The effect of rifampicin-resistance and other risk factors on the recovery rate in patients with prosthetic joint infection

PhD thesis

Gergely Krizsán, MD

Doctoral School of Semmelweis University,
Operative Medicine Division

Supervisor: Gábor Skaliczki, MD, PhD

Official Reviewers:
Sándor Kiss, MD, PhD
László Rudolf Hangody, MD, PhD

Head of the Complex Examination Committee:
György Szőke, MD, DSc

Members of the Complex Examination Committee:
Imre Szerb, MD, PhD
Áron Lazáry, MD, PhD
Gábor Fazekas, MD, PhD

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1. Introduction

Prosthetic joint infections (PJIs) have become significant medical challenge over the last decades as a result of increasing number of arthroplasties and the higher age of patients involed, among other reasons. The implantation of prosthetic devices is a high risk surgical procedure with possible complications including early, low-grade and haematogenic infections. PJIs represent significant burden for both patients and health care providers. Treatment strategies are based on the combination of surgery and prolonged antibiotic therapy. The probability of biofilm formation and its stage should also be considered as it is more difficult to effectively treat PJIs when mature biofilm has already been formed on the surface of the implant. Rifampicin is a regular component of the antibiotic combination due its excellent activity against biofilms. Resistance towards rifampicin is a significant challenge resulting in longer hospitalisation, increased costs and higher mortality.

PJIs are mostly but not exclusively caused by various bacteria. Gram-positive bacteria include Staphylococcus spp., Streptococcus spp., Enterococcus spp., Corynebacterium spp. and Cutibacterium spp. Gram-negative bacteria comprise members of the *Enterobacterales* order (eg. *Escherichia coli*) and nonfermenters such as *Pseudomonas aeruginosa*.

PJIs should be classified on the basis of previously described score systems and clinical course to optimise treatment and follow up plan. Patient-related factors and microbiological findings are essential to provide appropriate management of such infections.

2. Objectives

We investigated the effects of various factors on the recovery rates of patients with prosthetic joint infection undergoing two-stage revision and patients undergoing DAIR (Debridement, Antibiotics and Implant Retention) procedure.

I. The effect of risk factors in patients undergoing two-stage revision. Which patient-related and -unrelated factors have significant impact on recovery rates? How does rifampicin-resistance of the causative agent influence recovery rates?

II. The effect of risk factors in patients undergoing DAIR procedure. Which patient-related and -unrelated factors have significant impact on recovery rates? How does rifampicin-resistance of the causative agent influence recovery rates?

III. The clinical significance of the isolated microorganism(s). What is the prevalence of different microorganisms in the rifampicin-sensitive and in the rifampicin-resistant group? Are there polymicrobial infections recognised? Is there any evidence for the development of rifampicin-resistance during antimicrobial therapy? Is rifampicin-resistance related to previous rifampicin-based regimes? What antimicrobial regimes are used in the treatment?

IV. Draw conclusions in relation to clinical practice. Which factors should be considered when estimating recovery rates? Which factors are associated with higher recovery rates? Can these factors be influenced? How can various factors help the decision as to what type of orthopaedic method should be preferred?

3. Methods

3.1. Study population

3.1.1. Patients undergoing two-stage revision

We retrospectively reviewed the medical records of 73 patients (41 males and 32 females) admitted to the Department of Orthopaedics, Semmelweis University, undergoing two-stage revision due to low-grade PJI between 2017 and 2019. Past medical history, risk factors, comorbidities and clinical details were collected and analysed. Short-term and long-term outcome, previous surgical and antibiotic therapies were also reviewed. Sex, ASA score and clinical conditions such as hypertension, chronic heart failure, chronic renal failure, chronic pulmonary diseases, type 1 and 2 diabetes mellitus (DM), haematological and thyroid disorders, liver cirrhosis, stroke and rheumatoid arthritis were investigated. Patients were classified by body mass index (BMI) according to the WHO score system. Participants were divided into two groups according to rifampicin sensitivity result(s) of the microorganism(s) causing PJI.

3.1.2. Patients undergoing DAIR procedure

We retrospectively reviewed the medical records of 67 patients (37 males and 30 females) admitted to the Department of Orthopaedics, Semmelweis University, undergoing DAIR procedure due to early onset PJI between 2014 and 2021. Past medical history, risk factors, comorbidities and clinical details were collected

and analysed. Factors included the affected joint, previous trauma, treatment duration, antibiotic regime(s), administration of jet lavage, exchange of mobile elements and revision before and after DAIR procedure. Sex, age, comorbidities including diabetes mellitus, chronic obstructive pulmonary disease, rheumatoid arthritis, chronic renal failure, liver cirrhosis, thyroid diseases, hypertension and coagulation abnormalities as well as ASA score and BMI were reviewed. In our study patients were divided into two groups according to rifampicin sensitivity result(s) of the microorganism(s) causing PJI.

3.2. Score systems

Based on our data, CRIME80 and KLIC scores were calculated preoperatively to estimate the risk of failure of DAIR procedure and the recurrence of PJI. Obtained scores can be used to select patients not suitable for DAIR procedure and cases when the efficacy and outcome of treatment are doubtful.

3.3. Microbiological background

Clinical specimens were processed in the Clinical Microbiological Diagnostic Laboratory (Institute of Laboratory Medicine, Semmelweis University). Microbiology reports (including antibiograms) were collected and the clinical significance of each isolate was assessed. We have investigated polymicrobial infections in patients undergoing two-stage revision as well as those undergoing DAIR procedure.

The antibiotic susceptibility pattern was reviewed for all significant pathogens including multidrug resistant organisms (MDROs). Isolates were divided into two groups based on their rifampicin sensitivity. Development of rifampicin-resistence during treatment was investigated by comparing the antibiotic sensitivity profile of the same microorganism in different specimens taken during the course of infection.
We also reviewed antimicrobial regimes used to treat PJIs including choice of antimicrobial agent(s) as well as route, dose and duration of therapy. It was also investigated whether patients had received rifampicin prior to their current orthopaedic infection.

3.4. Statistical analysis

The statistical analysis was performed by using the R software (R Core Team 2022) [123] and its ggplot2 package for figures [124]. After describing data, a logistic regression model was fitted: we used recovery rate as the outcome and rifampicin-resistance as the explanatory variable. The effect was controlled for sex, age, BMI and DM as possible or known confounders. After taking into consideration possible multicollinearity (based on graphs and variance inflation factor [vif] values) and possible interactions (based on common sense, graphs, model fit diagnostics and information criteria), the interaction effect between rifampicin-resistance and age was also included in the final model. The model fit was acceptable based on model diagnostic plots. Decisions were made on null-hypothesis using 5% as significance level. No multiplicity correction was made.

4. Results

4.1. Patients undergoing two-stage revision

4.1.1. Rifampicin-resistance and patient-related factors

The overall recovery rate was 83.6% (61 out of 73 patients), 96.5% among patients within the rifampicin-sensitive group and 60.0% in the resistant group. 15 patients (20.5%) had type 2 diabetes mellitus and none had type 1. 48 patients had hip, 22 had knee, 2 had shoulder and 1 had elbow joint infection.

Table 1. Effect estimates of risk factors with its 95% confidence interval based on a regression model (patients undergoing two-stage revision)

Predictors	Odds ratio (recovered vs. not recovered)	95% confidence interval	p-value
(intercept)	29.4181	11.2922 – 54.7758	0.0063
Rifampicin-resistance: Resistant	(-)25.1947	(-)49.2322 – (-)8.5634	0.0109
Age 1 year	(-)0.2985	(-)0.5918 – (-)0.0921	0.0143
Sex: Male	2.3837	0.5985 – 4.6502	0.0176
BMI 1 kg/m^2	(-)0.1557	(-)0.3669 – 0.0097	0.0906
Diabetes mellitus: Diabetic	(-)2.9763	(-)5.9344 – (-)0.6499	0.0217
Rifampicin-resistance and Age interaction: Resistant: 1 year	0.3052	0.0845 – 0.6159	0.0181

The following variables had significant impact on recovery rates: rifampicin-resistance, age, sex and type 2 diabetes mellitus, however, we found no clear evidence for the effect of body mass index (Table 1.). Recovery rates were found significantly higher in male patients.
22.6% of our patients had type 2 diabetes mellitus in the sensitive and 15.0% in the resistant group. Age had a remarkable impact on recovery rates in the rifampicin-sensitive group (there is a significant declination after an age-threshold) but this effect was found minimal in the resistant group (Figure 1.). The declination in recovery rates starts at the age of 70 years and reaches 50% after 80 years in the nondiabetic group, whereas the same events occur approximately 10 years earlier in the diabetic group (start of declination at 60 years, 50% recovery at 70 years of age). These findings suggest significantly negative effect of age, diabetes mellitus and rifampicin-resistance on clinical outcomes.
Most of the patients had previous surgery of the affected joint: 49 out of 53 (92.5%) in the sensitive group and all patients in the resistant group. 9.4% of the patients (5 out of 53) had fracture as a risk factor for PJI in the rifampicin-sensitive and 30.0% (6 out of 20 patients) in the -resistant group.

4.1.2. Microbiological background

Fifty-three out of 73 patients (72.6%) had PJI caused by rifampicin-sensitive and 20 (27.4%) by rifampicin-resistant microorganism. We found that rifampicin-sensitive species was isolated in 80.3% among

recovered patients and in 33.3% in patients with treatment failure (Figure 2.).

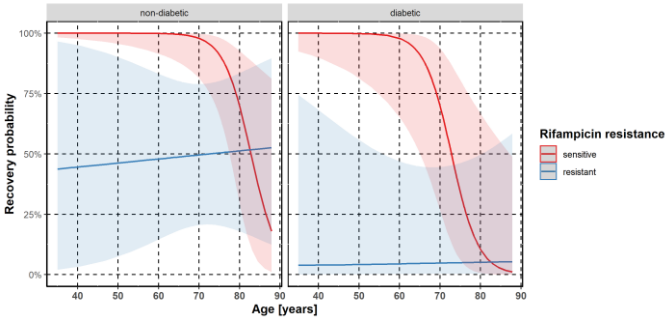

Figure 1. Predicted recovery probability based on a regression model (for female, at mean BMI) (patients undergoing two-stage revision)

Staphylococcus spp. were predominant in the sensitive group (66.7% of the isolates), most of which were coagulase-negative Staphylococcus spp. (27 isolates). *S. aureus* was isolated in 9 cases including one MRSA strain. The majority of Staphylococcus spp. were sensitive to rifampicin: 9 out of 10 *S. aureus* and 27 out of 32 coagulase-negative Staphylococcus spp. *Cutibacterium acnes* was cultured in 8.2% of the patients (6 cases). An unusual pathogen, *Arthrobacter scleromae* was isolated in one case. *Streptococcus agalactiae* was the predominant streptococcal isolate in our patients (7 out of 11 cases). *Haemophilus parainfluenzae* was the causative agent in one case.

The pathogen distribution was significantly different in the rifampicin-resistant group. Gram-negative rods and Enterococcus spp. represented the majority of isolates. Most of the Gram-negative rods belonged to

Enterobacterales order ("coliforms"). One *Pseudomonas aeruginosa* isolate represented nonfermenters. *E. faecalis* was isolated in 5 cases (9.6% of the patients), *E. casseliflavus* and *E. faecium* in 1 case each. One *S. aureus* (MSSA) and 5 *S. epidermidis* strains were isolated. A rifampicin-resistant strain of *Corynebacterium striatum* and *Mycobacterium goodii/smegmatis* was also found. Four patients had polymicrobial infection in the sensitive and one in the resistant group.

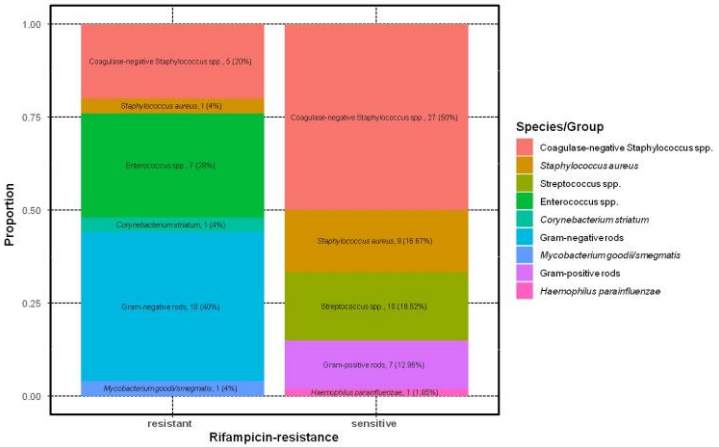

Figure 2. Pathogen distribution of rifampicin-resistant and -sensitive isolates (count, percentage) (patients undergoing two-stage revision)

15.0% of the patients had previous rifampicin treatment in the resistant group (all of them in combination) and none in the sensitive group. We observed the development of rifampicin-resistance in three cases.

4.2. Patients undergoing DAIR procedure

4.2.1. Rifampicin-resistance and patient-related factors

The overall recovery rate was 74.6% (50 out of 67 patients), 72.3% among patients within the rifampicin-sensitive and 76.9% in the resistant group. Significant pathogens were isolated in 60 out of 67 cases. 11 patients (16.4%) had diabetes mellitus (DM): 2 had type 1 and 9 had type 2. 44 patients had hip, 21 had knee, 1 had shoulder and 1 had elbow joint infection.

Table 2. Effect estimates of risk factors with its 95% confidence interval based on a regression model (patients undergoing DAIR procedure)

Predictors	Odds ratio (recovered vs. not recovered)	95% confidence interval	p-value
(intercept)	7.5069	0.1021 – 803.8825	0.3697
Rifampicin-resistance: Resistant	1.2372	0.3046 – 6.3043	0.7766
Age 1 year	0.9892	0.9478 – 1.0259	0.5801
Sex: Male	0.7513	0.2048 – 2.5711	0.6534
BMI 1 kg/m^2	1.0003	0.8985 – 1.1203	0.9956
Diabetes mellitus: Diabetic	0.3948	0.0876 – 1.8473	0.2206

The effect of selected factors such as rifampicin-resistance, sex, age, DM and BMI were investigated in a multivariate regression model. We found no statistically

significant effect of these variables on recovery rates (Table 2.).
We can assume a clinically important impact of age on recovery rates both in the rifampicin-sensitive and in the resistant group as well as the negative clinical effect of diabetes mellitus on recovery rates in our cohort. (Figure 3.). We found no significant effect of CRIME80 and KLIC score on recovery rates neither in the rifampicin-sensitive nor in the -resistant group.

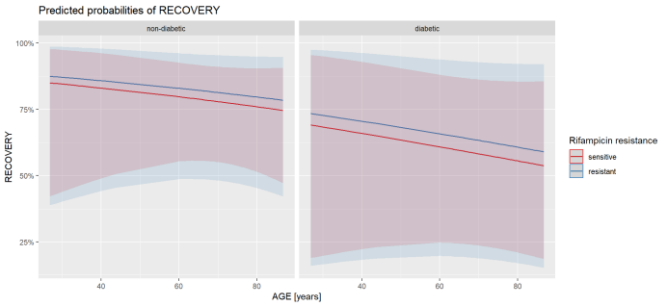

Figure 3. Predicted recovery probability based on a regression model (for female, at mean BMI) (patients undergoing DAIR procedure)

4.2.2. Microbiological background

Fourty-seven out of 67 patients (70.1%) had PJI caused by rifampicin-sensitive and 13 (19.4%) by rifampicin-resistant microorganism. We found that rifampicin-sensitive species was isolated in 77.3% among recovered patients and 81.3% in patients with treatment failure (Figure 4.).

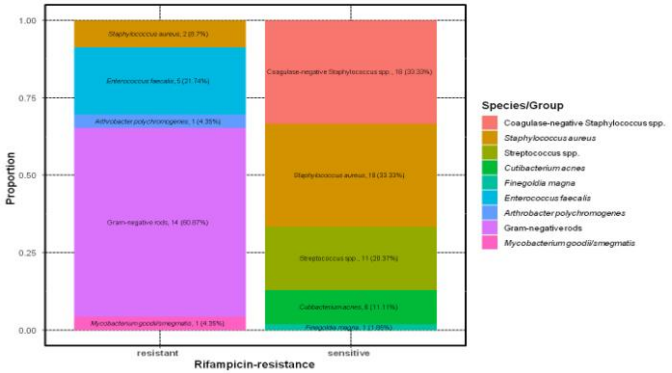

Figure 4. Pathogen distribution of rifampicin-resistant and -sensitive isolates (count, percentage) (patients undergoing DAIR procedure)

Staphylococcus spp. were predominant in the rifampicin-sensitive group (66.7%) including 18 *S. aureus* and 18 coagulase-negative Staphylococcus spp. Among Streptococcus spp., *S. dysgalactiae* was isolated in 5 cases and *S. agalactiae* in 4 cases. *C. acnes* was the causative agent in six cases.

The pathogen distribution was significantly different in the rifampicin-resistant group: Staphylococcus spp. were less prevalent. Instead, Gram-negative rods (12 *Enterobacterales* and 2 *P. aeruginosa* strains) as well as 5 *E. faecalis* were cultured. A rifampicin-resistant strain of *Arthrobacter polychromogenes* and *Mycobacterium goodii/smegmatis* was also isolated. Development of rifampicin-resistance was not observed and none of the patients had received previous rifampicin treatment. Three patients had polymicrobial infection in the sensitive and four in the resistant group.

5. Conclusions

5.1. Patients undergoing two-stage revision

1., Rifampicin-resistance, age, sex and type 2 diabetes mellitus had significant impact on recovery rates but not the BMI. Correlation between age and recovery was seen in the rifampicin-sensitive group with a rapid declination after the age of 70 years. In diabetic patients, we found similar trends with some marked differences.
2., Majority of the patients had PJI caused by rifampicin-sensitive microorganism and rifampicin-resistance was associated with significantly lower recovery rates. The most frequent isolates were coagulase-negative Staphylococcus spp. in the sensitive group, whereas Enterococcus spp. and Gram-negative rods were predominant in the resistant group. Polymicrobial infections were also identified. Previous rifampicin treatment was seen only in the resistant group and development of rifampicin-resistance was observed in three cases of staphylococcal infections.

5.2. Patients undergoing DAIR procedure

1., Rifampicin-resistance, BMI and sex had no statistically significant impact on recovery rates, however, increasing age and diabetes may have a negative clinical impact on clinical outcome.
2., The majority of the patients had PJI caused by a rifampicin-sensitive microorganism, however, rifampicin-resistance was not associated with lower recovery rates. The most frequent isolates were

Staphylococcus spp. in the sensitive and Gram-negative rods in the resistant group. Polymicrobial infections were also identified. No development of rifampicin-resistance was observed and none of the patients had previous rifampicin treatment.

5.3. Clinical relevance

1., Recognition of microbiological and patient-related factors may help estimate and reduce treatment failure rates after two-stage revision surgery and DAIR procedure performed in patients with PJI.
2., The significance of the isolated microorganism(s) should always be carefully assessed to distinguish true pathogens from colonisers and contaminants. In order to prevent the development of rifampicin-resistance, appropriate combinations should be used and delayed administration of rifampicin may be required.

6. Bibliography of the candidate's publications

Publications related to current PhD-thesis:

Krizsán G, Sallai I, Veres D S, Prinz Gy, Szekér D, Skaliczki G.
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PMID: 25551459, doi: 10.1186/s12941-014-0058-9.