ADDITIONAL FILE 1

Impact of a restrictive antibiotic policy on the acquisition of extended-spectrum beta-lactamase-producing Enterobacteriaceae in an endemic region: a quasi-experimental, before-and-after, propensity-matched cohort study in a Caribbean intensive care unit

Christophe Le Terrier, MD[1,2]* ; Marco Vinetti, MD,[1,3]* ; Paul Bonjean, MD[4] ; Régine Richard, RN[1] ; Bruno Jarrige, MD[5] ; Bertrand Pons, MD[1] ; Benjamin Madeux, MD[1] ; Pascale Piednoir, MD[1] ; Fanny Ardisson, MD[1] ; Elain Elie, MD[1] ; Frédéric Martino, MD[1] ; Marc Valette, MD[1] ; Edouard Ollier, MD, PhD[4] ; Sébastien Breurec, MD, PhD[6,7,8,9] ; Michel Carles,MD, PhD[1,7] ; Guillaume Thiéry, MD[10,11]

* Contributed equally to this work

[1] Division of Intensive Care, University Hospital of Guadeloupe, Pointe-à-Pitre/Les Abymes, French West Indies, France

[2] Division of Intensive Care, Geneva University Hospitals, Geneva, Switzerland

[3] Division of Intensive Care, Saint-Pierre Clinic, Ottignies, Belgium

[4]Division of Clinical Epidemiology, University Hospital of Saint-Etienne, Saint-Etienne, France

[5] Division of Hospital Infection Control, University Hospital of Guadeloupe, Pointe-à-Pitre/Les Abymes, French West Indies, France

[6] Laboratory of Clinical Microbiology, Faculty of Medecine Hyacinthe Bastaraud, University of Antilles, Pointe-à-Pitre, French West Indies, France

[7] Faculty of Medecine Hyacinthe Bastaraud, University of Antilles, Pointe-à-Pitre, French West Indies, France

[8] INSERM Center for Clinical Investigation 1424, Pointe-à-Pitre/Les Abymes, French West Indies, France

[9] Transmission, Reservoir and Diversity of Pathogens Unit, Institut Pasteur de Guadeloupe, Pointe-à-Pitre, French West Indies, France

[10] Division of Intensive Care, University Hospital of Saint-Etienne, Saint-Etienne, France

[11] University Jean Monnet, Saint-Etienne, France

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Corresponding author:

Christophe Le Terrier, MD

Division of Intensive Care

Geneva University Hospitals

4 Rue Gabrielle-Perret-Gentil

1211 Geneva 14, Switzerland

Tel: +41 775 53 27 41

E-mail: leterrier.icu@gmail.com

ORCID: 0000-0002-5455-5576

Alternative corresponding author:

Guillaume Thiéry, MD

Division of Intensive Care

University Hospital of Saint-Etienne

Avenue Albert Raimond

42270 Saint-Priest-en-Jarez / France

Tel: +33 4 77 12 78 62

E-mail: guillaume.thiery@chu-st-etienne.fr

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Part 1. Initiation of antibiotic therapy

Stable patient (no septic shock, no severe acute respiratory distress syndrome [ARDS], no bacterial meningitis) with suspicion of clinical sepsis:

- Collection of a complete bacteriological chart (blood cultures, urine, sputum, puncture of any other suspect liquid);
- Abstention of antibiotic treatment until microbiological evidence of infection obtained:

  Lung: 10^5 CFU/ml in quantitative endotracheal suction specimen or 10^3 CFU/ml in distal pulmonary samples.
  Urinary tract: 10^5 CFU/ml in urinary samples with significant leukocyturia (white cell count >10^4/ml).
  Abdominal: Any isolation in a sterile liquid (ascitis/peritoneal fluid).
  Blood samples: Any isolation not considered contaminating (e.g., coagulase-negative staphylococci).
  Any cavity/sterile space (pleura, joints, cerebrospinal fluid, etc ...): Any isolation.

Unstable patient (in septic shock, severe ARDS or suspicion of bacterial meningitis):

- Collection of a complete bacteriological chart (blood cultures, urine, sputum, puncture of any suspicious liquid).
- After sampling, immediate initiation of a combination therapy with a dose of aminoglycoside (except for treatment of an abscess or anaerobic infection).

Part 2. Choice of the molecule

General rules

• No empirical use of carbapenem or piperacillin/tazobactam (to be used only in the case of documentation with an antibiogram leaving no other choice).
• As narrow a spectrum as possible.
• No empirical coverage of subdiaphragmatic anaerobes (unless clearly indicated in management, e.g., colonic perforation).
• No empirical coverage of *Pseudomonas aeruginosa*, unless clearly indicated in management, e.g., acute chronic obstructive pulmonary disease colonised with *P. aeruginosa* or late ventilator-associated pneumonia (VAP).
• Monotherapy in definitive antibiotic treatment, except endocarditis.
• Use of single-dose aminoglycoside for spectrum broadening and sparing of broad-spectrum beta-lactams while waiting for microbiological data.

Protocolised specific empirical treatments

- Cefuroxime (+ metronidazole if submesocolic location) for community peritonitis
- Cefuroxime for community biliary peritonitis
- Cefoxitin or temocillin +/- metronidazole for nosocomial (tertiary) peritonitis
- Cefotaxime + spyramycin for community-acquired pneumonia
- Cefazolin for dilapidated wounds with open fractures and for facial smashing
- Cefuroxime or ciprofloxacin for urinary tract infections
- Amoxicillin for suspicion of leptospirosis
- Cefuroxime for early VAP (<5 days)
- Ceftazidime plus cloxacillin for late VAP (> 5 days)

Part 3. Duration therapy

Short and fixed duration of all antibiotic therapies, other than those defined in the long-term antibiotic therapy group (see below)

- **5 days** for community-acquired pneumonia;
- **4 days** for secondary peritonitis (from the surgical intervention)
- **24 h** for proximal digestive perforations operated within 24 hours
- **<24 h** for traumatic digestive perforations (any kind) operated within 12 hours
- **1-3 days** for dilapidated wounds with open fractures
- **24 h** for facial smears (with sinus fracture)
- **7 days** for coagulase-negative staphylococci bacteremia
- **14 days** for *Staphylococcus aureus* bacteremia
- **5 days** for leptospirosis
- **7 days** for pyelonephritis
- **7-21 days** for bacterial meningitis
    - **7 days** if *Neisseria meningitidis* or *Haemophilus influenzae*
    - **10 days** if *Streptococcus pneumonia*
    - **14-21 days** for other aetiologies, depending on the germ
- **7 days** for VAP
- **7 days** maximum for any other infection.

Long-term therapies (≥14 days), in collaboration with the infectiology team:

- Osteitis and severe skin and soft tissue infections
- Endocarditis
- Spondylodiscitis
- Empyema and pulmonary abscess
- Deep abscess undrained and/or resistant to antibiotic therapy
- Complicated infected thrombophlebitis

II/ Additional Tables and Figures

Table 1 Sepsis category on ICU admission and ICU-acquired during the study period.

Sepsis category	Conventional strategy period 2014 n=738	Restrictive strategy period 2015 n=803	*p* value
On ICU admission[a] n (%)	**n= 237 (32.1)**	**n= 211 (26.3)**	**<0.01**
Leptospirosis	10 (1.4)	16 (2.0)	0.33
Pulmonary infection	111 (40.8)	83 (34.9)	0.17
Urinary infection	34 (12.5)	44 (18.5)	0.06
Cutaneous infection	8 (2.9)	13 (5.5)	0.15
Catheter-related bloodstream infection	5 (1.8)	9 (3.8)	0.18
Intraabdominal infection	58 (21.3)	55 (23.1)	0.63
Endocarditis	7 (2.6)	7 (2.9)	0.80
Central nervous system infection	23 (8.5)	13 (5.5)	0.19
Bone infection	3 (1.1)	3 (1.3)	1
Ear, nose and throat infection	3 (1.1)	9 (3.8)	0.05
others	28 (10.3)	18 (7.6)	0.28
Acquired during ICU length of stay[a] n (%)	**n= 178 (24.4)**	**n= 135 (16.8)**	**<0.01**
Pulmonary infection	108 (61.0)	61 (44.2)	<0.01
Urinary infection	24 (13.6)	22 (15.9)	0.55
Cutaneous infection	4 (2.3)	6 (4.3)	0.34
Catheter-related bloodstream infection	24 (13.6)	20 (14.5)	0.81
Intraabdominal infection	10 (5.6)	32 (23.2)	<0.01
Endocarditis	2 (1.1)	2 (1.4)	1
Central nervous system infection	11 (6.2)	3 (2.2)	0.08
Bone infection	0 (0)	3 (2.2)	0.08
Ears, nose and throat infection	2 (1.1)	2 (1.4)	0.80
others	28 (15.8)	16 (11.6)	0.70

[a] Multiple diagnoses were possible for the same patient.
When not specified, results are n (%). In bold, *p* values <0.05

SAPS II: Simplified Acute Physiology Score II; ICU: intensive care unit; ESBL-E: extended-spectrum beta-lactamase–producing Enterobacteriacea*e;* SD: standard deviation

Figure 1a. Absolute main differences before and after weighted adjustment in the main analysis sample.
b. absolute main differences before and after weighted adjustment in the subgroup receiving antibiotherapy.

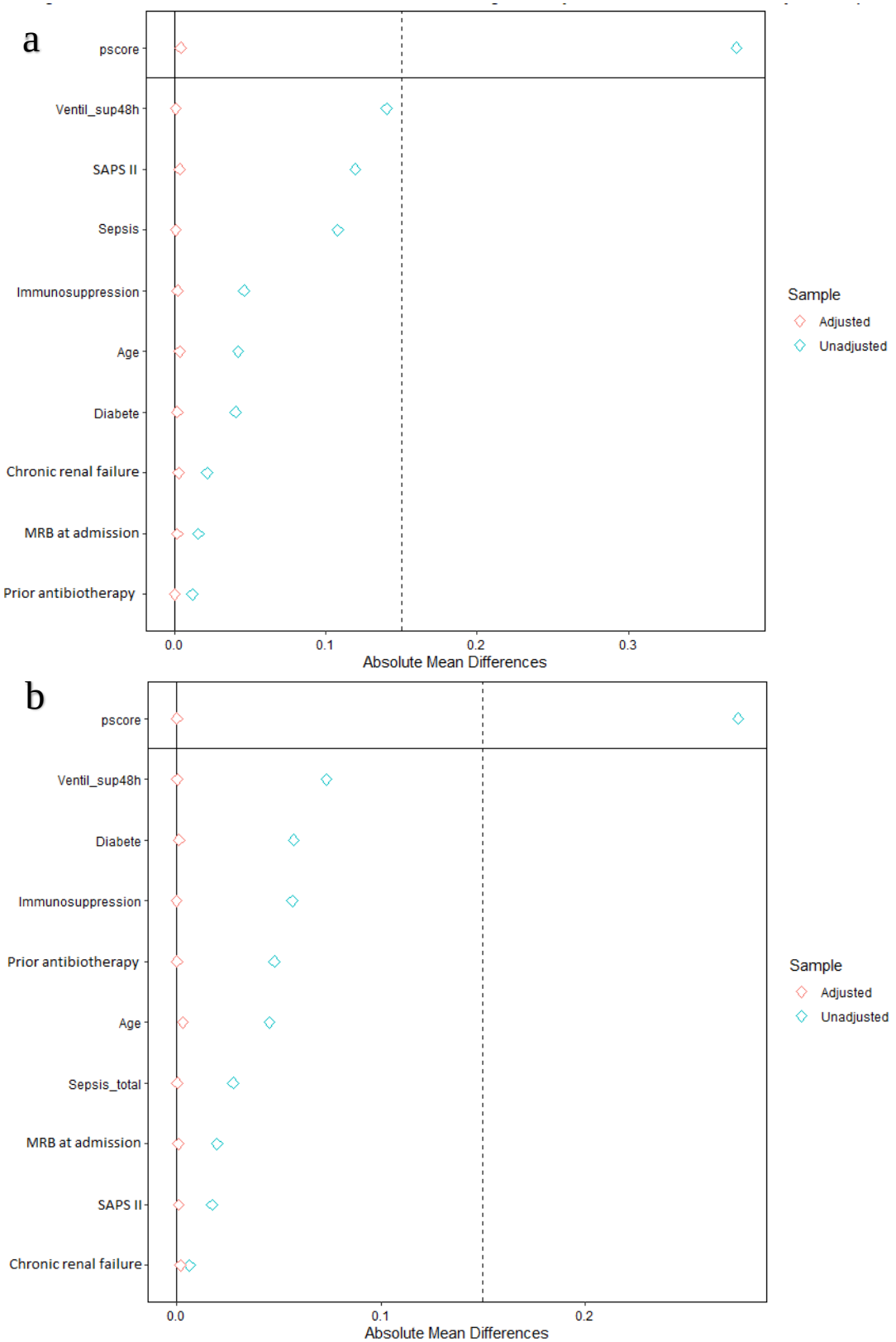

Figure 2 ROC curve of the propensity score in the main analysis.