Interventional Study of Bone and Joint Infections related gut Dysbiosis (OSIRIS study): first results of a prospective multicenter trial

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INTRODUCTION

Bone and joint infections (BJI) often require a prolonged antimicrobial chemotherapy that can affect the gut microbiota. Few days of treatment are sufficient to induce dysbiosis, an intestinal disorder characterized by accumulation of microbiota imbalance, host-microbiota crosstalk dysfunction and inflammation. Dysbiosis and antibacterial pressure can induce the selection of multidrug resistant bacteria (MDRB) and/or some bacterial pathogens such as *Clostridium difficile*.

The OSIRIS project is a multicenter interventional study investigating the impact of antibiotics on clinical conditions and gut microbiota in patients with BJI treatment. The aim of OSIRIS is to analyze relationships between antibiotics and dysbiosis in order to evaluate the potential of Fecal Microbiota Transfer (FMT) as a strategy to restore the gut ecosystem. Here, in a first step of the global study, we investigated the emergence of MDRB and *C. difficile* in gut microbiota of BJI patients receiving a prolonged antimicrobial therapy.

Overall, the objective will be to restore the patient's gut microbiota using an autologous FMT strategy named **MaaT031**.

STUDY OBJECTIVES

- **Primary objective**:

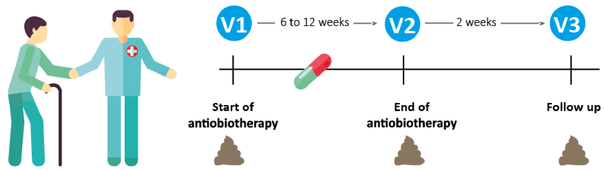
→ Evaluate the impact of antibiotic treatment on diarrhea in patients with BJI and its correlation to gut microbiota alteration

- **Secondary objectives**:

- Characterize of the gut dysbiosis and its prevalence in patients with BJI and under antibiotic treatment
- Quantify the proportion of extended-spectrum beta-lactamase (ESBL) producing bacteria after and before treatment
- Evaluate fecal MDRB carriage incidence
- Evaluate health economy parameters
- Identify the targeted population with suspicion of infections, experiencing diarrhea events and eligible for MaaT031 microbiotherapy

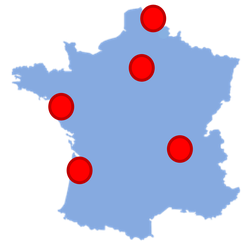
STUDY FLOW CHART - METHODS - POPULATION

- Fecal samples from patients treated for BJI were collected along 3 visits:



- Screening of ESBL/Carbapenemase-producing enterobacteriaceae (CPE)/Vancomycin Resistant Enterococci (VRE)/MRSA carriage : stools plating on selective chromogenic media (bioMérieux)
- Species identification : Vitek MS (bioMérieux)
- Antimicrobial phenotypes confirmation : disk-diffusion method
- *Clostridium difficile* presence : tested by quick test (*C. diff* Quick Check complete, Alere) and confirmed by PCR (Xpert *C. difficile*, Cepheid)

French participative hospitals:
- Bordeaux, Pellegrin Hospital
- Lyon, Croix-Rousse Hospital
- Nantes, Hôtel-Dieu
- Paris, Groupe hospitalier Diaconesses Croix Saint-Simon
- Centre Hospitalier de Tourcoing, CHRU de Lille



Studied population and clinical data

- 62 patients included, 54 evaluable
- 40 males / 22 females
- Prosthetic-joint infection: 21
- Osteosynthesis: 14
- Native BJI: 27
- Average age: around 60 years
- Body Mass Index mean: 27.4
- Episodes of cumulative diarrhea (defined as a minimum of 3 liquid stools per day during 3 days):
  - V1: 1 episode
  - V2: 11 episodes
  - V3: 6 episodes
- Average term of antimicrobial therapy : 65.5 days

RESULTS

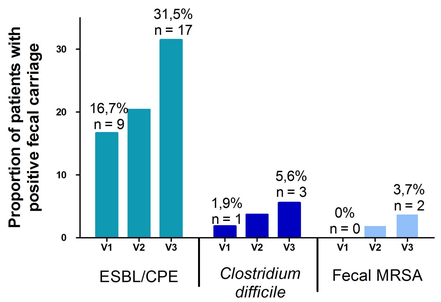


Fig 1: Proportion of fecal carriage of ESBL/CPE, *Clostridium difficile* and fecal MRSA during the treatment of evaluable patients (n = 54)

→ The data reveal an increase of MDRB fecal carriage between V1 and V3:
- ESBL: 16.7% – 29.6%
- *C. difficile:* 1.9% – 5.6%
- Fecal MRSA: 0% – 3.7%

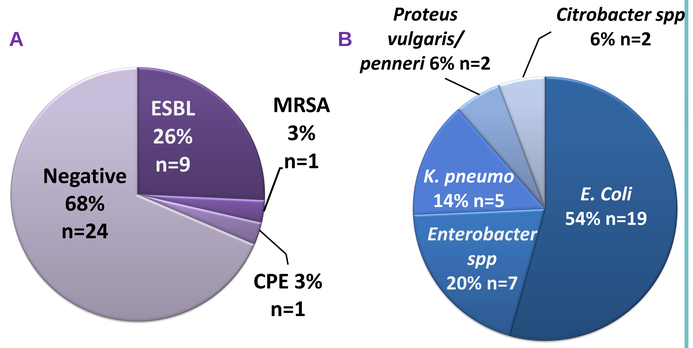


Fig 2: **A. Acquisition** of MDRB among the patients without MDRB at baseline and for who V3 data were available. **B.** Proportion of species detected among the ESBL isolated at V1, V2 and V3 (n=35)

→ Among MDRB that patients acquire during the antibiotic therapy, the most detected are **ESBL** (82%, 9/11)

→ The predominant species of ESBL is ***Escherichia coli*** (54%), followed by *Enterobacter spp* (20%)

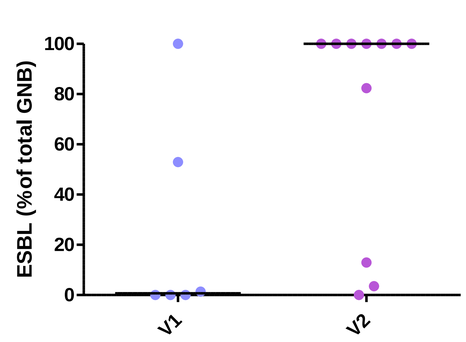


Fig 3: Quantification of ESBL among gram negative bacteria (GNB, relative abundance in %) in the intestinal microbiota of 13 patients at V1 and/or V2

→ The quantification data reveal an important increase to a higher proportion of ESBL at V2:
- V1 median at 0,71% of GNB
- V2 median at 100% of GNB

CONCLUSIONS

Our results report an acquisition of MDRB after BJI treatment. The qualitative analysis confirms the expected predominance of ESBL bacteria. The quantitative analysis reveals an increase of the ESBL ratio in carriers between V1 and V2. These data clearly demonstrate the impact of antibiotics treatments on the fecal microbiota ecology and strongly support the interest of an approach such as **MaaT031**.

The objective of **MaaT031** product is to restore the original microbiota of the patients after a long-term antimicrobial chemotherapy as in BJI, in order to limit the dissemination of bacteria such as ESBL-positive bacteria, toxigenic *C. difficile*, MRSA or CPE that represent a health threat and have a huge healthcare cost.

Clinical data, **Fecal biomarkers** of gut inflammation and **Next Generation Sequencing** of fecal microbiota are currently under analysis.

Overall, the results from the OSIRIS study will drive the next development steps of an **autologous microbiotherapy strategy** to treat patients under long-term antimicrobial therapy and eradicate MDRB carriage and dissemination in hospitals and within the community.

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