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Microbial Disruption Indices to Detect Colonization With Multidrug-Resistant Organisms

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Abstract

OBJECTIVE.—To characterize the microbial disruption indices of hospitalized patients to predict colonization with multidrug-resistant organisms (MDROs).

DESIGN.—A cross-sectional survey of the fecal microbiome was conducted in a tertiary referral, acute-care hospital in Boston, Massachusetts.

PARTICIPANTS.—The study population consisted of adult patients hospitalized in general medical/surgical wards.

METHODS.—Rectal swabs were obtained from patients within 48 hours of hospital admission and screened for MDRO colonization using conventional culture techniques. The V4 region of the 16S rRNA gene was sequenced to assess the fecal microbiome. Microbial diversity and composition, as well as the functional potential of the microbial communities present in fecal samples, were compared between patients with and without MDRO colonization.

RESULTS.—A total of 44 patients were included in the study, of whom 11 (25%) were colonized with at least 1 MDRO. Reduced microbial diversity and high abundance of metabolic pathways associated with multidrug-resistance mechanisms characterized the fecal microbiome of patients colonized with MDRO at hospital admission.

CONCLUSIONS.—Our data suggest that microbial disruption indices may be key to predicting MDRO colonization and could provide novel infection control approaches.

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Infections caused by multidrug-resistant organisms (MDROs) are associated with significant mortality and carry an important economic burden.[1] Microbiome dysbiosis, defined as an imbalance between beneficial and potentially deleterious microorganisms,[2] is associated with increased risk of MDRO colonization and infection.[3,4] The Centers for Disease Control and Prevention (CDC) has begun to work on developing microbiome disruption indices (MDIs): characteristics of microbiome dysbiosis that can identify patients at increased risk of MDRO colonization, infection, and transmission.[5] MDIs could be used to develop rapid MDRO detection methods and to prompt placement of patients on isolation precautions in an effort to limit MDRO spread.

We previously reported MDIs in the fecal microbiomes of patients who acquired MDROs during their hospitalization and showed that a greater abundance of *Lactobacillus* spp. was suggestive of protection against MDRO acquisition.[4] Other potential biomarkers predicting MDRO colonization include reductions in microbial diversity and the relative abundance of the anaerobic compartment of the microbiome.[6,7]

In the current study, we sought to characterize the MDIs of hospitalized patients who were colonized with MDRO at hospital admission. We also used metagenomic inference to include indices of metabolic pathways that could predict MDRO colonization at hospital admission.

METHODS

Study Population

Adult patients hospitalized (<48 hours) on medical/surgical wards in a 649-bed, tertiary-care center in Boston, Massachusetts, were approached for study participation. The exclusion criteria included (1) patients unable to consent, (2) those with conditions that precluded rectal sampling (eg, with colostomy bags), and (3) specimens that did not have sufficient DNA for sequencing. The hospital's institutional review board approved the study protocol, and informed consent was obtained from all subjects prior to specimen and data collection.

Data and Sample Collection

After patients agreed to participate, clinical and demographic data were collected, including the Charlson comorbidity index[8] and exposure to antimicrobials or healthcare-associated facilities in the prior 3 months. Rectal specimens were obtained by inserting a sterile, double-tipped cotton swab (Starswab II; Starplex Scientific, Cleveland TN) 0.5–1.0 cm into the anus. Samples were then transported to a central laboratory located in the study hospital within 1–2 hours after collection. Once in the laboratory, the first tip of the swab was immediately processed for MDRO identification using standard techniques,[9] and the second tip was placed in a 20% glycerol vial and stored at −80°C for subsequent assessment of microbial communities.

Microbiological Methods

Identification of MDROs and antimicrobial susceptibility testing were performed as previously described using the Clinical and Laboratory Standards Institute (CLSI)

methodology.[10,11] MDROs included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant gram-negative bacilli (MDRGN). MDRGN were defined as gram-negative bacteria resistant to >3 of the following antimicrobials: ampicillin/sulbactam or piperacillin/tazobactam, ceftriaxone or ceftazidime (in case of *Pseudomonas* spp. only ceftazidime), ciprofloxacin, gentamicin, or meropenem.

16S rRNA Sequencing and Bioinformatic Approach

For each rectal specimen, bacterial DNA was extracted as described.[4] Subsequently, the 16S rRNA amplicon library was generated by polymerase chain reaction (PCR) using a barcoded primer set targeted to the V4 variable region.[12] Amplicons were then sequenced on an MiSeq sequencer (Illumina, San Diego, CA) at the Tufts University Core Facility using a paired-end 250-bp protocol with reads merged as described.[12]

Subjects were classified according to the presence or absence of MDRO colonization (ie, MDRO+ [positive] or MDRO− [negative], respectively). Relevant patient characteristics were compared between the 2 groups using the Wilcoxon rank-sum test or the Fisher exact test. A significance level of $P \leq .05$ was used for all statistical tests. Statistical analyses were performed using STATA version 13.0 software (StataCorp, College Station, TX).

Bioinformatic analyses were performed using the QIIME version 1.7 software package[13] following the pipeline previously reported.[4] First, within-sample microbial diversity (α diversity) was estimated using the Shannon index[14] and was compared between MDRO+ and MDRO− patients. Second, associations between microbial diversity and MDRO colonization were analyzed using multiple logistic regression with the Shannon index as the predictor and MDRO colonization with ≥1 MDRO species as the outcome variable. To account for potential confounders, other risk factors for MDRO acquisition were included a priori as covariates if they were statistically significant on univariate analyses. Third, the diagnostic performance of the Shannon index was investigated by running receiver operating characteristic curves (ROCs) and estimating the area under the ROC curve (AUC).

Differences in community composition between MDRO+ and MDRO− were analyzed by estimating weighted and unweighted UniFrac distances[15] and were visualized using principal coordinates analysis (PCoA).[16] Within- and between-group distances were compared using nonparametric testing (ie, 999 Monte Carlo permutations, Bonferroni-corrected). In addition, differential sample clustering according to MDRO status was investigated using the adonis test implemented in QIIME pipeline. Differentially abundant bacterial taxa at any phylogenetic level between groups were determined by performing linear discriminant analysis (LDA) effect size (LEfSe) analysis, using an LDA score of 2.0 as the cutoff and an α level of 0.05.[17]

Finally, the functional profile of each sample was analyzed using reconstruction of unobserved states (PICRUSt) to infer the metagenome from the 16S rRNA data. Functional profiles were assessed using the PICRUSt Predict Metagenome tool.[18] The quality of the metagenome prediction was estimated by calculating the mean nearest sequenced taxon index (NSTI), where low values (<.06) indicate accurate prediction.[18] The predicted Kyoto Encyclopedia of Genes and Genomes (KEGG) orthology terms where then analyzed using

LEfSe (LDA score ≥2.0 and α value ≤0.01) to identify genes that were differentially abundant between MDRO+ and MDRO− groups. The pathways and gene descriptions of KEGG orthology terms were then obtained from the KEGG Brite database.[19]

RESULTS

Clinical Characteristics and MDRO Colonization

From May 27, 2013, to January 24, 2014, 49 patients completed the study. Of these, 5 patients were excluded due to unsuccessful sequencing of the rectal sample. The median age of the study cohort was 66 years (interquartile range [IQR], 59–75 years), and 34 (77%) were male. Furthermore, 11 patients were colonized with at least 1 MDRO at hospital admission, among whom 5 patients were cocolonized with >1 MDRO, and 7 patients (63.6%) had a history of MDRO colonization in the previous year. The MDROs isolated at baseline were *Escherichia coli* (n = 4), *Klebsiella pneumoniae* (n = 3), *Proteus mirabilis* (n = 1), *Citrobacter freundii* (n = 1), *Pseudomonas aeruginosa* (n = 1), VRE (n = 3), and MRSA (n = 3).

Compared to MDRO− patients, MDRO+ patients had a significantly higher Charlson comorbidity index (7 [IQR, 6–9] vs 4 [IQR, 3–7]; $P = .05$). The MDRO+ patients were more frequently exposed to healthcare-associated facilities (90.9% vs 57.6%; $P = .07$), and they had greater antimicrobial exposure during the 3 months prior admission (90% vs 48.4%; $P = .02$). Age, gender, diabetes mellitus, obesity, gastrointestinal disease, and current use of proton pump inhibitors were similar between MDRO+ and MDRO− patients ($P > .5$) (Tables 1 and 2).

Fecal Microbiome Assessment

A total of 44 baseline rectal specimens were successfully sequenced, yielding 3,638,570 high-quality 16S rRNA gene sequences after quality filtering, with a median number of sequences per sample of 84,752 (IQR, 68,472–96,133). Alpha diversity metrics were estimated at a sequencing depth of 7,300 reads per sample. The overall range of the Shannon index in the study population was 1.53–6.65. The median Shannon index differed significantly between MDRO+ and MDRO− patients (3.03 [IQR, 2.40–4.57] vs 4.43 [IQR, 3.96–4.93]; $P = .005$) (Figure 1A), and it was inversely associated with MDRO colonization (odds ratio [OR] for each additional increment of the Shannon index, 0.23; 95% confidence interval [95% CI], 0.09–0.62; $P = .004$). The inverse association between the Shannon index and MDRO colonization remained significant after adjusting for the Charlson index, prior antimicrobial exposure, and prior stay in healthcare-associated facilities (adjusted odds ratio [OR], 0.26; 95% CI, 0.07–0.92; $P = .04$). The AUC of the ROC curve for the Shannon index as a predictor of MDRO− status was 0.79 (95% CI, 0.61–0.96) (Figure 1B). For a Shannon index cutoff ≥3.62, the sensitivity and specificity to detect MDRO− patients was 93.9% and 63.6%, respectively. Using this optimal cutoff, the Shannon index correctly classified 86.4% of the 44 patients according to their MDRO status.

The composition of the bacterial communities of MDRO+ and MDRO− patients also differed significantly. First, the within-group distances were significantly lower in MDRO−

compared to MDRO+ patients (Bonferroni corrected, nonparametric $P = .01$), indicating that samples among MDRO− patients were more homogeneous than the samples of MDRO+ individuals (Figure 2A). Second, between-group distances were higher than within-group distances, suggesting that marked differences in community composition were present when comparing MDRO− versus MDRO+ patients (Figure 2A). The principal coordinates analysis (PCoA) of unweighted UniFrac distances showed differential clustering of samples according to MDRO status (Figure 2B). The analysis of differentially abundant taxonomic features between groups is shown in Figure 3.

Overall, 20 genes were identified with significant differences in relative abundance between MDRO+ and MDRO− patients and are summarized in Table 3. MDRO colonization was correlated with increased abundance of genes related to multidrug-resistance: the 2-component systems, and membrane transport (phosphotransferase systems, and ATP-binding cassette transporters). MDRO− status was associated with higher abundance of amino acid and nucleotide metabolism genes (Figure 4).

DISCUSSION

Several MDIs were associated with colonization with MDRO among patients at hospital admission. Compared with MDRO− patients, the intestinal microbiota of MDRO+ patients had substantially lower microbial diversity, even after adjusting for potential confounders of MDRO colonization, including prior stay in healthcare-associated facility and antimicrobial exposure. Reduced microbial diversity has been associated with adverse clinical outcomes. Among patients undergoing hematopoietic stem-cell transplantation, a profound decrease in microbial diversity preceded intestinal domination by specific bacterial pathogens and increased the risk of subsequent VRE or gram-negative bacteremia.[3] In the same patient setting, low intestinal microbial diversity has been shown to be an independent predictor of mortality.[20] Similarly, the intestinal microbiota of patients with recurrent *Clostridium difficile* infection (CDI), in particular those with severe disease, is also characterized by reduced microbial diversity compared to controls.[21] Although data suggest that reduced microbial diversity itself does not constitute a causal mechanism for developing disease, it may be considered a biomarker of a disrupted microbiota.[22]

Substantial differences in the composition of bacterial communities between the MDRO− and MDRO+ patients were also identified. These included a greater abundance of *Enterococcus* spp. and microbiota belonging to *Bacteroidales* order, among MDRO+ and MDRO− patients, respectively. These findings are consistent with previous reports showing severe disruptions in the fecal microbiota of hospitalized patients exposed to antimicrobials. Thus, higher abundances of pathogens such as enterococci may reflect an impaired colonization resistance. Several bacterial taxa have been associated with colonization resistance against transient pathogens, including MDROs. For example, a greater abundance of *Lactobacillus* spp. characterized the fecal microbiota of patients that remained uncolonized with MDRO during hospitalization.[4] *Clostridium scindens* has been shown to have a potentially protective effect against *C. difficile* and *Barnesiella* spp. against VRE colonization.[22,23] Lastly, successful eradication of MDRO using fecal microbiota transplantation in patients with hematologic disease has been reported, with a high

abundance of members of the *Bacteroidales* order characterizing the post-FMT microbiota of patients in whom MDRO was successfully eradicated.[24] In this study, the microbiome of patients not colonized with an MDRO also showed greater abundance of the *Bacteroidales* order, suggesting that this order may reflect a healthier microbiome that is more resistant to MDRO colonization.[24]

Metagenomic prediction revealed a higher abundance of genes among MDRO+ patients related to several pathways implicated in multidrug resistance: the 2-component system, the ATP-binding cassette system, and the phosphotransferase system.[25–27] These results are consistent with our phenotypic identification of MDROs using classical culture-dependent microbiological methods, and they highlight the potential to identify metabolic pathways and their byproducts as potential biomarkers of MDRO colonization, which may be widely applicable considering the functional stability of the human microbiome.[28] A recent study by Zhernakova et al[29] showed that the protein chromogranin A, retrieved from the stool, had a strong negative correlation with microbial diversity in the gut, suggesting that this fecal biomarker could be used to ascertain gut health. The results of our study and others, suggest that similar biomarkers could be identified in the future that would predict MDRO colonization.

Our study has several limitations. First, our results are subject to unrecognized bias because the number of samples was relatively small. Therefore, the associations described should be interpreted with caution; no causal relationship between microbiome features and MDRO colonization can be established. Furthermore, as a cross-sectional study, the differences in microbiome characteristics cannot be considered predictive of the outcome. Second, the case definition (MDRO detection) was based on cultures that have variable sensibility, conveying a risk of misclassification bias. However, participants were extensively exposed to antimicrobials, which maximizes the sensitivity of the MDRO detection approach.[10] Third, antimicrobial use is a well-recognized confounder in microbiome studies.[30] Although prior and current antimicrobial exposures were variables considered in the analysis, differential exposure to types of antimicrobials between MDRO+ and MDRO− patients may have occurred. Finally, the functional prediction for a given bacterial community based on 16S rRNA sequence data may be subject to limitations when the availability of reference genomes is scarce. However, the low mean NSTI value (0.05) reported in this study indicates that closely related genomes were available and supports the accuracy of the prediction.[18]

Substantial advancement in characterizing microbiome dysbiosis predictive of disease states has been made.[31] Microbiome research focusing on MDRO transmission dynamics is at a younger stage. The findings of this study begin to characterize MDIs associated with MDRO colonization, including an independent and inverse association with microbiome diversity, differences in bacterial community structures, and metabolic pathways. Future larger studies are required to increase our understanding and application of microbiome analyses toward limiting MDRO transmission and spread, with the future goal of developing rapid tests that could detect MDRO colonization at hospital admission.

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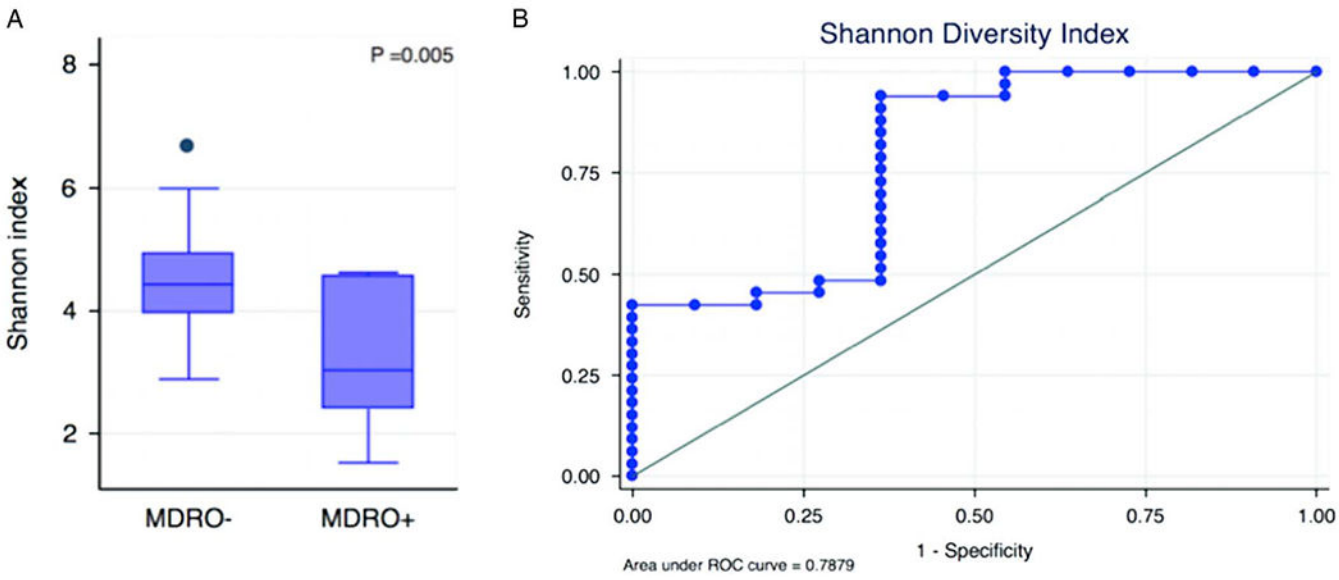

FIGURE 1.

Microbial disruption indices associated with MDRO colonization at hospital admission: (A) microbial diversity compared between MDRO− and MDRO+ patients, and (B) the area under receiver operating characteristic (ROC) curve for the Shannon index as a predictor of MDRO− status.

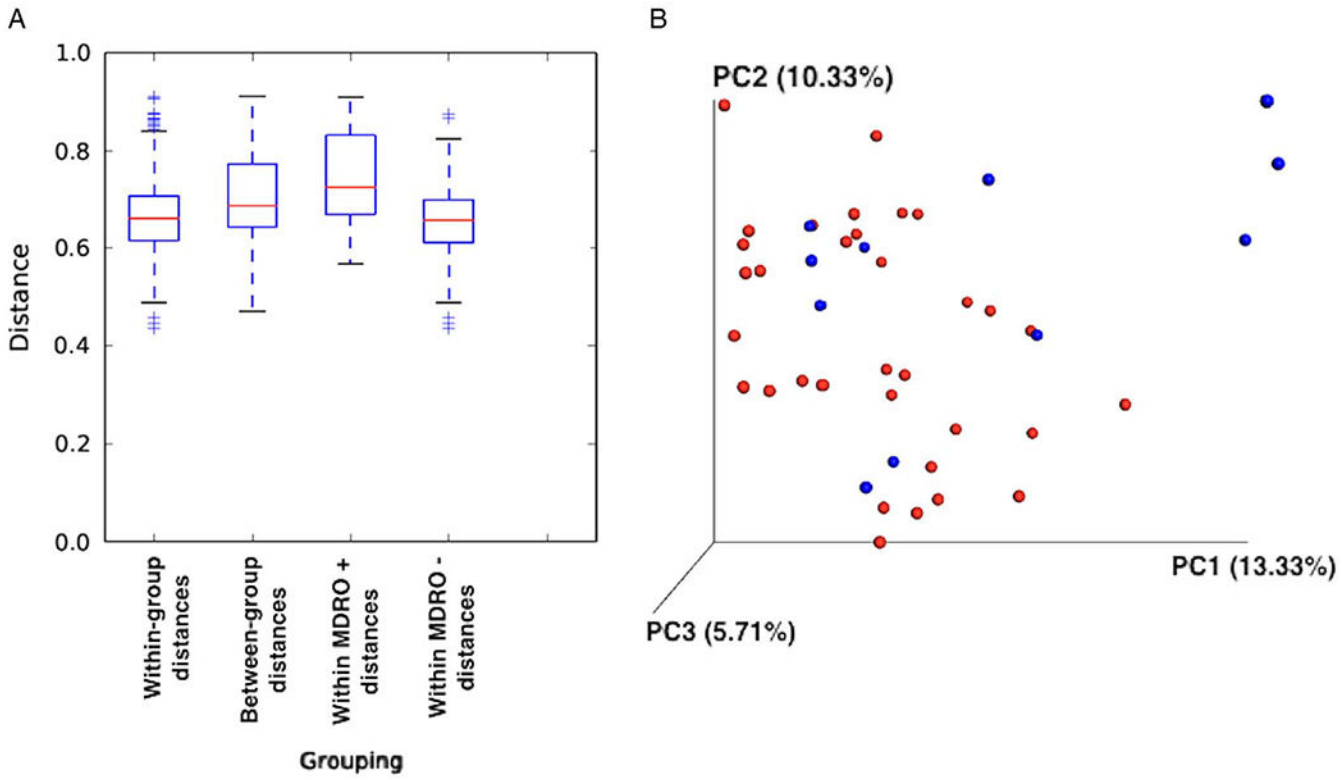

FIGURE 2.

Unweighted UniFrac distances. (A) Between-group distances were significantly higher than within-group distances (Bonferroni corrected, nonparametric $P = 0.01$). (B) Principal coordinate analysis (PCoA) of unweighted UniFrac distances according to MDRO colonization status ($P = 0.01$, $R^2 = 0.04$). Blue dots, MDRO+; red dots, MDRO−.

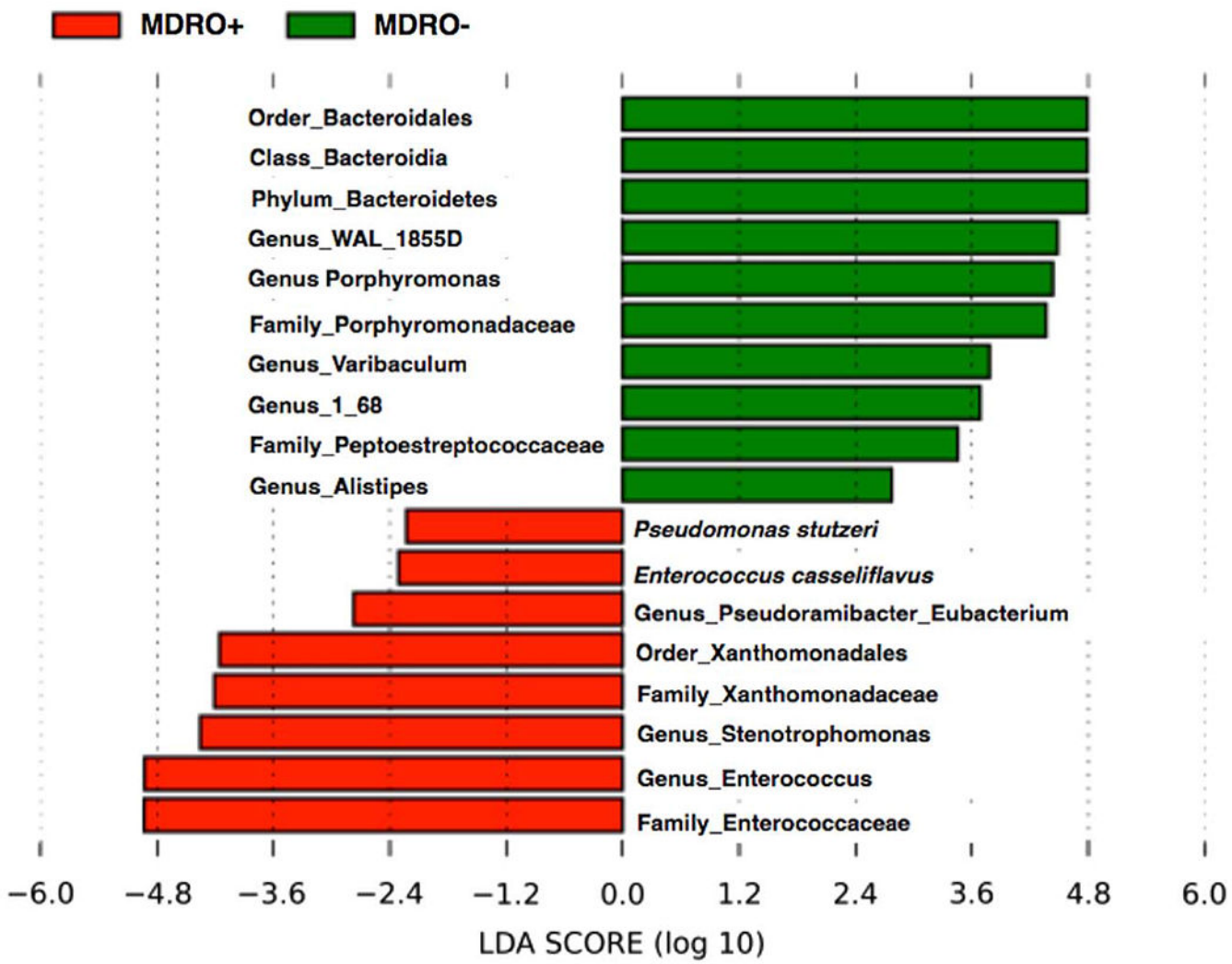

FIGURE 3.

Linear discriminant analysis (LDA) effect size (LEfSe) showing differential abundance of taxa between MDRO+ and MDRO−.

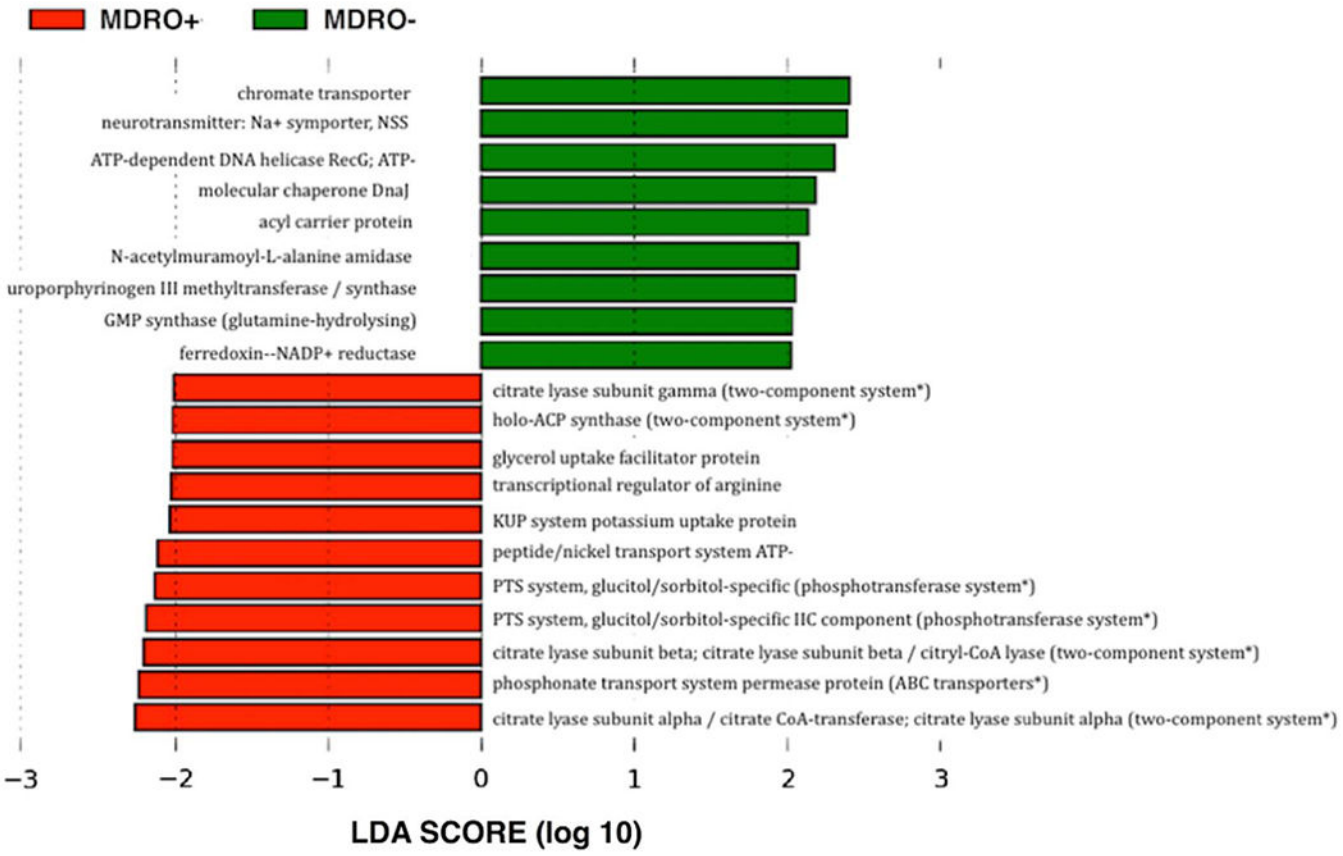

FIGURE 4.

Linear discriminant analysis (LDA) effect size (LEfSe) output showing differential abundance of functions observed according to the metagenomic prediction, mean nearest sequenced taxon index, 0.05 (SD ± 0.03). *Predicted metabolic pathways associated with multidrug-resistance mechanisms.

TABLE 1.

Clinical and Demographic Characteristics of the Study Population

Patient Characteristic	MDRO− (N = 33), No. (%)	MDRO+ (N = 11), No. (%)	*P* Value
Age, median (IQR)	65.32 (13.1)	68.8 (27.7)	.26
Male	25 (75.8)	9 (81.8)	1.00
Charlson comorbidity index, median (IQR)	4 (4)	7(3)	.05
Diabetes mellitus	15 (45.5)	6 (54.6)	.73
Obesity	12 (36.4)	3 (27.3)	.72
Gastrointestinal disease	14 (42.4)	7 (63.6)	.30
Reason for hospitalization			
Infectious disease	16 (48.5)	11 (100)	.003
Noninfectious disease	17 (51.5)	0	
Long-term proton pump inhibitors[a]	13 (39.4)	6 (54.6)	.49
Long-term histamine H_2 receptor antagonist[a]	3 (9.1)	0	.56
Resident in an HCAF <12 m before enrollment	19 (57.6)	10 (90.9)	.07
Interval between admission and rectal sample	1 (1)	1 (1)	.28

NOTE. IQR, interquartile range; HCAF, healthcare-associated facility; MDRO, multidrug-resistant organism.

[a]Therapy >14 days.

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TABLE 2.

Prior and In-Hospital Antimicrobial Exposure

Variable	MDRO− (N = 33), No. (%)	MDRO+ (N = 11), No. (%)	*P* Value
Overall antimicrobial exposure prior 3 months	15 (48.4)	10 (90.9)	.02
In-hospital antimicrobial exposure	25 (75.8)	11 (100)	.17
Median number of antimicrobials at the time of rectal sample (IQR)	3 (1–3)	3 (2–4)	.28

NOTE. IQR, interquartile range.

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TABLE 3.

Differentially Abundant Genes Associated With Multidrug-Resistance Mechanisms That Significantly Differed Between MDRO− and MDRO+ According to the Metagenomic Prediction of 16S rRNA Sequence Data

Pathway	KOID	Function	LDA score	*P* value
Two-component system	K01646	Citrate lyase subunit gamma	MDRO+2.00	.002
	K05964	Holo-ACP synthase	MDRO+2.01	.005
	K01644	Citrate lyase subunit beta; citrate lyase subunit β/citryl-CoA lyase	MDRO+2.20	.005
	K01643	Citrate lyase subunit α/citrate CoA-transferase; citrate lyase subunit α	MDRO+2.26	.001
Phosphotransferase system, fructose and mannose metabolisms	K02781	PTS system, glucitol/sorbitol-specific IIA component	MDRO+2.13	.004
	K02783	PTS system, glucitol/sorbitol-specific IIC component	MDRO+2.18	.004
ABC transporters	K02042	Phosphonate transport system permease protein	MDRO+2.23	.007

NOTE. LDA, linear discriminant analysis; ACP synthase, 4′-phosphopantetheinyl transferase; PTS system, phosphotransferase system; ABC, adenosine triphosphate-binding cassette.