Increased Rate of Enteric Bacteria As Cause of Periprosthetic Joint Infections In Patients With Liver Cirrhosis

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Research Article

Keywords: PJI, rifampicin, rifaximin, enteric bacteria, liver cirrhosis, TKA, THA

Posted Date: December 14th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1120920/v1

Version of Record: A version of this preprint was published at BMC Infectious Diseases on April 19th, 2022. See the published version at https://doi.org/10.1186/s12879-022-07379-2.

Abstract

Introduction: Periprosthetic joint infections (PJI) are a major complication in joint-arthroplasty. While Rifampicin is one of the few antimicrobial agents, that penetrate the bacterial biofilm and therefore is often used as an additional agent to treat PJI, rifampicin-resistant pathogens are also known to be cross-resistant to other approved rifamycins (rifambutin, rifaximin and rifapentine). Moreover, rifaximin, a broad-spectrum antibiotic with poor intestinal absorption, is used to prevent episodes of hepatic encephalopathy. As transient resistances to rifampin may emerge in patients after taking rifaximin the aim of this study was to examine the microbial pattern of periprosthetic joint infections in cirrhotic patients and to test the hypothesis that intake of rifaximin increases the rate of resistance to rifampicin in periprosthetic joint infections.

Methods: A cohort of cirrhotic patients and PJI (n=25) was analysed on the characteristics of bacterial isolates from sonication and tissue analysis. In a second step a subgroup analysis on the development of rifampicin resistant bacterial specimens, depending on the intake of rifaximin (8 rifaximin intake patients vs. 13 non rifaximin intake patients) was performed.

Results: Gram-negative bacteria were found in nearly 30% of the specimens. By comparison of the single bacterial isolates, rifampicin resistance was detected in 69.2% (9/13) of the rifaximin-intake samples. In contrast, the non-rifaximin-intake isolates only were resistant to rifampicin in 22.2% (4/18) of the cases (p=0.01). The odds ratio for developing a rifampicin-resistance through rifaximin intake was calculated as OR=13.5.

Conclusion: Periprosthetic joint infections have a high incidence of being caused by gram-negative bacteria in cirrhotic patients. Due to this change in microbial pattern and the innate resistance to rifampicin of most of gram-negative bacteria, the therapy with rifampicin should be carefully considered. The association between the use of rifaximin and developed resistance to rifampicin has a major impact on the treatment of PJI.

Introduction

The risk for periprosthetic infections, estimated at around 1-2 % for total knee arthroplasties (TKA) and 1 % for total hip arthroplasties (THA) in the general population (1,2) increases to 3.7 % for THA and around 2.7 % for TKA in cirrhotic patients (3). Cirrhotic patients suffer from deteriorated bone microarchitecture (4) and are more prone to falls (5,6), leading to an elevated fracture risk (7,8) and may end in joint replacement operations. Due to a compromised antibacterial immune response in cirrhotic patients (8,9), periprosthetic joint infections (PJI) become even more a disastrous and feared complication in arthroplasty (10).

Gut microbiome alterations (dysbiosis) in cirrhotic patients are frequently reported (11-15) and lead to higher abundance and relative overgrowth of *Staphylococcaeae, Enterobacteriaceae* and *Enterococcaceae* (11,15)*. Even sarcopenia has been linked to microbiome alterations in cirrhotic patients. Accordingly, a Europe-wide study showed that bacterial infections (e.g. urinary tract infections, respiratory tract infections, spontaneous bacterial peritonitis, septicaemia, bacteraemia* (16)*) in cirrhotic patients are mainly caused by gram-negative bacteria such as Escherichia coli, Enterococcaceae, Klebsiella pneumonia due to increased intestinal bacterial translocation* (17). *In contrast to that,* in non-cirrhotic patients, common pathogens in periprosthetic infections are biofilm-forming species such as *Staphylococcus aureus species* (18,19). The foreign body of the prosthesis provides a surface where bacterial exopolysaccharides can adhere (20,21) which leads to low susceptibility to antibiotic treatment (21). Therapy in those cases requires a prolonged antibiotic treatment, preferably with a drug combination that is effective against biofilm bacteria, including rifampicin (around 70% (22)) or doxycycline (23). Besides S. aureus species other types of bacteria like *Pseudomonas aeruginosa* show similar biofilm growth (24,25). Because the minimum inhibitory concentration

(MIC) is up to 100-1000 times higher in biofilms than without (20), therapy in those cases requires a prolonged antibiotic treatment regime, preferably with a drug combination that is effective against biofilm bacteria, including rifampicin or doxycycline (23).

With its potent activity against a variety of pathogens, rifampicin, which inhibits the bacterial RNA synthesis by binding and blocking the beta subunit of the RNA-polymerase (26), is a widely used antibiotic drug in joint, foreign body and valve infections (27). Rifampicin is one of the few antimicrobial agents, that penetrates the bacterial biofilm.

Rifampicin-resistant pathogens are also known to be cross-resistant to other approved rifamycins (rifambutin, rifaximin and rifapentine) (28). Rifaximin, a broad spectrum antibiotic with poor intestinal absorption (<0,4%), prevents episodes of hepatic encephalopathy in patients with liver cirrhosis (29-32). Several studies have shown the reduction of neuropsychiatric and neuromuscular dysfunctions in hepatic encephalopathy with a specialized treatment, that consists mainly in cleaning bowels and therefore reducing the gut-derived toxic substances (29-32). The study results, leading to the FDA-approval in 2010, showed that patients who took rifaximin for a period of 6 months up to 2 years prevented this cohort of 299 patients from a relapse of hepatic encephalopathy (HE) (33,34). Consensus guidelines support long-term rifaximin use along with non-absorbable disaccharides such as lactulose in patients with recurrent episodes of HE (35).

Resistance to rifamycin in *Staphylococcus aureus* is mediated primarily by mutations in the rpoB gene (36), but seems to be reversible after months without rifampicin (28). In patients with cirrhosis, long-term intake of rifaximin was associated with a appearance of rifampicin-resistance in skin colonizing *Staphylococcus spp.* (37,38), despite the low plasma concentrations of rifaximin (34). Three months after the end of treatment, the mutant population is once again overcome by the wildtype strain (37,39).

The aim of this study was to examine the microbial pattern of periprosthetic joint infections in cirrhotic patients and to test the hypothesis that intake of rifaximin increases the rate of resistance to rifampicin in periprosthetic joint infections.

Patients and methods:

For this retrospective case-control study a database search was performed for patients with the combination of liver cirrhosis and periprosthetic joint infections, who were admitted between January 2009 and September 2020 at the University Hospital of Bonn. Cases were excluded if surgical or antibiotic treatment was started prior to admission, or if no bacteria was isolated from intraoperative specimens. Furthermore, no fungi or mycoplasma were considered.

Initially, the database search retrieved 45 patients. Due to missing bacterial specimen, missing data, or due to fungal or a mycobacterial infection 20 patients had to be excluded. Finally, 25 patients with 60 bacterial strains were included in the analysis (table 1 and 2). The leading cause for cirrhosis in the study cohort was alcohol, followed by viral hepatitis, while none of the patients suffered from an autoimmune or biliary cause. Cirrhosis classification scores were calculated upon operation date.

In the first step of the analysis the cohort was examined for the overall microbial pattern of the periprosthetic joint infections. In the second step of the analysis, all bacterial isolates with unknown susceptibility or with innate resistance to rifampicin were excluded and patients then assigned either to the rifaximin-intake or the no-rifaximin group. Hence 8 patients were assigned to the rifaximin-intake and 13 to the no-rifaximin intake group.

Bacteria were identified through bacteriological cultures and sonication. To this end, explants were added to a sterile saline solution and vortexed for 30 seconds. The resulting sonication fluid was then cultured (40). Additional

statistical analysis was performed using IBM SPSS version 22 (SPSS Inc, IBM, Chicago, IL) for patient age, sex, duration of rifaximin-intake, the MELD-Score (Model for End-Stage Liver Disease) and the Child-Pugh-Score. Normality was assessed by using histograms and equality of variances by using the Shapiro-Wilk test. Demographic characteristics and read-outs of different findings as well as quantitative parameters were compared by using the Mann-Whitney-U test. For comparison of qualitative parameters, Fisher exact test was used. To classify the risk to develop a resistance to rifampicin when taking rifaximin Odds ratio was computed. Continuous data are reported as mean (standard deviation, SD) or median (minimum-maximum, MIN/MAX). The reported p values are 2-sided, with a significance level of 0.05. A post-hoc power analysis was performed with G-Power (University of Dusseldorf, Germany). The study was approved by the local ethic committee (330/19) and conducted according to the principles of the declaration of Helsinki.

Results

Patients' demography revealed a balanced distribution of age and sex. The joint infections affected total hip arthroplasties (18/25; 72%), knee arthroplasties (7/25; 28%). The underlying diseases of cirrhosis were in 56% alcohol abuse (14/25) and viral hepatitis (5/25; 20%).

In more than half of the samples gram-positive bacteria were detected (44/60; 73.3%), with *Staphylococci* and *Streptococci* being the biggest fraction (27/60; 45%) (Table 2). In 26.7% (16/60) of the specimen gram-negative bacteria such as *Escherichia coli, Klebsiella oxytoca, Enterobacteriaceae, Proteus spp., Serratia marcescens and Pseudomonas aeruginosa were found. 37 of all strains found are commonly known for the capability of producing biofilms (61.7%). Most of the 25 (20/25, 80%) Staphylococcal strains (S. epidermidis, S. haemolyticus, S. intermedius and S. lugdunensis) were coagulase-negative and 20% were S. aureus (5/25). Table 3 displays the susceptibility to the most important substance groups of antibiotics. S. epidermidis was mostly resistant to sultamicillin (11/12; 91.7%).*

By comparison of the single bacterial isolates, rifampicin resistance could be detected in 69.2% (9/13) for the rifaximin-intake samples. By contrast, the non-rifaximin-intake isolates only were resistant to rifampicin in 22.2% (4/18) of the cases (p=0.01, see figure 1). The odds ratio for developing rifampicin-resistance by taking rifaximin was calculated as 13.5. Post-hoc power analysis revealed a medium to high power (0.73) and a high effect (d=0.86).

No association between susceptibility to rifampicin and age (p=0.6), MELD-Score (p=0.92) or sex (p=0.35) could be revealed. No significant correlation was found between susceptibility to rifampicin and the individual duration of rifaximin intake (p=0.2). Within 6 months post-operatively 11 of 25 (44%) patients in this cohort died. Survival after six months was not dependent on the susceptibility to rifampicin (p=0.66).

Discussion

The aim of this study was to examine the microbial pattern of periprosthetic joint infections in cirrhotic patients, as it is known from other bacterial infections that, due to increased bacterial translocation from the intestine. The second aim was to find evidence for the hypothesis that in patients with liver cirrhosis and rifaximin intake, the resistance to rifampicin in periprosthetic joint infections increases.

Out data indicate that PJIs in cirrhotic patients are in 26.7% (16/60) of the cases associated with gram-negative bacteria, while non-cirrhotic patients mostly suffer from PJIs caused by *CoNS* (30-43%), *Staphylococcus aureus* (12-23%) or *Streptococci* (9-10%) (41-45). Gram-negative bacteria (3-6 %) or *Enterococci* (3-7%) are found less often in non-cirrhotic patients, which highlights the importance of our findings (22,Pandey:2000fz; 45). This result is in line

with the high frequency of Gram-negative infections in patients with cirrhosis (16). However, our data indicate a similar shift in periprosthetic joint infections for the first time. The difference in the microbial pattern in this cohort coincides with the findings of bacterial dysbiosis and other bacterial infections in cirrhotic patients (17). *Gut microbiome transition due to cirrhosis and alcohol seems to induce differences in bacterial colonisation all over the human body system. Concordantly to that, most of the examined patients suffered from alcoholic cirrhosis (56%), where microbiome transition is described most elaborately* (11,14,46). *The underlying reasons for gut microbiome transition are yet fully understood. Therapeutic considerations should include the higher rate of intestinal bacteria with a larger amount of gram-negative and anaerobic bacteria and hence a shift in susceptibility to antibiotic agents.*

The detected difference between the RI- and the NRI-group suggests that rifaximin may induce rifampicin resistance in PJIs. In this cohort the resistance did not seem to be dependent on the duration of rifaximin intake, which might be due to the fact that all patients had been taking rifaximin for at least 4 weeks prior to development of PJI and because resistance to rifaximin can be detected early (47). It has earlier been reported that intake of rifaximin may induce cross-resistance to rifampicin (37,38) in healthy individuals. However, this is the first study to analyse the impact of rifaximin intake on the microorganisms causing periprosthetic joint infections in cirrhotic patients.

In an in-vitro study Rothstein et al. described that cross-resistances among rifamycin species have a great impact on the therapeutical benefit of these antibiotics. The reported resistance regularly occurred during intake, but rapidly disappeared after discontinuation of the drug (28). In almost 50% of 198 skin bacterial isolates, especially *Staphylococcus spp.*, from 25 patients, Chang et al. found resistance to rifampicin during the intake of rifaximin (37). In accordance to the results from Rothstein et al. the prevalence of resistance decreased after stopping rifaximin therapy (37). In contrast to that, Valentin et al. showed remaining rifampicin-resistant strains nine weeks after discontinuation of rifaximin (38). However, rifaximin therapy is usually given for long periods of time in patients with cirrhosis. Though, the administration of rifampicin in cirrhotic patients is never uncomplicated due to liver-related side effects.

The cohort of this study suffered from a relatively high mortality rate of 40 % (10/25). In the literature, cirrhotic patients are nearly ten times more likely to die after joint infections as patients without liver disease (3). In this cohort, we did not detect any hints for a significantly higher mortality rate in the subgroup of patients with rifampicin resistance. Our cohort, however, suffered in 11.7% from obligate and facultative anaerobic bacterial infections (*Clostridium difficile, Cutibacterium acnes, Enterobacter cloacae*; 7/63), although the literature describes a portion of only 3-6% in PJI (48).

Even if the cohort of this study is small, our findings indicate that the patients' medical history with regard to former or current rifaximin intake should be carefully noted. As rifampicin is widely used due to its singular bactericidal activity within biofilm, alternative antibiotics for patients with rifampicin resistance are scarce. As most cirrhotic patients on rifaximin suffer from multimorbidity, such as peripheral arterial disease, osteoporosis, cardiovascular disease, they have an elevated prevalence of joint implants, which may become infected due to the compromised immune system. *Some gram-negative bacterial strains found in this study are intrinsically resistant to rifampicin.* Because rifampicin is a widely used antibiotic in periprosthetic joint infection, this shift has to be seriously considered in the empirical antibiotic treatment of cirrhotic patients.

Conclusion

Periprosthetic joint infections have a high incidence of being caused by gram-negative bacteria in patients with liver cirrhosis. Due to this change in microbial pattern and the innate resistance to rifampicin of most of gram-negative

bacteria, the therapy with rifampicin should be carefully considered. Additionally, the association between the use of rifaximin and developed resistance to rifampicin has a major impact on the treatment of periprosthetic joint infections in this cohort. Before empiric antibiotic therapy is started, careful attention should be paid to the medical history in patients with liver cirrhosis.

Abbreviations

MIC	Minimum inhibitory concentration
MELD	Model of End Stage Liver Disease-Score
NAFLD	Nonalcoholic fatty liver disease
RI-group	Rifaximin intake group
NRI-group	No Rifaximin intake group
PJI	Periprosthetic joint infections
TKA	Total knee arthroplasty
THA	Total hip arthroplasty
HE	Hepatic encephalopathy
CoNS	Coagulase negative *Staphyloccoci*

Declarations

Ethics approval and consent to participate:

The study was approved by the local ethic committee (Ethics Committee of the Medical Faculty, University Hospital Bonn, University of Bonn, Building 74/4th floor, Venusberg-Campus 1, 53105 Bonn, Germany, Number of ethic committees statement concerning this study: 330/19) and no informed consent was needed due to the retrospective character of the study. The study was conducted according to the principles of the declaration of Helsinki.

Consent for publication:

Not applicable

Competing interests and funding:

All authors declare that they have no competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

Availibility of data and materials.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Uta S. Koepf – conceptualization, writing, statistics, data management, review process

Sebastian Scheidt – conceptualization, writing, statistics, data management, review process

Christian P. Strassburg – conceptualization , review process

Dieter C. Wirtz – review process

Thomas Randau - review process

Philipp Lutz – conceptualization, writing, data management, review process

All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Tables

Table 1 - patients characteristics

	all (n=25)	RI-group (n=8)	NRI-group (n=11)
patients demography			
female	*13*	*3*	*7*
male	*12*	*5*	*4*
age (years)#*	*60.3 (30-77; ±11)*	*60.5 (38-75; ±11.9)*	*62.8 (50-77; ±7)*
characteristics of joints and rifaximin intake			
THA	*18*	*5*	*9*
TKA	*7*	*3*	*2*
rifaximin intake	*8*	*8*	*/*
duration of rifaximin intake (months)#*	*/*	*24.75 (4-60; ±18)*	*/*
characteristics of liver cirrhosis in patients			
Cirrhosis underlying disease			
alcoholic cirrhosis	*14*	*4*	*8*
viral hepatitis	*5*	*2*	*2*
drug toxicity	*1*	*1*	*/*
post-ischemic/mof	*1*	*/*	*1*
unknown origin	*2*	*1*	*1*
NAFLD	*2*	*/*	*1*
*MELD *#*	*13.4 (6-36; ±6.6)*	*11.9 (8-18; ±3)*	*16.6 (10-36; ±8.1)*
Child Pugh			
A	*16*	*4*	*8*
B	*7*	*4*	*1*
C	*2*	*/*	*2*
Survival after 6 months	*14/25*	*5/8*	6/11

* standard deviation; # minimum/maximum

Table 1: Characteristics of the patients and the underlying diseases, TKA: total knee arthroplasty; THA: total hip arthroplasty; MELD: Model of end stage liver disease score; NAFLD: non-alcoholic fatty liver disease; mof: multiorgan failure; RI-group: patients with rifaximin intake; NRI-group: patients without rifaximin intake

Table 2 - characteristics of bacterial isolates

Bacterial isolates	total (n=60)		RI-group (n=13)		NRI-group (n=18)	
	n	%	n	%	n	%
Staphylococcus aureus	5	8.3	1 (0)	7.7	4 (0)	22.2
Staphylococcus epidermidis	12	20	5 (5)	38.5	7 (1)	38.9
Staphylococcus haemolyticus	3	5	2 (2)	15.4	1 (0)	5.6
Staphylococcus hominis	3	5	2 (0)	15.4	1 (0)	5.6
Staphylococcus lugdunensis	1	1.7	1 (0)	7.7	/	/
Staphylococcus intermedius	1	1.7	/	/	1 (0)	5.6
Streptococcus mitis/oralis	1	1.7	/	/	/	/
Streptococcus salivarius	1	1.7	/	/	/	/
Cutibacterium acnes	2	3.3	1 (1)	7.7	1 (0)	5.6
Enterococcus faecalis	7	11.7	1 (1)	7.7	1 (1)	5.6
Enterococcus faecium	6	10	/	/	1 (1)	5.6
Enterococcus hirae	1	1.7	/	/	1 (1)	5.6
Clostroides difficile	1	1.7	/	/	/	/
Enterobacter cloacae	4	6.7	/	/	/	/
Pseudomonas aeruginosa	4	6.7	/	/	/	/
Escherichia coli	2	3.3	/	/	/	/
Klebsiella oxytoca	1	1.7	/	/	/	/
Proteus mirabilis	2	3.3	/	/	/	/
Proteus vulgaris	1	1.7	/	/	/	/
Serratia marcescens	2	3.3	/	/	/	/

(n) amount of isolates with resistance to Rifampicin

Table 2: Bacterial isolates in the NRI-/RI-group (Rifaximin intake or no rifaximin intake) and susceptibility to Rifampicin in both groups (in brackets).

Table 3 - resistogram of bacterial isolates

Bacterial isolates	total (n=60)	Sultamicillin			Piperacilline Tazobactam			Cephalosporin*			Carbapeneme°			Fluorquinolone^		
	n	r	s	n	r	s	n	r	s	n	r	s	n	r	s	n
Staphylococcus aureus	5	1	2	2	1	1	3	1	3	1	0	1	4	3	1	1
Staphylococcus epidermidis	12	11	0	1	8	0	4	10	0	2	4	0	8	9	2	1
Staphylococcus haemolyticus	3	2	0	1	1	0	2	0	3	0	0	0	3	3	0	0
Staphylococcus hominis	3	0	2	1	0	1	2	0	2	1	0	0	3	0	2	1
Staphylococcus lugdunensis	1	0	1	0	0	1	0	1	0	0	0	1	0	0	1	0
Staphylococcus intermedius	1	1	0	0	0	0	1	0	1	0	0	1	0	0	1	0
Streptococcus mitis/oralis	1	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0
Streptococcus salivarius	1	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0
Cutibacterium acnes	2	0	2	0	0	1	1	0	0	2	0	2	0	0	1	1
Enterococcus faecalis	7	0	6	1	0	6	1	6	0	1	0	6	1	1	3	3
Enterococcus faecium	6	6	0	0	6	0	0	6	0	0	6	0	0	3	0	3
Enterococcus hirae	1	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0
Clostroides difficile	1	0	1	0	0	1	0	0	0	1	0	1	0	0	0	1
Enterobacter cloacae	4	4	0	0	0	4	0	1	3	0	0	4	0	0	4	0
Pseudomonas aeruginosa	4	0	1	3	1	3	0	1	3	0	0	4	0	0	4	0
Escherichia coli	2	1	1	0	0	2	0	0	2	0	0	2	0	2	0	0
Klebsiella oxytoca	1	0	1	0	0	1	0	0	1	0	0	1	0	1	0	0
Proteus mirabilis	2	1	1	0	0	2	0	0	2	0	0	2	0	0	2	0
Proteus vulgaris	1	1	0	0	0	1	0	0	1	0	0	1	0	0	1	0
Serratia marcescens	2	1	1	0	1	1	0	0	1	1	1	1	0	1	1	0

r = resistant, s = sensitive, n = not evaluated; * = Ceftriaxon/Cefuroxim, ° = Meropenem, ^=

Ciprofloxacin/Levofloxacin

Table 3: Resistogram of all bacterial isolates of the most important substance groups of antibiotics.

Figures

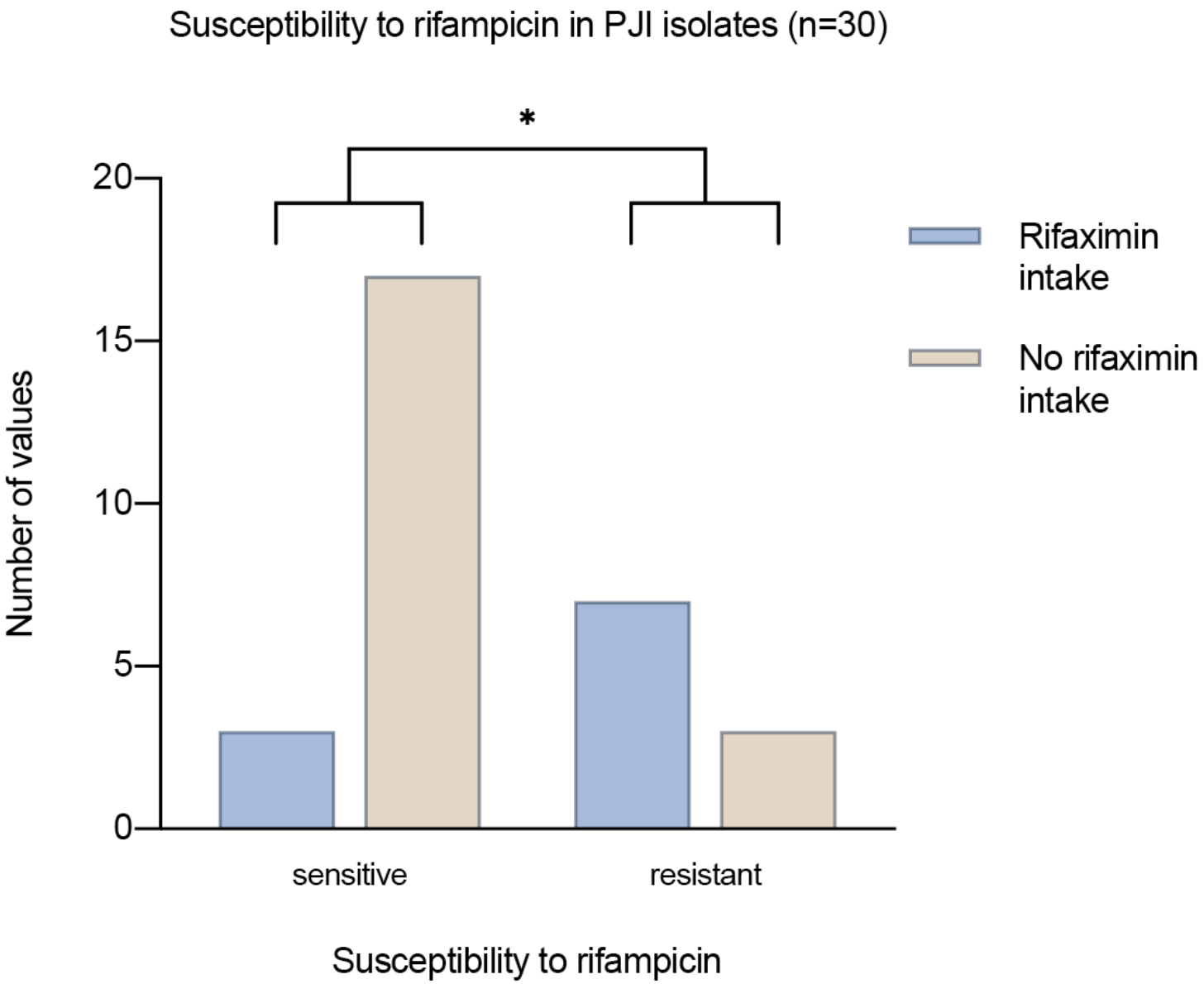

Figure 1

In periprosthetic joint infection, both groups (RI; NRI) had sensitive and resistant microbes, but differ in regard to their rifaximin intake; * = significant difference (p=0.01).