygenation therapy are common and frequently involve multidrug-resistant organisms. In addition, they have a negative impact on patients' outcomes. (*Crit Care Med* 2017; 45:1726–1733)

Critical Care Medicine
Society of Critical Care Medicine
The Intensive Care Professionals

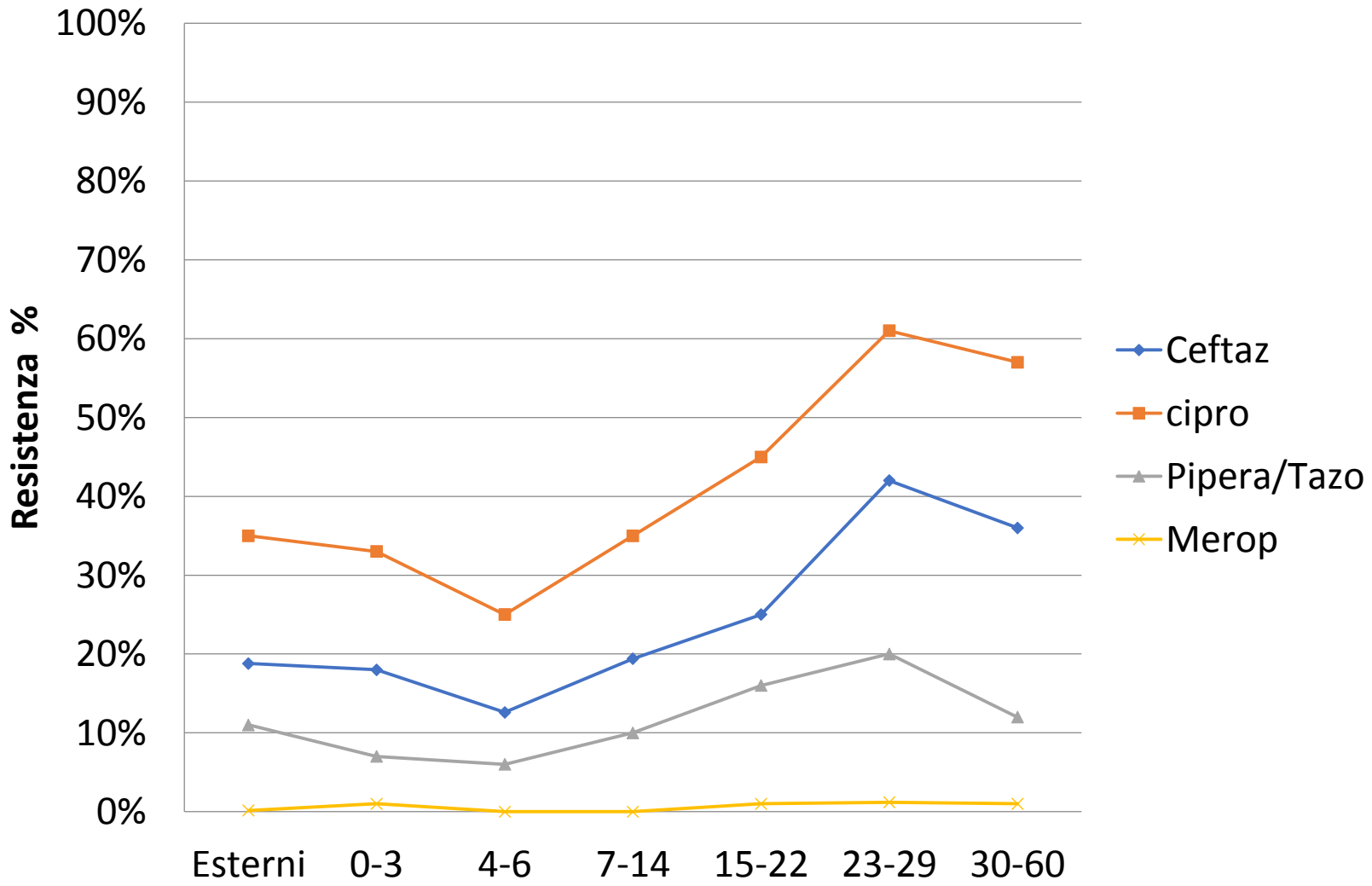
ICU length of stay: infected vs non-infected patients



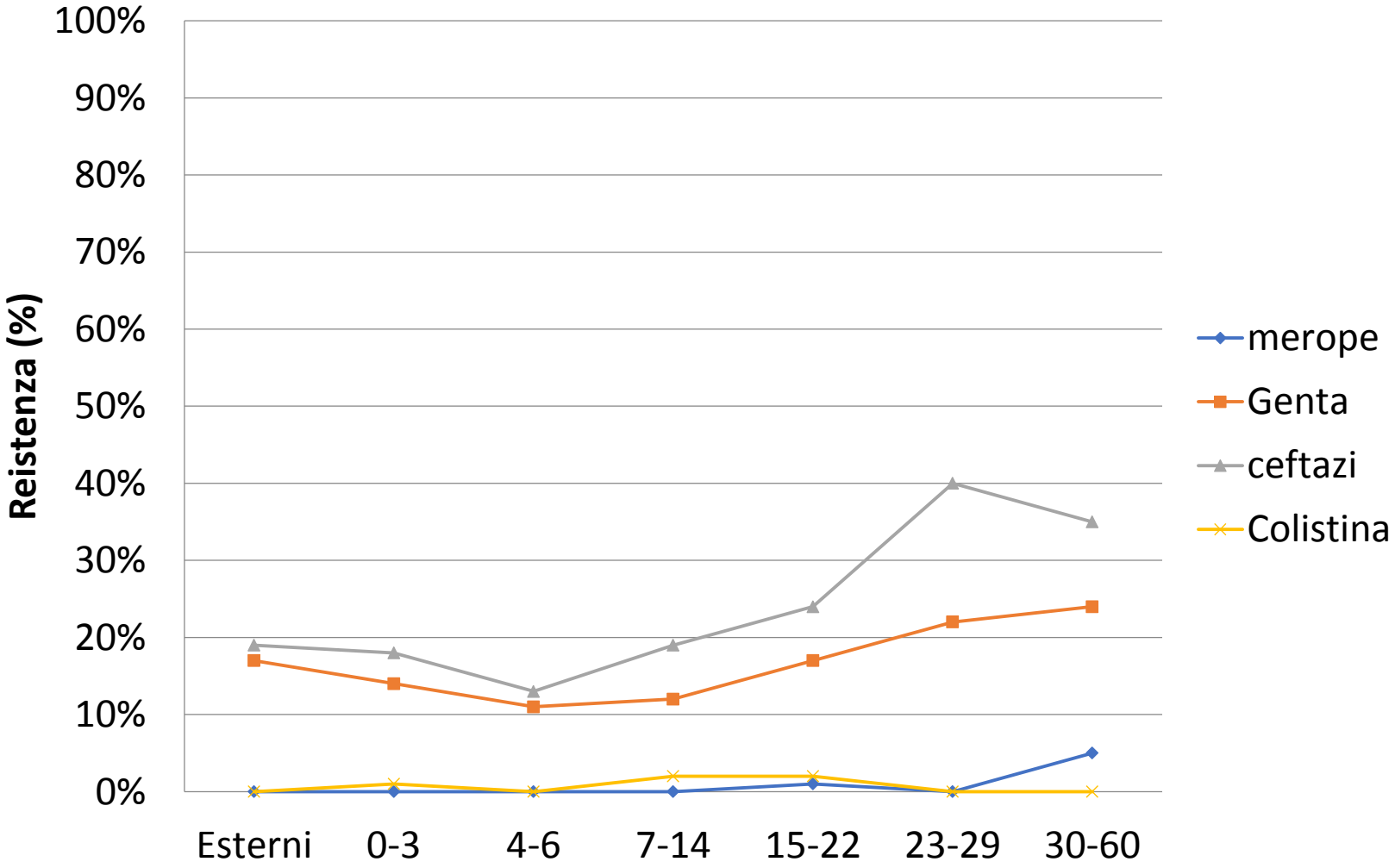
Probability of being infection-free



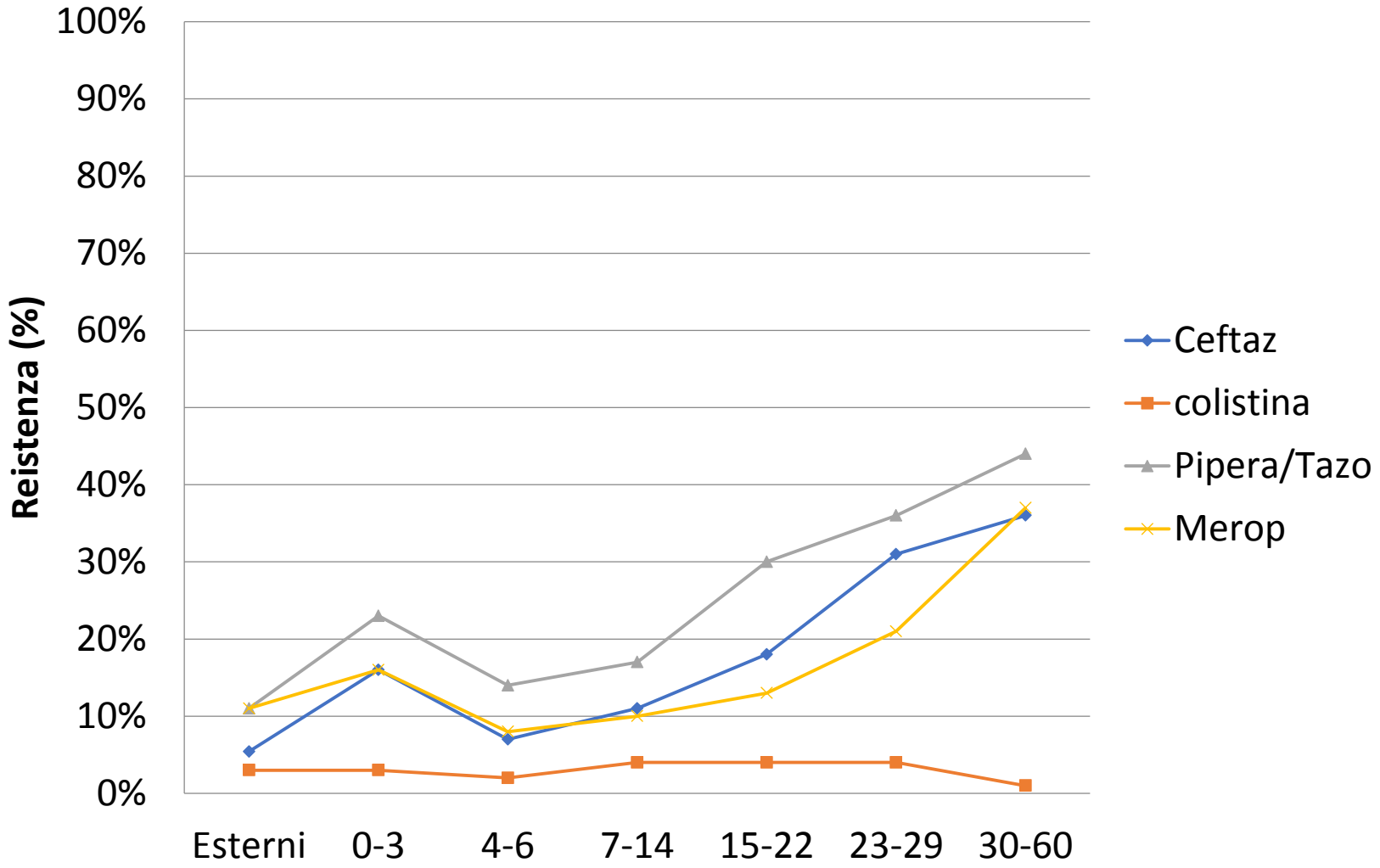
Resistenze per giornate di degenza : *E.coli* 2013-2015



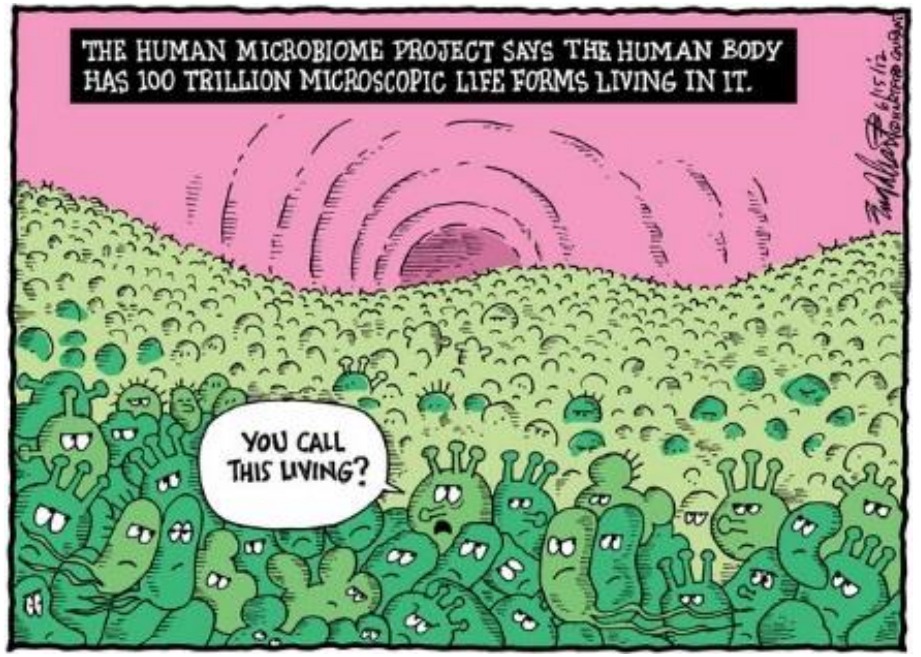
Resistenze per giornate di degenza: *K.pneumoniae* 2013-2015



Resistenze per giornate di degenza: *P. aeruginosa* 2013-2015



"… in relative terms, we are the small creatures living in an enormous and complex ecosystem of microbes… "



Intensive Care Med (2019) 45:733–737
https://doi.org/10.1007/s00134-018-05516-7

LETTER

Microbiota in ICU, not only a gut problem

L. Alagna[1*], A. Bandera[1,2], A. Patruno[3], A. Muscatello[1], G. Citerio[3,4] and A. Gori[1,2]

Composition and dynamics of the respiratory tract microbiome in intubated patients

Kelly et al. Microbiome (2016) 4:7
DOI 10.1186/s40168-016-0151-8

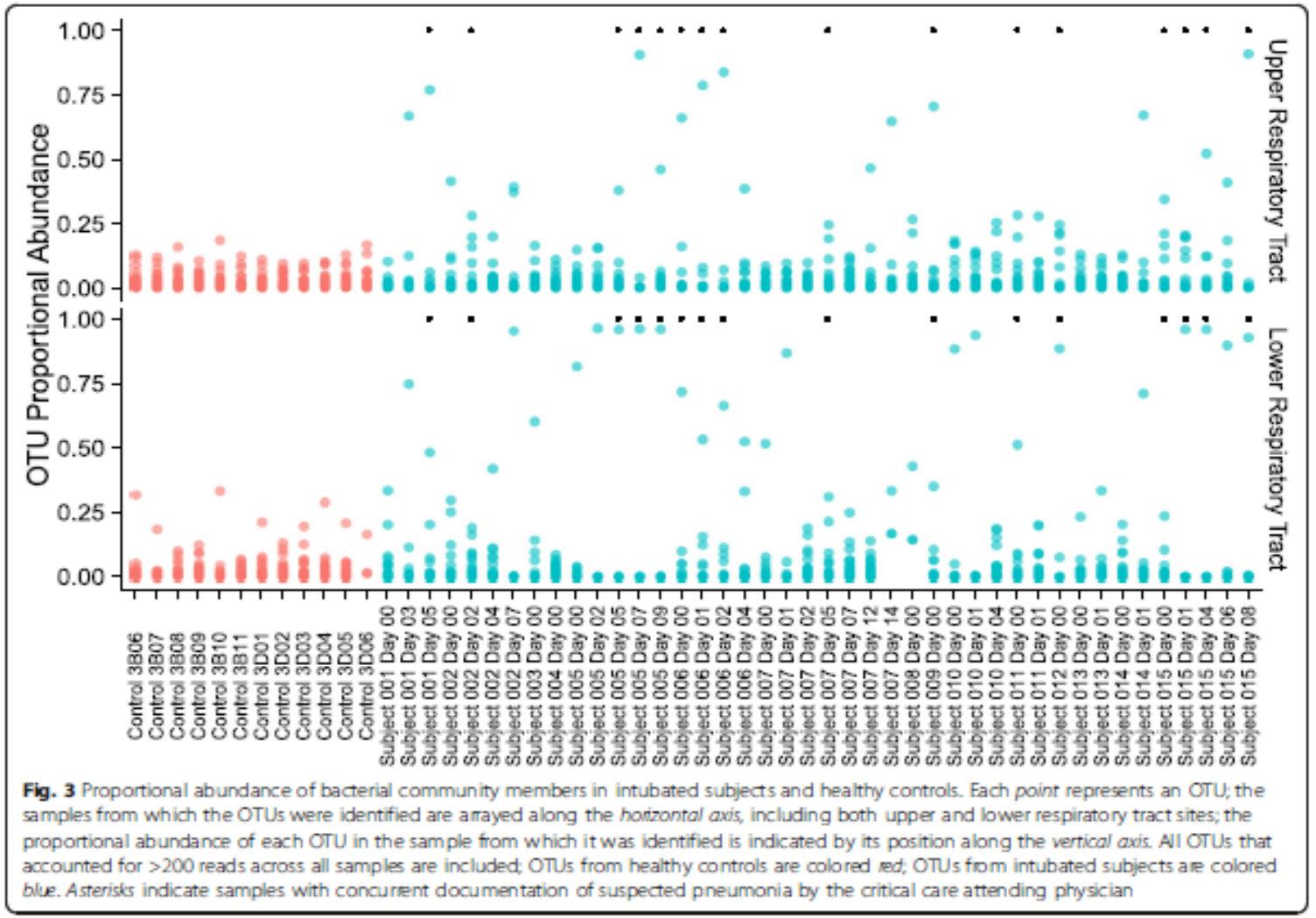


Fig. 3 Proportional abundance of bacterial community members in intubated subjects and healthy controls. Each *point* represents an OTU; the samples from which the OTUs were identified are arrayed along the *horizontal axis*, including both upper and lower respiratory tract sites; the proportional abundance of each OTU in the sample from which it was identified is indicated by its position along the *vertical axis*. All OTUs that accounted for >200 reads across all samples are included; OTUs from healthy controls are colored *red*; OTUs from intubated subjects are colored *blue*. *Asterisks* indicate samples with concurrent documentation of suspected pneumonia by the critical care attending physician

Intensive Care Med
https://doi.org/10.1007/s00134-019-05645-7

WHAT'S NEW IN INTENSIVE CARE

Fecal microbiota transplantation in the ICU: perspectives on future implementations

Laura Alagna[1], Bastiaan W. Haak[2] and Andrea Gori[1,3*]

Take home message

FMT has the potential to recover dysbiosis associated with critical illness. Future studies should identify the target population, optimal timing, mode of administration and the ultimate effect on patients' outcome in the ICU setting.

BMJ 2017;358:j4339 doi: 10.1136/bmj.j4339 (Published 2017 September 19)

NEWS

Few novel antibiotics in the pipeline, WHO warns

Zosia Kmietowicz

The BMJ

New antibiotics agains carbapenem resistance Gram negatives

Category	Current Status
"Old" β-lactam antibiotics combined with new β-lactamase inhibitors	
Ceftazidime-avibactam	FDA-approved
Imipenem-relebactam	FDA-approved
Meropenem-vaborbactam	FDA-approved
Aztreonam-avibactam	Phase 3 trial
New β-lactam antibiotics	
Ceftolozane (combined with tazobactam)	FDA-approved
Cefiderocol (S-649266)	Phase 3 trial
Non-β-lactam antibiotics	
Plazomicin	FDA-approved
Eravacycline	FDA-approved

FDA = Food and Drug Administration; IDIQ = indefinite delivery/indefinite quantity

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

Ryan K. Shields,[a,c] M. Hong Nguyen,[a,c] Liang Chen,[d] Ellen G. Press,[a] Brian A. Potoski,[a,c,e] Rachel V. Marini,[c] Yohei Doi,[a,c] Barry N. Kreiswirth,[d] Cornelius J. Clancy[a,b,f]

Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA[a]; XDR Pathogen Laboratory, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[b]; Antibiotic Management Program, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[c]; Public Health Research Institute Tuberculosis Center, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA[d]; Department of Pharmacy & Therapeutics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA[e]; VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA[f]

ABSTRACT There are no data comparing outcomes of patients treated with ceftazidime-avibactam versus comparators for carbapenem-resistant *Enterobacteriaceae* infections. At our center, ceftazidime-avibactam treatment of carbapenem-resistant *Klebsiella pneumoniae* bacteremia was associated with higher rates of clinical success ($P = 0.006$) and survival ($P = 0.01$) than other regimens. Across treatment groups, there were no differences in underlying diseases, severity of illness, source of bacteremia, or strain characteristics (97% produced *K. pneumoniae* carbapenemase). Aminoglycoside- and colistin-containing regimens were associated with increased rates of nephrotoxicity ($P = 0.002$).

Resistances to ceftazidime-avibactam have already emerged…

Clinical Infectious Diseases

BRIEF REPORT

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,3,4,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[6] Ellen G. Press,[1] Barry N. Kreiswirth,[6] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,3,4]

Patient	Age (Sex)	Underlying Disease	CRE Pathogen	Type of Initial Infection	Initial Treatment Regimen (Duration, d)	Clinical Outcome at 30 d	Time to Microbiologic Failure (d)	Cause of Microbiologic Failure and Outcome at 90 d	C/A MIC (μg/mL) of Pretreatment Isolate	C/A MIC (μg/mL) of Recurrent Isolate
1	66 (F)	Double lung transplant	ST258, KPC-3 CR-Kp	Purulent tracheobronchitis	C/A (71)	Failure	10	Progression to empyema	1	2
2	66 (F)	Double lung transplant	ST258, KPC-3 CR-Kp	Pneumonia	C/A (10)	Failure	14	Recurrence: Pneumonia, treated with C/A for an additional 14 d	2	32, 256[a]
							28	Persistent pneumonia, treated with meropenem and gentamicin until death	Not applicable	256
3	68 (M)	Metastatic colon cancer	CTX-M CR *Escherichia coli*	Pneumonia	C/A (11)	Failure	18	Recurrence: Pneumonia, treated with C/A for 14 d and survived	4	Not available for testing
4	61 (M)	Metastatic colon cancer	CTX-M CR *E. coli*	Bacteremia	C/A (7), gentamicin (4)	Failure	19	Recurrence: Bacteremia, treated with C/A for 7 d and survived	1	0.5
5	46 (M)	Kidney transplant	ST258, KPC-2 CR-Kp	Pyelonephritis with secondary bacteremia	C/A (17)	Success	34	Recurrent UTI, treated with C/A for 21 d and survived	1	1, 2[a]
6	73 (M)	Esophageal cancer status post-esophagectomy	ST258, KPC-3 CR-Kp	Pneumonia	C/A (15)	Success	34	Respiratory colonization, not treated	2	2
							58	Respiratory colonization, not treated	Not applicable	64, 128[a]
							76	Recurrent pneumonia, treated with meropenem and colistin for 14 d and survived	Not applicable	2, 64[a]
7	78 (M)	Amyotrophic lateral sclerosis	ST258, KPC-2 CR-Kp	Pneumonia	C/A (15), colistin (7)	Success	36	Recurrent UTI, treated with C/A for 7 d and survived	0.25	0.5
8	58 (F)	Morbid obesity s/p gastric sleeve surgery	ST258, KPC-3 CR-Kp	Intraabdominal infection	C/A (19)	Failure	41	Urine colonization, not treated and survived	4	32, >256[a]
9	75 (F)	Kidney-liver transplant	ST258, KPC-3 CR-Kp	Pyelonephritis	C/A (7)	Success	74	Recurrent UTI, treated with C/A for 21 d and survived	2	4
10	75 (M)	Bickerstaff encephalitis, paraplegia	ST258, KPC-2 CR-Kp	Bacteremia	C/A (14), gentamicin (3)	Success	84	Recurrent bacteremia, treated with meropenem, then ampicillin/sulbactam for 14 d and survived	0.25	2

Abbreviations: C/A, ceftazidime-avibactam; CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; CTX-M, cefotaximase; Kp, *Klebsiella pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; s/p, status-post; ST, sequence type; UTI, urinary tract infection.

[a] Two morphologies isolated from the same biologic specimen.

What is the BEST Combination therapy?

- It remains unclear whether ceftazidime-avibactam should be used as monotherapy or in combination for CRE
- Expert opinion: **Combination approach appears reasonable,** especially in severe infections and to potentially prevent resistance development
- Partners:
  - Colistin
  - Aminoglicosides (cUTI)
  - Fosfomicyn (HAP)
  - Tigecicline (cIAI)
  - Carbapenems

Ceftolozane-tazobactam for CR-pseudomonas

Clinical Infectious Diseases

BRIEF REPORT

Multicenter Evaluation of Ceftolozane/Tazobactam for Serious Infections Caused by Carbapenem-Resistant *Pseudomonas aeruginosa*

Jose M. Munita,[1,2,4] Samuel L. Aitken,[1,5] William R. Miller,[1,2] Federico Perez,[7] Rossana Rosa,[8,9] Luis A. Shimose,[8,9] Paola N. Lichtenberger,[9] Lilian M. Abbo,[8,9] Rupali Jain,[10] Masayuki Nigo,[2] Audrey Wanger,[3] Rafael Araos,[4] Truc T. Tran,[1,2] Javier Adachi,[6] Robert Rakita,[11] Samuel Shelburne,[6] Robert A. Bonomo,[7] and Cesar A. Arias[1,2,12]

Munita JM et al *Clin Infect Dis.* (2017) 65:158–61.

Clinical Infectious Diseases
MAJOR ARTICLE

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance

Ghady Haidar,[1] Nathan J. Philips,[2] Ryan K. Shields,[1,3,4] Daniel Snyder,[2] Shaoji Cheng,[4] Brian A. Potoski,[1,3,5] Yohei Doi,[1] Binghua Hao,[4] Ellen G. Press,[1] Vaughn S. Cooper,[2] Cornelius J. Clancy,[1,4,6a] and M. Hong Nguyen[1,3,4a]

[1]Department of Medicine, University of Pittsburgh, [2]Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine, [3]Antibiotic Management Program, and [4]XDR Pathogen Laboratory, University of Pittsburgh Medical Center, [5]Department of Pharmacy and Therapeutics, University of Pittsburgh, and [6]VA Pittsburgh Healthcare System, Pennsylvania

Conclusions. In this small study, ceftolozane-tazobactam was successful in treating 71% of patients with MDR-*P. aeruginosa* infections, most of whom had pneumonia. The emergence of ceftolozane-tazobactam resistance in 3 patients is worrisome and may be mediated in part by AmpC-related mechanisms. More research on treatment responses and resistance during various types of MDR-*P. aeruginosa* infections is needed to define ceftolozane-tazobactam's place in the armamentarium.

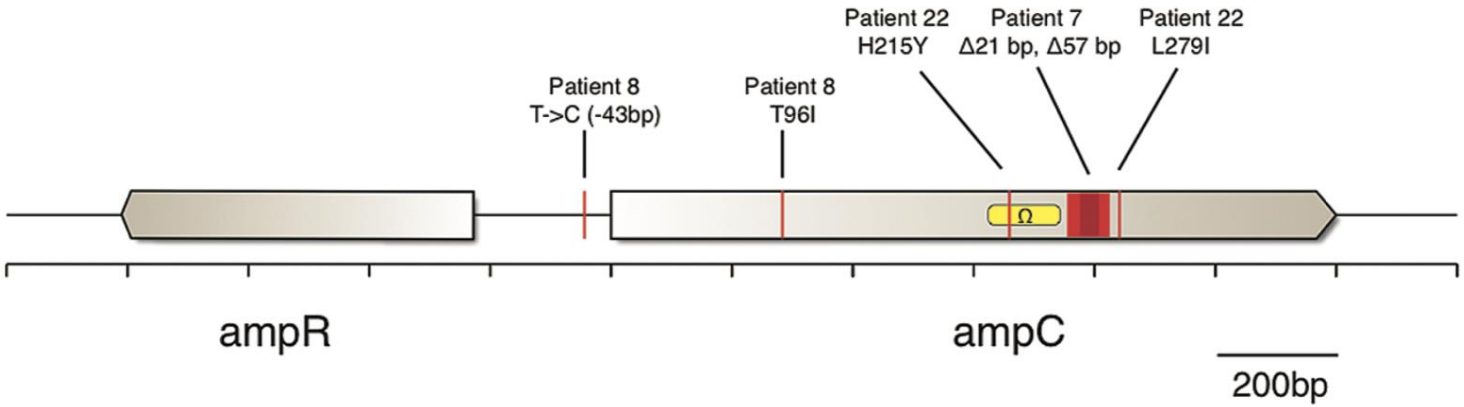


Diagram of mutations occurring in the *ampR-ampC* genomic region among resistant isolates.

ASPECT-NP: ceftolozane-tazobactam for nosocomial pneumonia

Articles

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

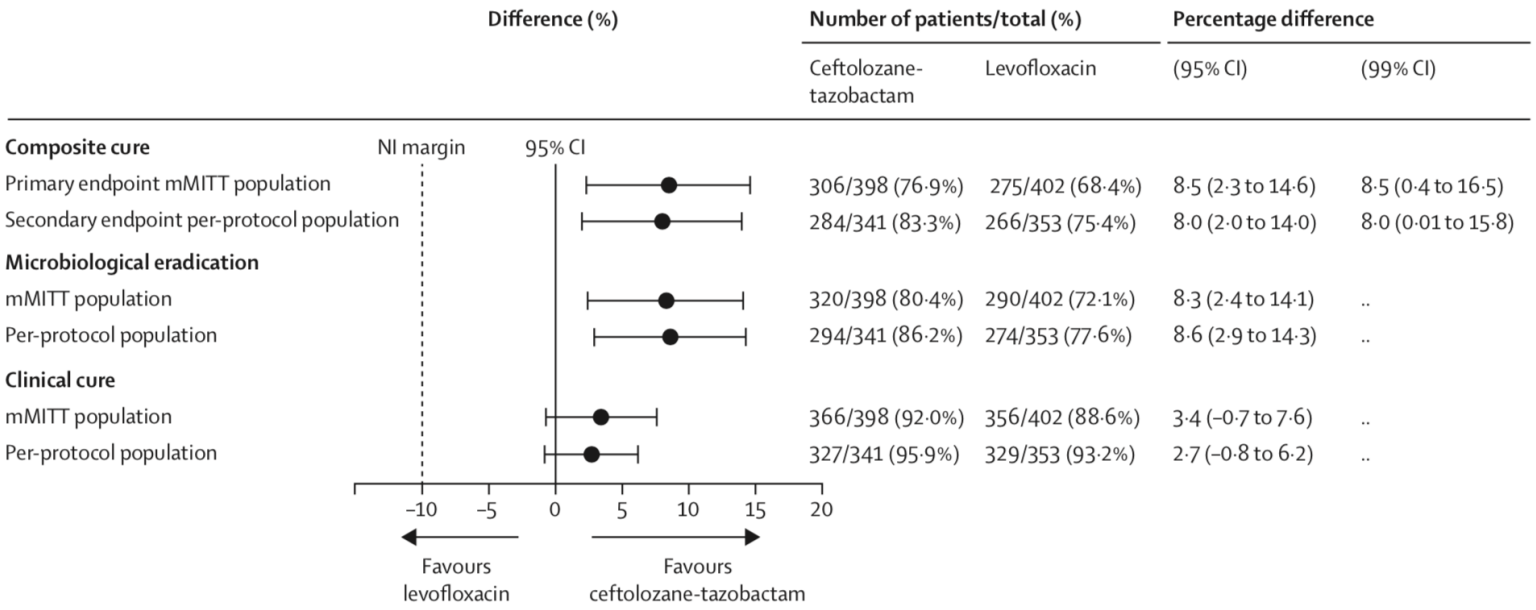
Marin H Kollef, Martin Nováček, Ülo Kivistik, Álvaro Réa-Neto, Nobuaki Shime, Ignacio Martin-Loeches, Jean-François Timsit, Richard G Wunderink, Christopher J Bruno, Jennifer A Huntington, Gina Lin, Brian Yu, Joan R Butterton, Elizabeth G Rhee

Interpretation High-dose ceftolozane–tazobactam is an efficacious and well tolerated treatment for Gram-negative nosocomial pneumonia in mechanically ventilated patients, a high-risk, critically ill population.

ASPECT-cUTI: Ceftolozane-tazobactam for cUTI

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche



Wagenlehner FM et al *Lancet*. (2015) 385:1949–56.

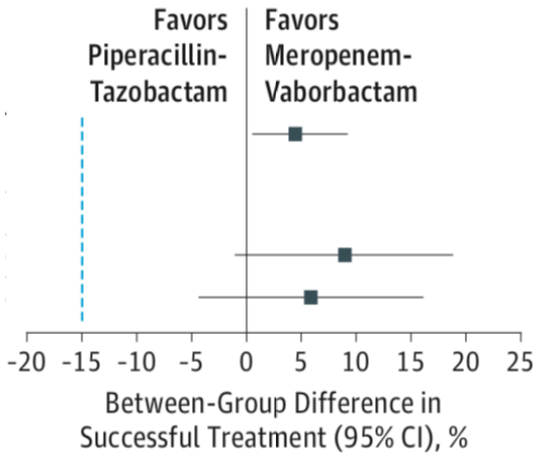
JAMA | Original Investigation

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

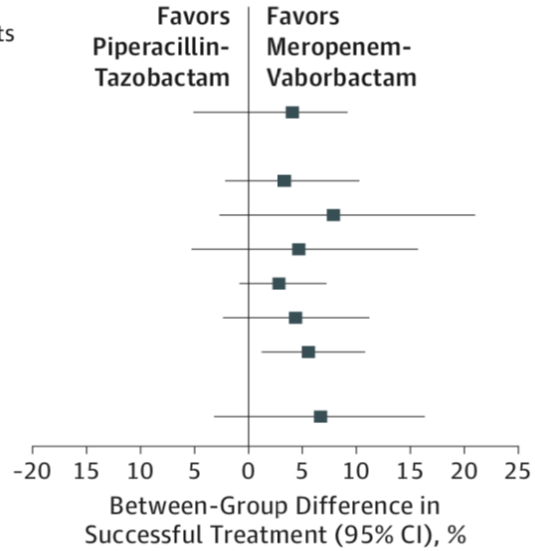
The TANGO I Randomized Clinical Trial

Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD; Juan P. Horcajada, MD, PhD; Claudia Murta, MD; Yaroslav Sarychev, MD; Ventsislav Stoev, MD; Elizabeth Morgan, BS; Karen Fusaro, BS; David Griffith, BS; Olga Lomovskaya, PhD; Elizabeth L. Alexander, MD; Jeffery Loutit, MBChB; Michael N. Dudley, PharmD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

Primary end points



Secondary end points



CONCLUSIONS AND RELEVANCE Among patients with complicated UTI, including acute pyelonephritis and growth of a baseline pathogen, meropenem-vaborbactam vs piperacillin-tazobactam resulted in a composite outcome of complete resolution or improvement of symptoms along with microbial eradication that met the noninferiority criterion. Further research is needed to understand the spectrum of patients in whom meropenem-vaborbactam offers a clinical advantage.

Kaye KS et al. *JAMA*. (2018) 319:788–99.

MEROPENEM VABORBACTAM for CRE

Infect Dis Ther (2018) 7:439–455
https://doi.org/10.1007/s40121-018-0214-1

ORIGINAL RESEARCH

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

- **Phase 3, randomized,** prospective, multicenter, multinational, open-label, active-controlled trial of **adults with infections due to CRE**
- **Aim: to evaluate the efficacy/safety of meropenem–vaborbactam monotherapy versus best available therapy (BAT) for CRE**
- **27 hospital sites in 8 countries** (Argentina, Brazil, Colombia, Greece, Israel, Italy, United Kingdom, United States) with known prevalence of KPC-producing CRE
- November 2014 and June 2017

Wunderink RG et al. *Infect Dis Ther*. (2018)

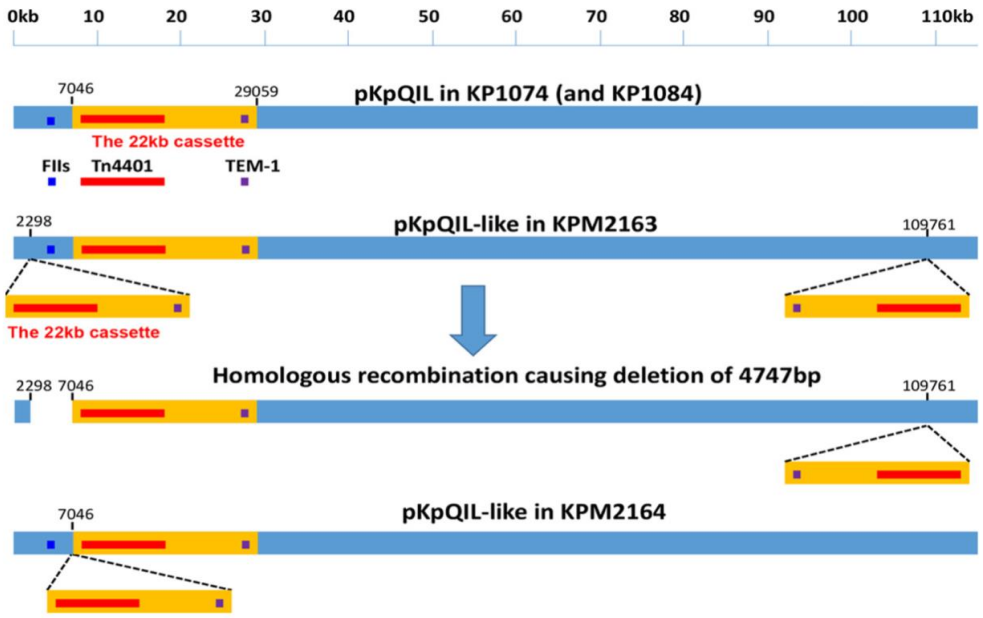
Resistances to meropenem-vaborbactam can develop

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Meropenem-Vaborbactam Resistance Selection, Resistance Prevention, and Molecular Mechanisms in Mutants of KPC-Producing *Klebsiella pneumoniae*

Dongxu Sun, Debora Rubio-Aparicio, Kirk Nelson, Michael N. Dudley, Olga Lomovskaya

The Medicines Company, San Diego, California, USA



Rearrangement of the pKpQIL-like plasmid in strains KPM2163 and KPM2164. In KPM2163, an approximately 22-kb region of pKpQIL (nucleotides 7046 to 29059) was duplicated and inserted at nucleotide 2298 and nucleotide 109761.

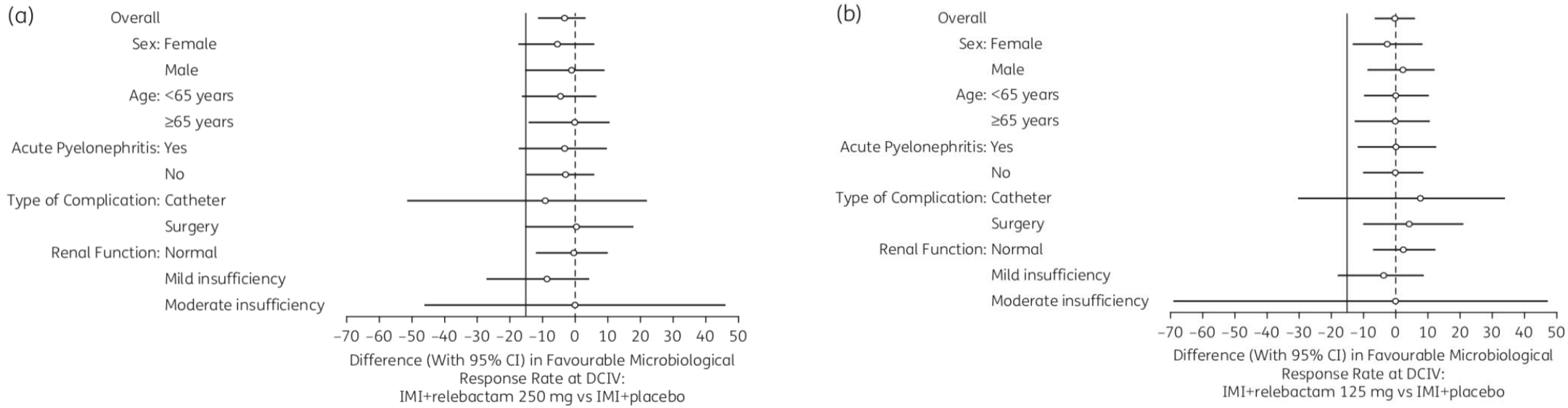
Antimicrob Agents Chemother. (2017) 61:e01694–17.

J Antimicrob Chemother 2017; **72**: 2616–2626
doi:10.1093/jac/dkx139 Advance Access publication 1 June 2017

Journal of Antimicrobial Chemotherapy

Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections

Matthew Sims[1], Valeri Mariyanovski[2], Patrick McLeroth[3], Wayne Akers[3], Yu-Chieh Lee[3], Michelle L. Brown[4], Jiejun Du[4], Alison Pedley[4], Nicholas A. Kartsonis[4] and Amanda Paschke[4]*



(a) imipenem/cilasta- tin relebactam 250 mg versus imipenem placebo and (b) imipenem/cilastatin relebactam125 mg versus imipenem placebo.

IMIPENEM RELEBACTAM (phase 3)

Activity against

- Ambler class A β-lactamases **(ESBL, KPC)**
- Amber class C β-lactamases **(AmpC)**

- The addition of relebactam improves the activity of imipenem against ***Pseudomonas*** → MIC reduced eightfold (different from mero-vabo)
- But **NOT against *Acinetobacter, Stenotrophomonas* and most anaerobes**

- Little is known about the potential for relebactam to select for resistance

- **Phase III** clinical trials
  - CRE
  - HAP/VAP

Clinical Infectious Diseases

MAJOR ARTICLE

IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections

Joseph S. Solomkin,[1] Janis Gardovskis,[2] Kenneth Lawrence,[3] Philippe Montravers,[4,5,6] Angie Sway,[7] David Evans,[8] and Larry Tsai[3]

[1]Department of Surgery, University of Cincinnati College of Medicine, Ohio; [2]Department of Surgery, Riga Stradins University, Latvia; [3]Tetraphase Pharmaceuticals, Watertown, Massachusetts; [4]Département d'Anesthésie-Réanimation, CHU Bichat Claude Bernard [5]Université Paris Diderot, PRESS Sorbonne Cité, and [6]Institut National de la Santé et de la Recherche Médicale (INSERM) UMR 1152, Paris, France; and [7]World Surgical Infection Society, Cincinnati, Ohio and [8]Department of Surgery, Ohio State University School of Medicine, Columbus

JAMA Surgery | Original Investigation

Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial

A Randomized Clinical Trial

Joseph Solomkin, MD; David Evans, MD; Algirdas Slepavicius, MD; Patrick Lee, MD; Andrew Marsh; Larry Tsai, MD; Joyce A. Sutcliffe, PhD; Patrick Horn, MD

Eravacycline against A.baumanni

International Journal of Antimicrobial Agents 51 (2018) 62–64

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible *Acinetobacter baumannii*

Harald Seifert [a,b,*,1], Danuta Stefanik [a], Joyce A. Sutcliffe [c], Paul G. Higgins [a,b]

[a] *Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Cologne, Germany*
[b] *German Center for Infection Research (DZIF), Partner Site Bonn-Cologne, Germany*
[c] *Tetraphase Pharmaceuticals, Watertown, Massachusetts, USA*

Seifert et al. *Int J Antimicrob Agents*. (2018) 51:62–4.

Eravacycline is suboptimal in cUTI

- IGNITE II and III pooled data

Drugs (2016) 76:567–588
DOI 10.1007/s40265-016-0545-8

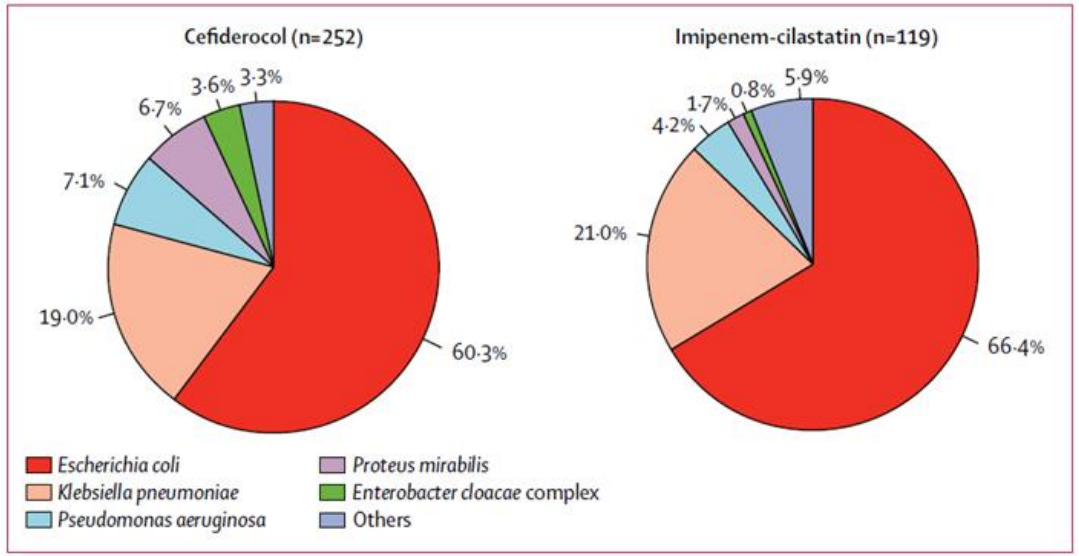
REVIEW ARTICLE

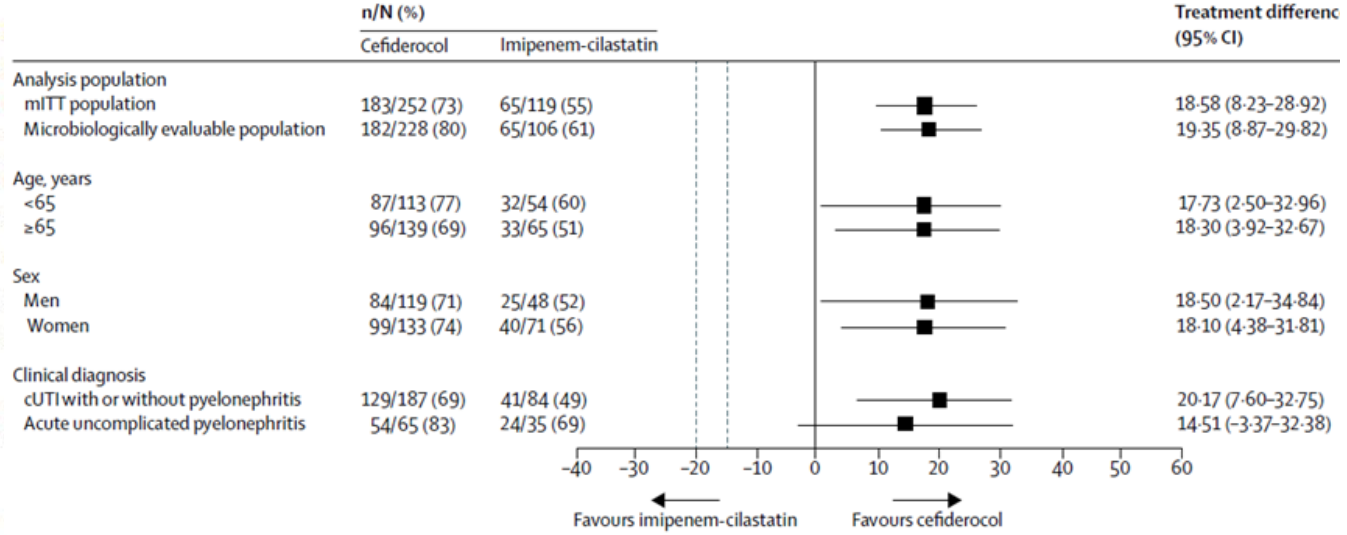
Review of Eravacycline, a Novel Fluorocycline Antibacterial Agent

George G. Zhanel[1,4,6] · Doris Cheung[2] · Heather Adam[1,6] · Sheryl Zelenitsky[2] · Alyssa Golden[1] · Frank Schweizer[1,3] · Bala Gorityala[3] · Philippe R. S. Lagacé-Wiens[1,7] · Andrew Walkty[1,4] · Alfred S. Gin[1,2,5] · Daryl J. Hoban[1,6] · James A. Karlowsky[1,7]

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial

Simon Portsmouth, David van Veenhuyzen, Roger Echols, Mitsuaki Machida, Juan Camilo Arjona Ferreira, Mari Ariyasu, Peter Tenke, Tsutae Den Nagata





Phase 2, multicentre, double-blind, parallel-group non-inferiority trial
67 hospitals in 15 countries

Lancet Infect Dis. 2018 Dec;18(12):1319-132

CEFIDEROCOL

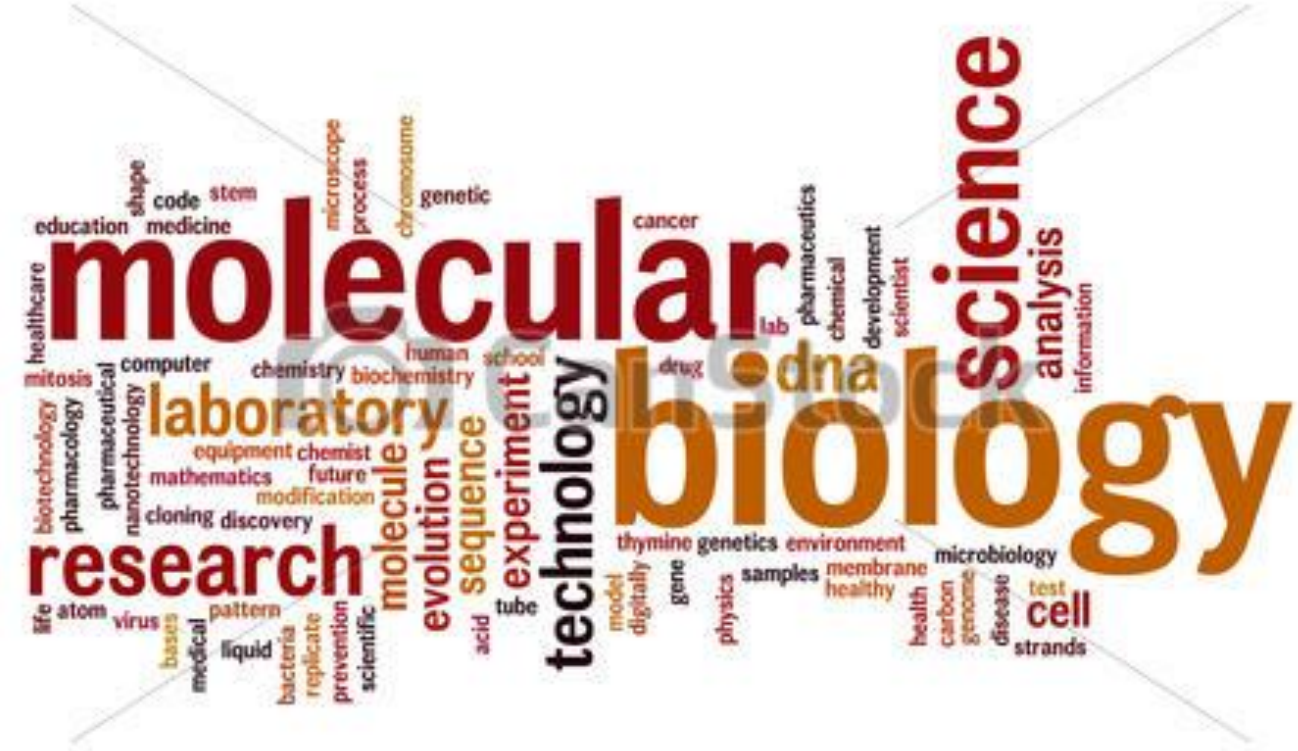
- **Phase 3**
- **Siderophore cephalosporin** → unique mechanism of action!
- Active against MDR *Acinetobacter*, MDR *pseudomonas*, CR-*Enterobacteriaceae*, *S. maltophilia*
- More potent than meropenem and caz-avi
- Promising option!
- 2 g every 8 h (q8 h) using a 3-h infusion

Antimicrobial and «Diagnostic» stewardship

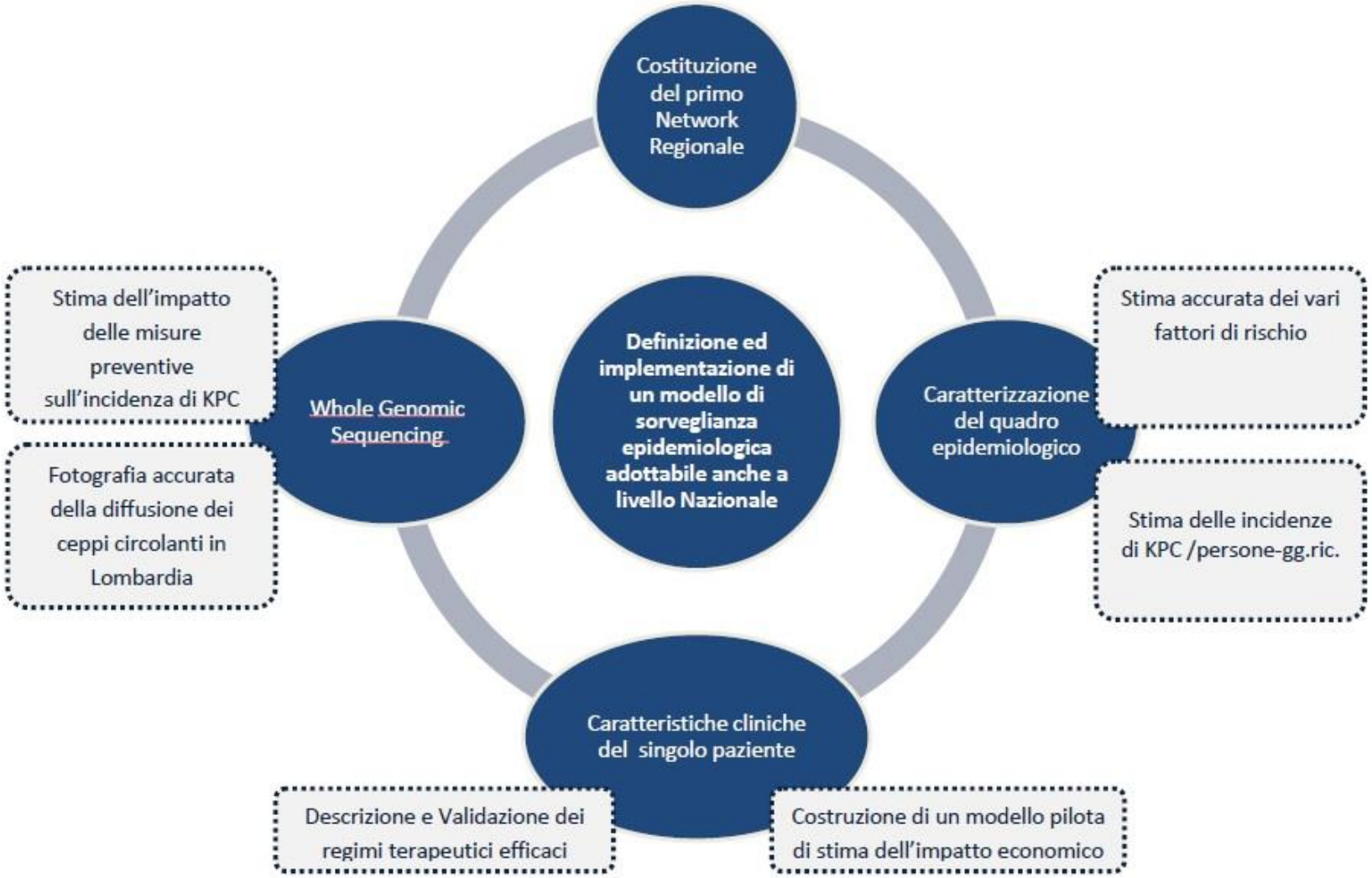
Nuovi strumenti diagnostici per:

- diagnosi eziologica rapida del patogeno e del meccanismi di resistenza
- stratificazione del paziente per gravità e prognosi

Global challenges...the need for innovation



Un approccio di studio innovativo



Rossi M et al. ESCMID 2018

Next-Gen Sequencing Technologies

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Whole-Genome Sequencing Accurately Identifies Resistance to Extended-Spectrum β-Lactams for Major Gram-Negative Bacterial Pathogens

Samuel A. Shelburne,[1,2,3] Jiwoong Kim,[4,5] Jose M. Munita,[3,6,7] Pranoti Sahasrabhojane,[1] Ryan K. Shields,[8] Ellen G. Press,[8] Xiqi Li,[9] Cesar A. Arias,[3,6,10,11] Brandi Cantarel,[4] Ying Jiang,[1] Min S. Kim,[4,5] Samuel L. Aitken,[3,12] and David E. Greenberg[3,13,14]

Test rapidi per l'identificazione di CRE

Geni che conferiscono resistenza

ID	Name	Occurence	
KPC	Klebsiella pneumoniae carbapenemase	+++ Most common All over Europe	95%
VIM	Verona integron-encoded metallo-beta-lactamase	++ All over Europe	
NDM	New Delhi metallo-beta-lactamase	+ Mostly in central Europe	
IMP	metallo-β-lactamases	+ Low occurrence	
OXA-48	Carbapenem-hydrolysing oxacillinase-48	++ Mostly in western Europe	
CMY		First described in 2006	5%
Others: OXA 181, IMP 18, GEF, SME, IMI, NMC,...			

Covered by Carba-R Not covered by Carba-R

Virulence factors

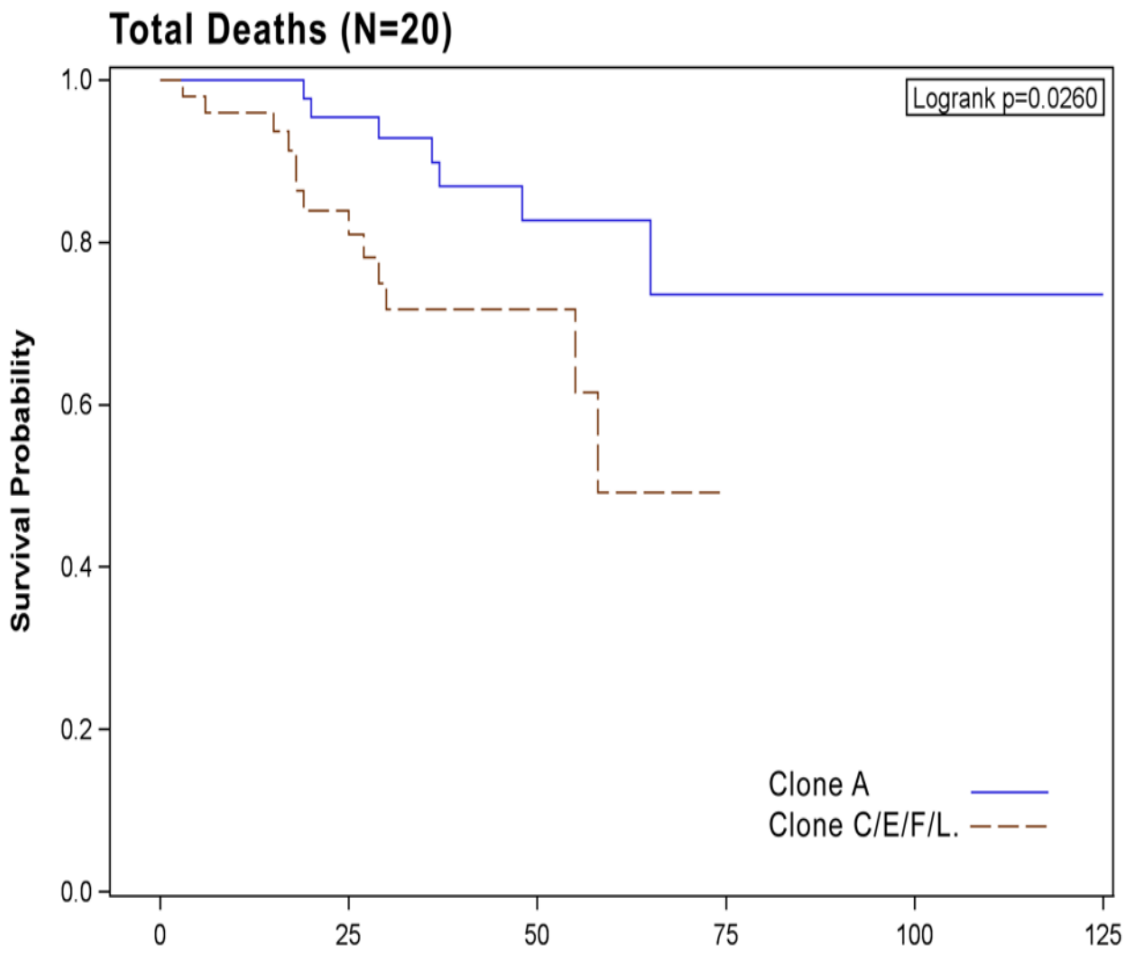
ST	n° strains	*wzi*	*k-type*			*Virulence factors*										KPC
37	2	14	*K14*	-	-				-	-	-	-	-	*mrkABCD*	-	**KPC-3**
11	1	75		-	-	*fyuA*	*irp1*	*irp2*	-	-	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-2**
101	5	137	*K17*	-	-	*fyuA*	*irp1*	*irp2*	-	-	*kFuABC*	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-2**
101	13	137	*K17*	-	-	*fyuA*	*irp1*	*irp2*	-	-	*kFuABC*	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-3**
149	3	62	*K62*	-	-	*fyuA*	*irp1*	*irp2*	-	-	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-3**
258	24	**29 (*cps-1*)**	*K41*	-	-	*fyuA*	*irp1*		-	-	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-2**
258	2	**154 (*cps-2*)**	-	-	-	-	-	-	-	-	-	-	-	*mrkABCD*	-	**KPC-3**
512	164	**154 (*cps-2*)**	-	-	-	-	-	-	-	-	-	-	-	*mrkABCD*	-	**KPC-3**
868	5	154 (*cps-2*)		-	-	-	-	-	-	-	-	-	-	*mrkABCD*	-	**KPC-3**
307	29	173	-	-	-	*fyuA*	*irp1*	-	-	-	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-2**
307	12	173	-	-	-	-	-	-	-	-	-	-	-	*mrkABCD*		**KPC-2**
307	50	173	-	-	-	*fyuA*	*irp1*	-	-	-	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-3**
395	4	2	*K2*	-	-	*fyuA*	*irp1*	*irp2*	*iucABCD*	*iutA*		-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-3**
1478	1	-	-	-	-	-	-	-	-	-	*kFuABC*	-	-	*mrkABCD*	-	**KPC-3**
15	4	24	*K24*	-	-	*fyuA*	*irp1*	*irp2*	-	-	*kFuABC*	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-3**
147	2	64	*K14.K64*	-	-	*fyuA*	*irp1*	*irp2*	*iucACD*	*iutA*	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-2**
111	1	-	-	-	-	-	-	-	-	-	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-2**
35	1	37	*K22.37*	-	-	-	-	-	-	-	-	*kvgAS*	*mceABCDF*	*mrkABCD*	-	**KPC-2**
104	1	102	*K31*	*allB*	*allD*	*fyuA*	*irp1*	*irp2*	-	-	-	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-3**
2502	1	137	*K17*	-		*fyuA*	*irp1*	*irp2*	-	-	*kFuABC*	-	-	*mrkABCD*	*ybtAEPQSTUX*	**KPC-3**
1562	1	81	*K81*	-	-	-	-	-	-	-	*kFuABC*	-	-	*mrkABCD*	-	**KPC-2**

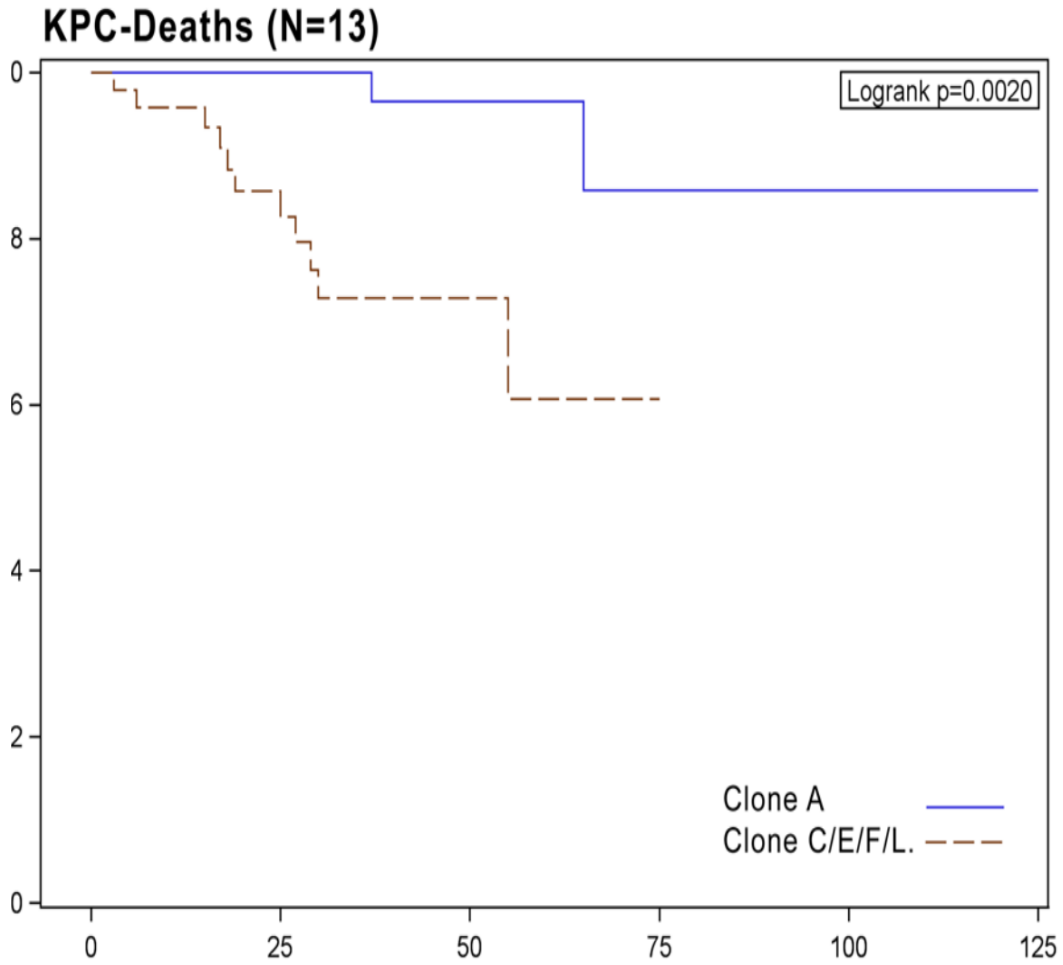
- 171 CC258 (87%) was associated to *cps-2* while 24 (12%) to *cps-1*
- *cps-1* associated *to KPC-2 , cps-2 KPC-3*

✓ Of note that studies by WGS of KPC infected/colonized patients could contribute in better understanding transmission of high-risk clones and the potential of virulence of *cps* and their ability to cause colonization and infection.

Courtesy of Floriana Gona

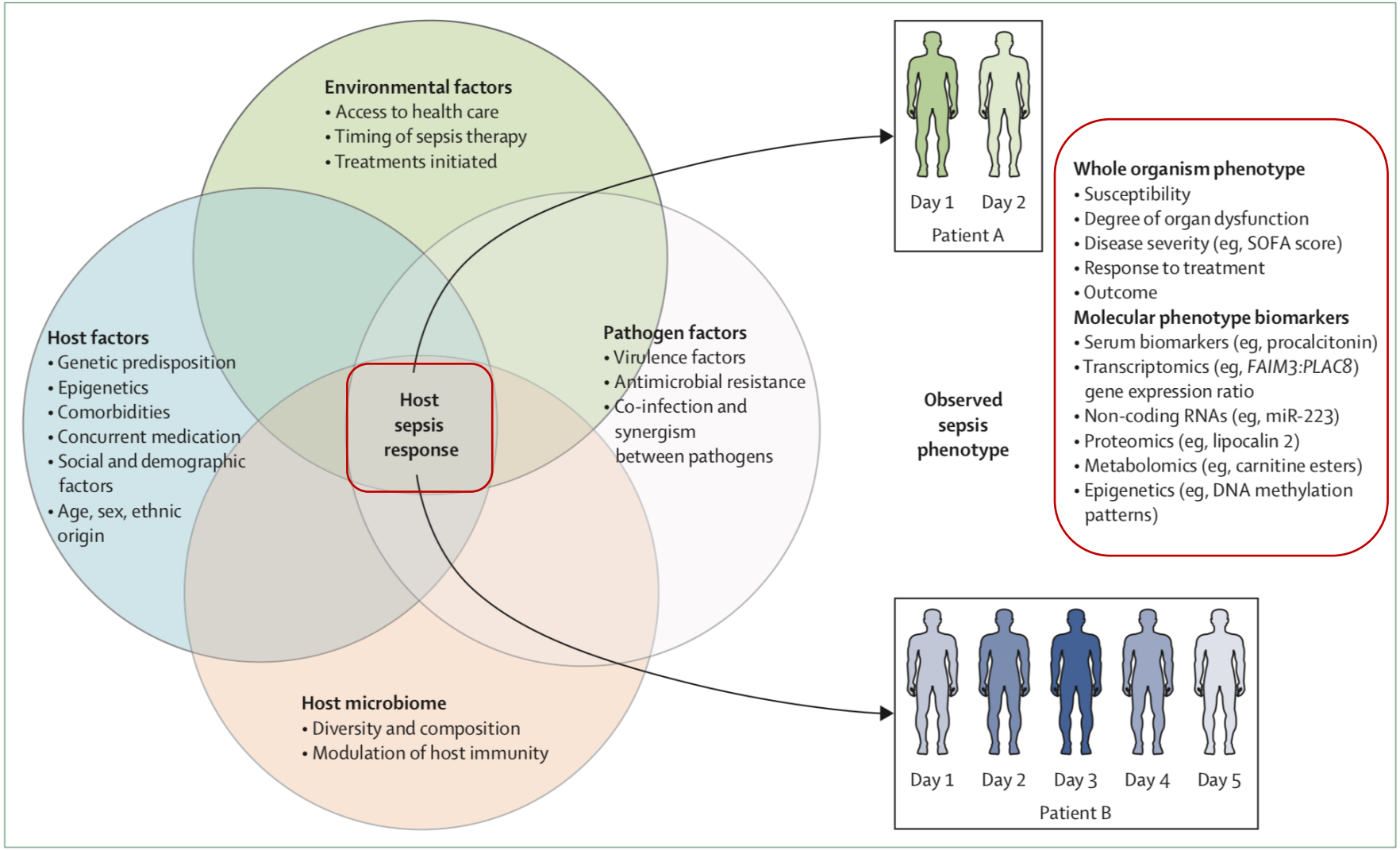
Impact of KPC-clones mortality of patients with KPC infection





Rossi M et al. Pathogens and Immunity 2017

Nuovi strumenti diagnostici: Host gene expression

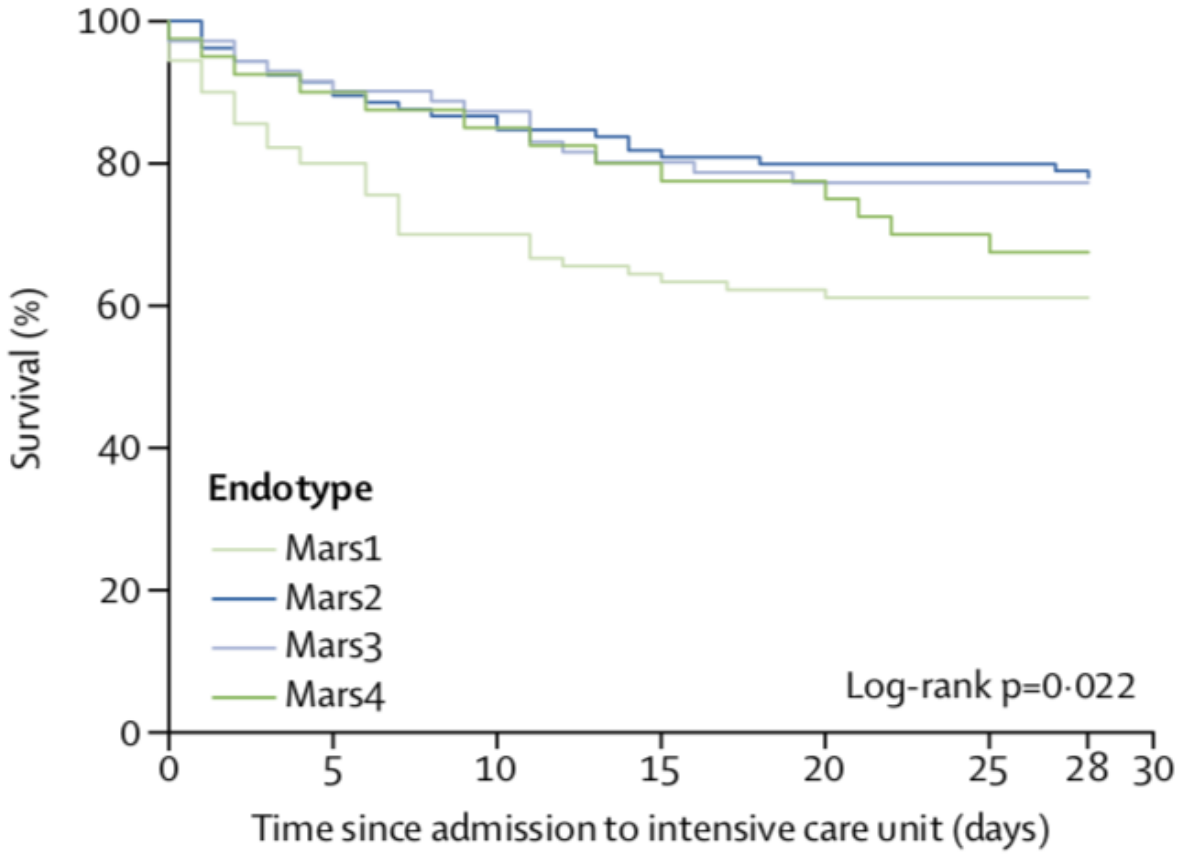


Goh C et al., *Lancet Respir Med* 2017

Nuovi strumenti diagnostici: Host gene expression

Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

- A **140-gene expression signature** reliably stratified patients with sepsis to the **four endotypes (Mars 1-4)**, one of which (Mars1) was consistently significantly associated with acute (28-day) and late (1-year) mortality
- The four endotypes could **not be predicted by demographic or clinical** covariates. The blood transcriptomes of these four endotypes had **distinct host response signatures**, including endotypes attuned to immunosuppression, hyperinflammation, or adaptive immune functions



Scicluna BP et al., *Lancet Respir Med* 2017

Infettivologo da considerarsi come valore aggiunto?

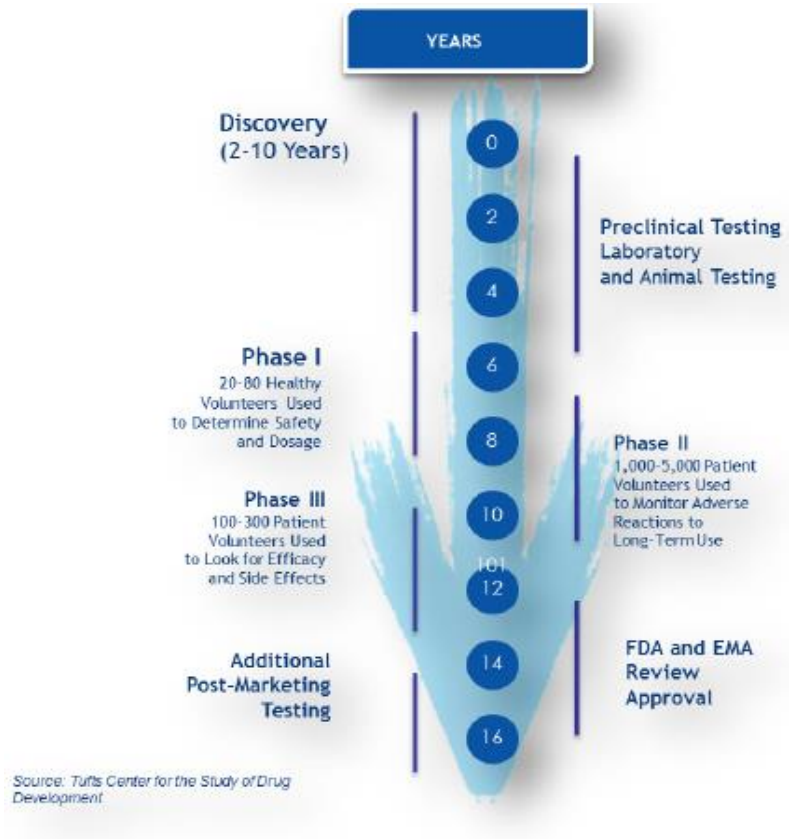
Impact of Routine Infectious Diseases Service Consultation on the Evaluation, Management, and Outcomes of *Staphylococcus aureus* Bacteremia

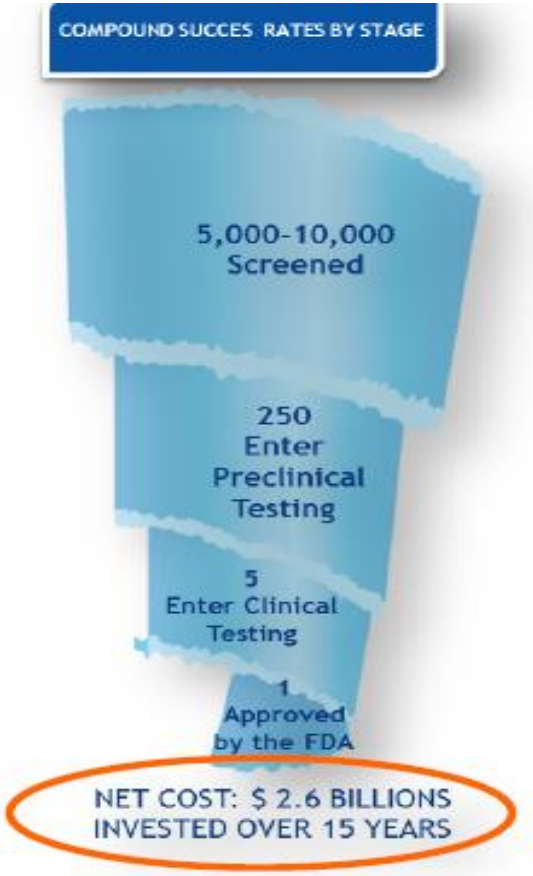
Timothy C. Jenkins,[1,3] Connie S. Price,[1,3] Allison L. Sabel,[2,4] Philip S. Mehler,[2] and William J. Burman[1,3]

[1]Division of Infectious Diseases and [2]Department of Patient Safety and Quality, Denver Health and Hospital Authority, and [3]Department of Medicine, Division of Infectious Diseases, and [4]Department of Preventive Medicine and Biometry, University of Colorado Health Sciences Center, Denver, Colorado

Conclusions. A policy of routine consultation with an infectious diseases specialist for patients with *S. aureus* bacteremia resulted in more-detailed evaluation, more-frequent detection of endocarditis and metastatic infection, and improved adherence to standards of care.

Ricerca e sviluppo dei farmaci: un processo lungo, complesso e molto costoso

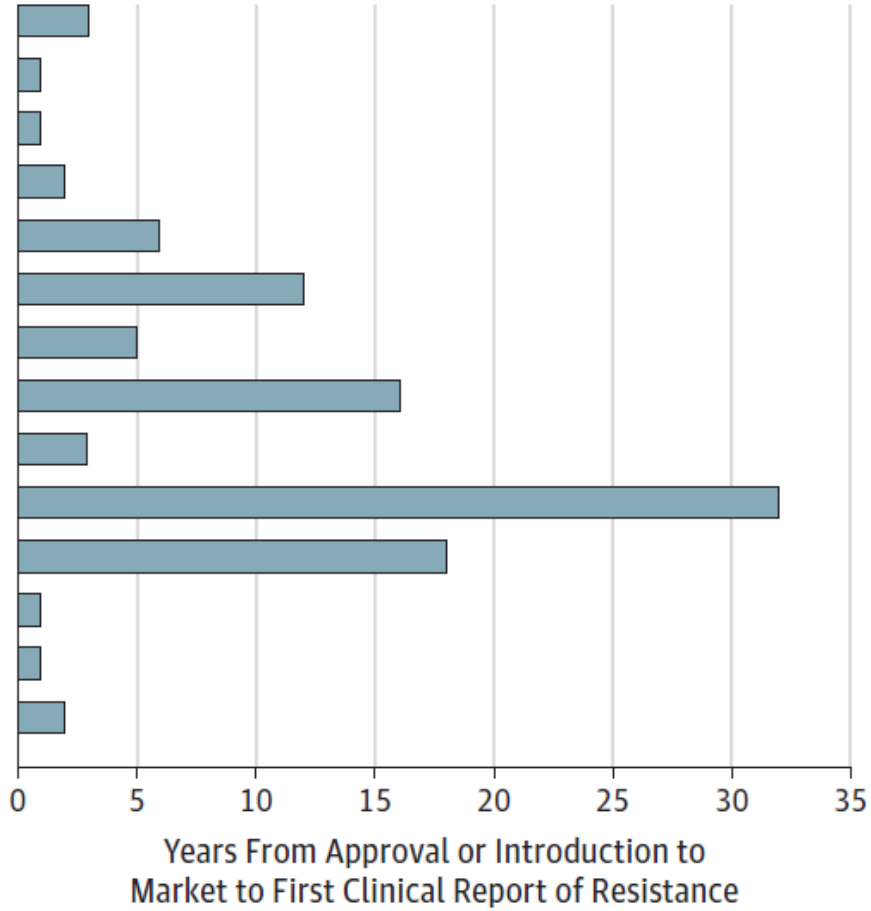




INAPPROPRIATE ANTIBIOTIC PRESCRIBING AND SALES

Time From Antibiotic Approval or Introduction
to Detection of Resistance in Clinical Samples

Class	Antibiotic	Year of Approval or Introduction to Market
β-Lactams	Penicillin	1942
	Methicillin	1960
	Cephalothin	1964
	Amoxicillin-clavulanic acid	1984
Carbapenems	Imipenem-cilastatin	1985
Amphenicols	Chloramphenicol	1950
Tetracyclines	Tetracycline	1953
Aminoglycosides	Streptomycin	1946
Macrolides	Erythromycin	1952
Glycopeptides	Vancomycin	1958
Quinolones	Nalidixic acid	1964
Streptogramins	Quinupristin-dalfopristin	1999
Oxazolidinones	Linezolid	2000
Lipopeptides	Daptomycin	2003



JAMA 2016;316:1193-1204

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Alessandra Bandera

Data retrieval and analysis
Silvia Limonta

Statistical analysis (IRCCS Mario Negri)
Liliane Chatenaud

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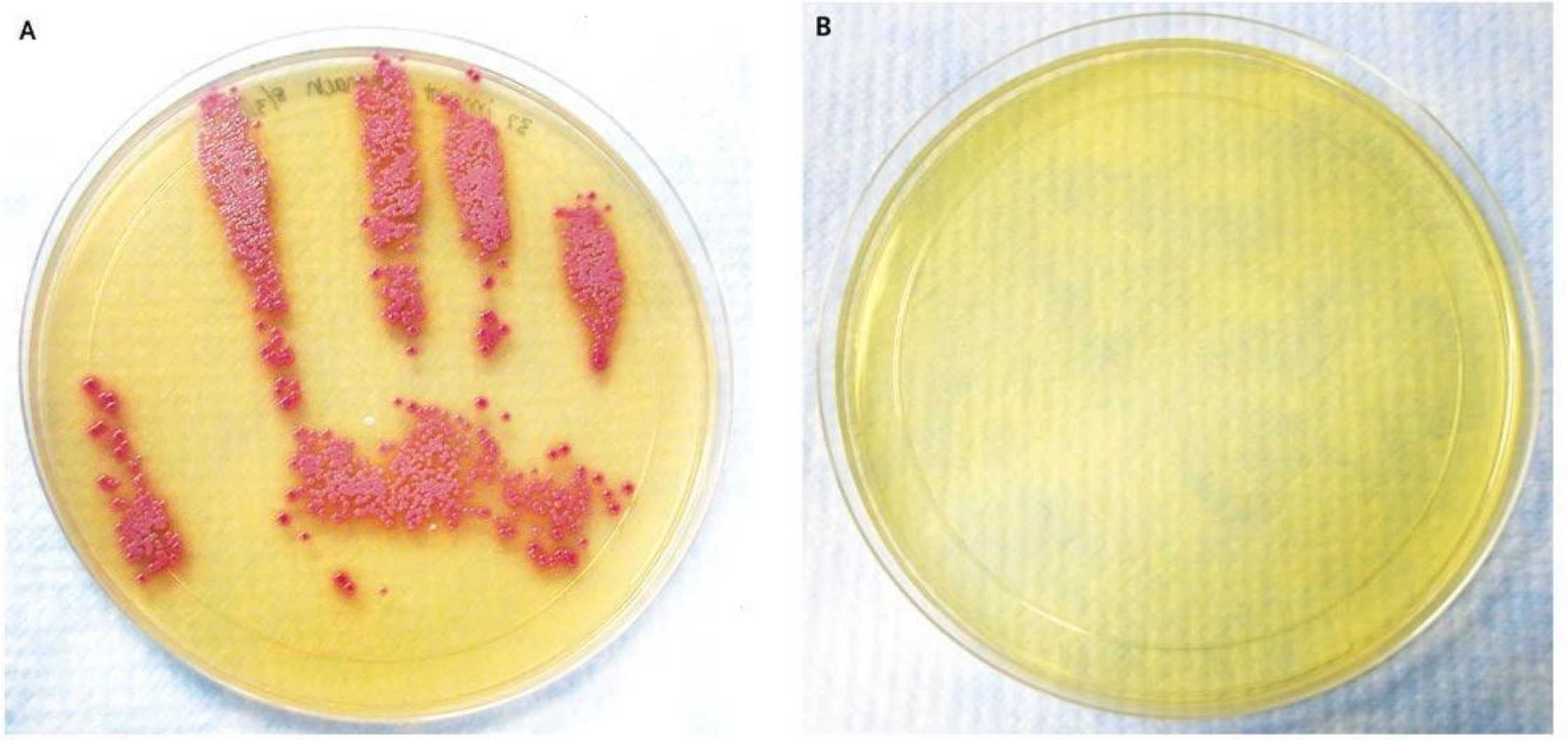
ASST Papa Giovanni XXIII di Bergamo
ASST della Valle Olona Ospedale di Busto Arsizio
ASST Lecco Ospedale A. Manzoni
ASST Grande Ospedale Metropolitano Niguarda - *(Consenso Informato)*
ASST Fate Bene Fratelli – L. Sacco - *(Consenso Informato)*
IRCCS San Raffaele di Milano - *(Consenso Informato)*
ASST Sette Laghi Ospedale di Circolo e Fondazione Macchi di Varese
Istituto Clinico Humanitas
Ospedale Maggiore Policlinico Fondazione IRCCS Ca' Granda
ASST Santi Paolo e Carlo Ospedale San Paolo - *(Consenso Informato)*
ASST di Cremona – Ospedale di Cremona
Asst Spedali Civili di Brescia
ASST di Lodi – Ospedale di Lodi
ASST di Mantova Ospedale Carlo Poma

***After the worker's hand had been cleaned with alcohol foam**, another hand imprint was obtained, and the resulting culture was negative for MRSA*



Donskey DJ et al., NEJM 2009