

Influence of Antibiotics in Intestinal Microbiota, and Association between Dysbiosis and Sepsis in Children Receiving Hematopoietic Stem Cell Transplants in Cali, Colombia

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RESEARCH OBJECTIVE

To describe the association between antibiotic use, gut microbiota modifications and sepsis in children with acute lymphoblastic leukemia (ALL) receiving a Hematopoietic Stem Cell Transplants (HSCT) in developing countries.

POPULATION STUDIED

- Prospective cohort study in 8 children with ALL.
- Weekly stool samples
- From day 0 until day 30 post HSCT, in a transplant unit from Cali-Colombia.

STUDY DESIGN

- Microbiota profiling.
- 16S rRNA gene sequencing.
- From day -30 until day +30 post HSCT, or until sepsis: Clinical condition and antibiotic consumption
- Sepsis: bacteremia or clinically documented infection.
- Associations:
 - Sepsis and antibiotic use (prior to the onset of sepsis).
 - Microbiota composition and diversity in relation to the development of sepsis.
- Bacteria were classified as protective or pathogenic according to previous reports

RESULTS

- Eight pediatric patients (mean age 9.6 (SD 4.9), 74% male, all mixed-race) had 34 stool samples collected for microbiota identification. Five of them developed sepsis (mean post HSCT day 15).
- Microbiota was significantly more diverse in patients who did not developed sepsis, while a single taxon of enterobacterales dominated in patients who developed sepsis (Figures 1 and 2).

RESULTS

- The association between different antibiotics and the proportion of protective or pathogenic microorganisms present in the stool is shown in Figure 3.
- 80% of patients who developed sepsis had a progressive expansion of pathogenic bacteria while protective bacteria declined in chronological association with antibiotic use.
- Patients without sepsis had a higher relative abundance of protective bacteria and a more balanced ratio of protective/pathogenic bacteria.
- Patients who developed sepsis had a trend towards a higher use of antibiotics (excluding antibiotic use after the sepsis episode): 8443.2 (95% CI 6753-10556) and 6367 (95%CI 4526-8956) per 1000 patients.

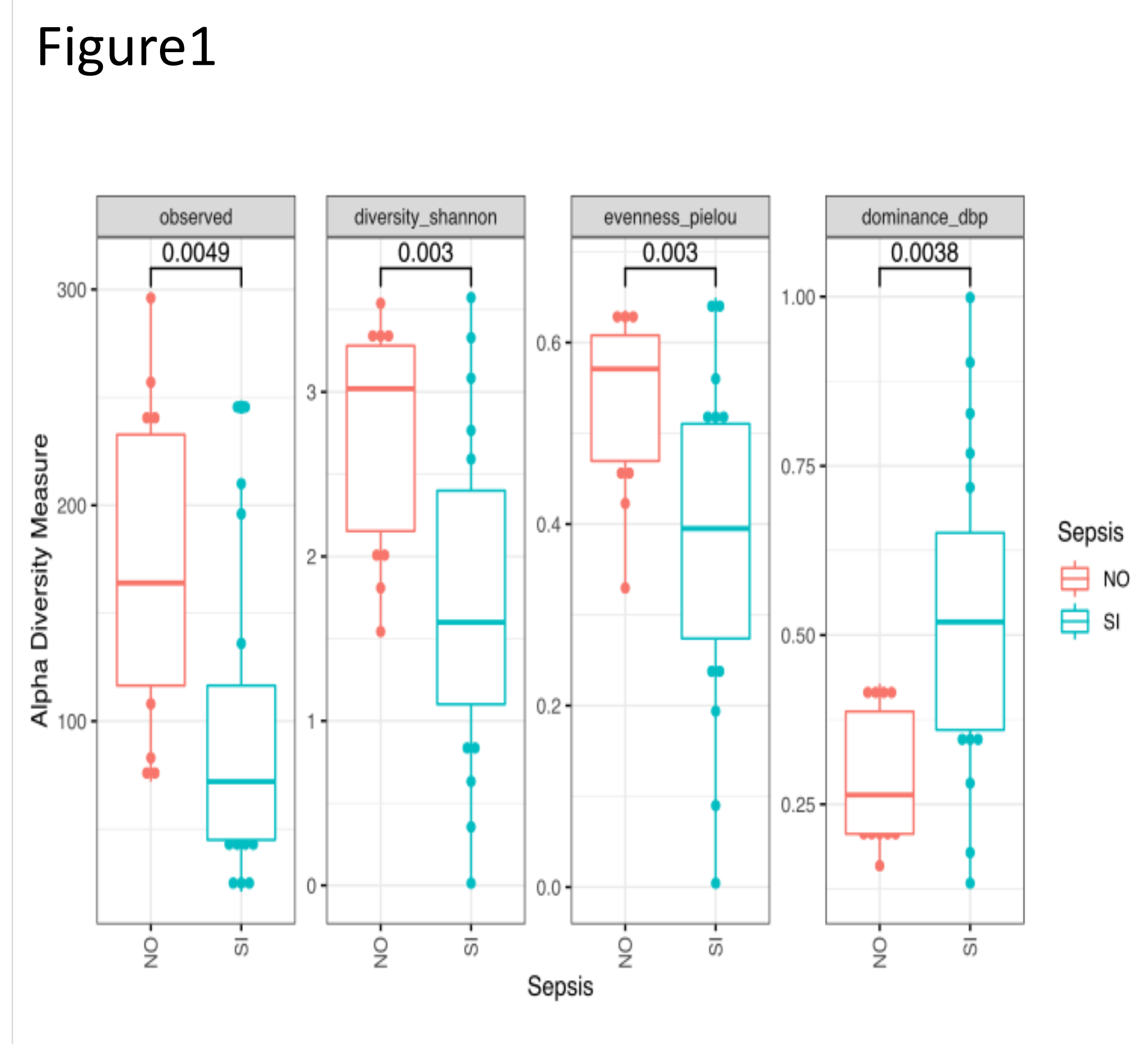


Figure 2

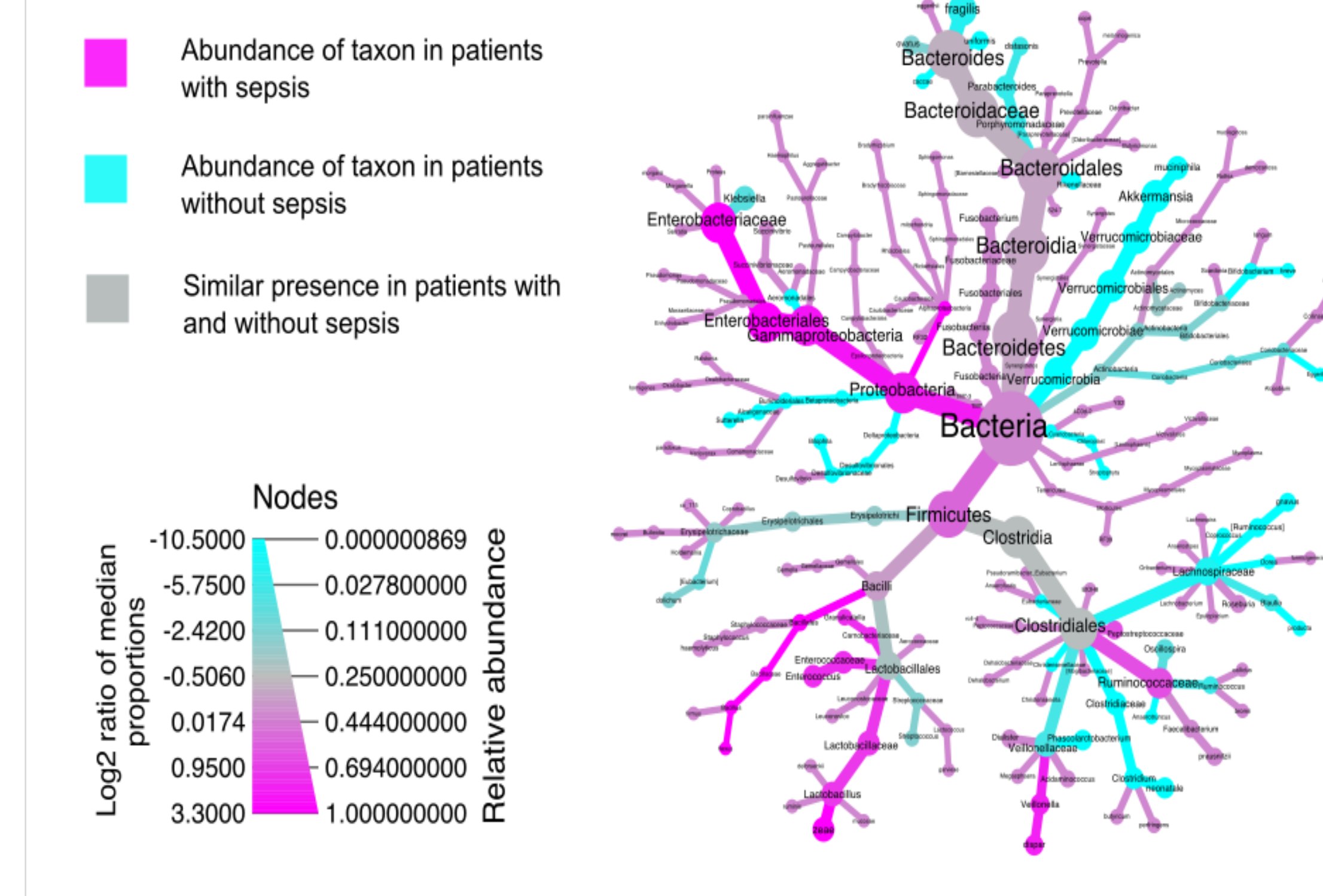
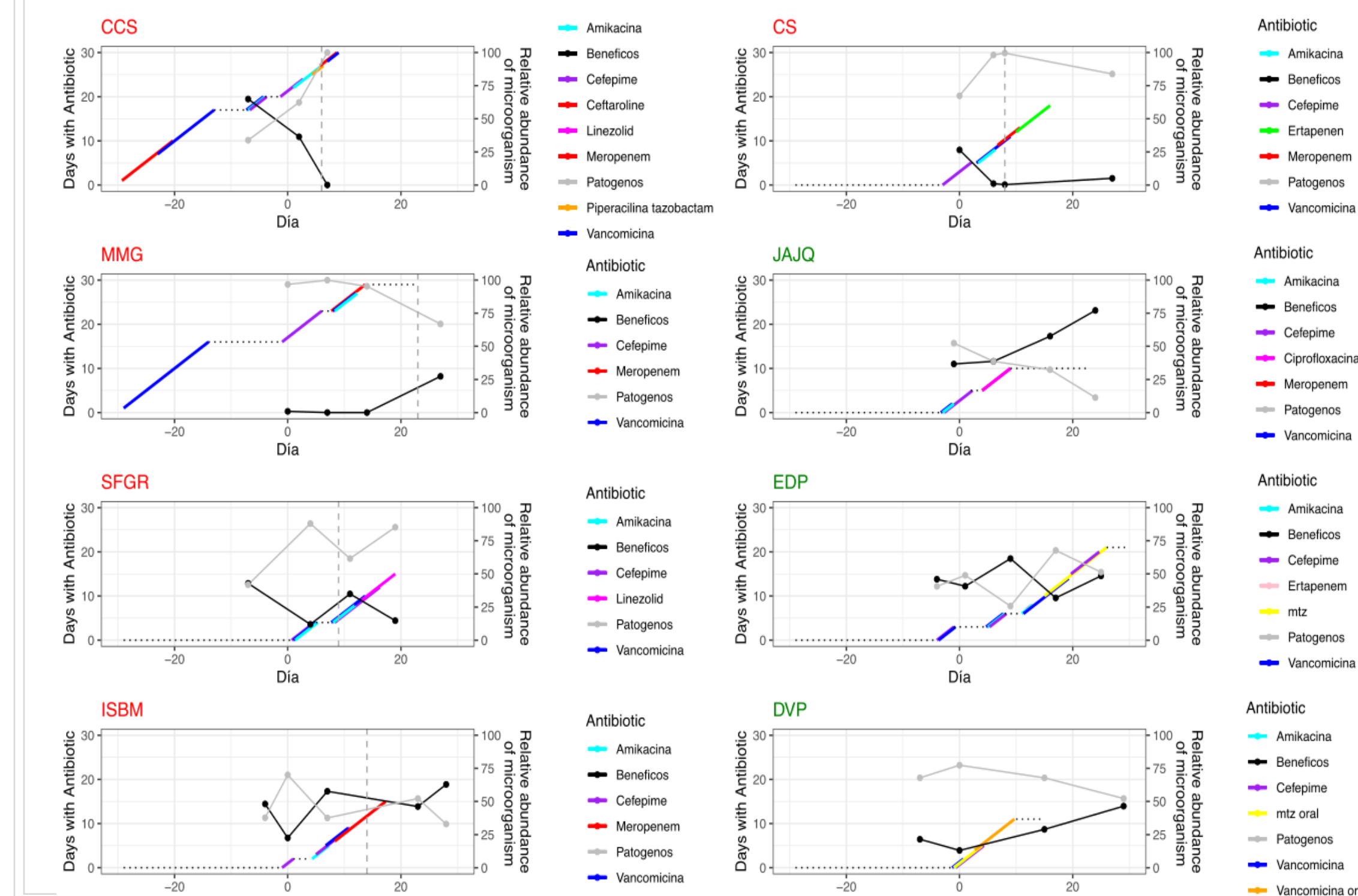


Figure 3



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CONCLUSION

In this cohort of children who received a HSCT, sepsis was a frequent complication. This adverse outcome may be associated with antibiotic-associated disruption in gut microbiota, leading to loss of microbial diversity and dominance of pathogenic Enterobacterales. Judicious use of antibiotics in pediatric HSCT units is of paramount importance in order to maintain a healthier microbiota balance that may reduce the risk of sepsis.

IMPLICATIONS FOR POLICY AND PRACTICE

- In pediatric HSCT recipients, fever is a common occurrence, leading to the frequent use of broad-spectrum antibiotics.
- In these patients, fever is often derived from non-infectious causes.
- The unnecessary use of antibiotics leads to antimicrobial resistance and graft versus host disease.
- In this hypothesis-formulating data, we identify that antibiotic use is associated with intestinal dysbiosis and possibly and increased risk of sepsis.
- Antimicrobial administration programs should be strengthened in hospital wards that care for children with hematologic malignancies and hematopoietic stem cell transplantation.
- Prioritizing stewardship programs by policy and decision makers at local and national level, and elaboration of guidelines by health institution may reduce the unwanted effects of antibiotics in fragile post-HSCT children.

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