Microbial findings and the role of difficult-to-treat pathogens in patients with periprosthetic infection admitted to the intensive care unit

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Abstract

Little is known about patients with Periprosthetic Joint Infection (PJI) admitted to the Intensive Care Unit (ICU). The purpose of this study was threefold: i) To report the microbiological findings of ICU-patients with PJI. ii) To compare the clinical data between Difficult-To-Treat (DTT) and non-DTT PJI. iii) To identify risk factors for mortality. This is a retrospective study from a tertiary healthcare center in Germany from 2012-2016. A total of 124 patients with 169 pathogens were included. The most common bacteria were *Staphyloccous aureus* (26.6%), *Staphyloccus epidermidis* (12.4%), *Enterococci* ssp. and *Escherichia coli* (respectively 9.4%). DTT PJI was diagnosed in 28 patients (22.6%). The main pathogens of DTT PJI were *Staphylococus epidermidis* (14.5%), *Escherichia coli* (12.7%), *Staphylococcus aureus* and *Candida* spp. (respectively 9.1%). Polymicrobial PJI, number of pathogens, ICU stay and mortality were significantly differrent between DTT PJI and non-DTT PJI ($p \leq 0.05$). Multivariate logistic regression identified prolonged ICU stay and DTT PJI as risk factors for mortality. In conclusion, we suggest, that the term of DTT pathogens is useful for the intensivist to assess the clinical outcome in ICU-patients with PJI.

Introduction

Periprosthetic Joint Infection (PJI) occurs in up to 5% of patients after total hip arthroplasty or total knee arthroplasty and is associated with considerable morbidity and healthcare costs.[1,2] Management of PJI requires complex treatment strategies including multiple surgical revision,long term antimicrobial treatment and compliance of the patients.

The role of biofilms in the pathogenesis of PJI is well known and led to antibiotic treatment with biofilm-active antibiotics such as rifampin against staphylococcal biofilms and ciprofloxacin against Gram negative biofilms.[3-5] Several clinical studies demonstrated higher success rates with this antibiotic treatment regimen compared to no biofilm-active antibiotic treatment regimens.[6,7]

PJI caused by pathogens, for which no biofilm-active antibiotics are available, are referred to as Difficult-To-Treat (DTT).[3,4,8] The treatment of DTT PJI is associated with a longer Length Of Stay (LOS), a higher number of revision surgeries, longer prosthesis-free intervals and longer antimicrobial treatment as well as an increased risk for reinfection of the prosthesis.[9-11] However, none of the aforementioned studies reported results of patients who required an Intensive Care Unit (ICU) treatment. Furthermore, patients who died during PJI treatment were excluded in these studies. The retrospective single-center study by Maaloum *et al.* is the only study reporting and analyzing the microbial findings and clinical outcome of 41 ICU-patients with PJI.[12] They reported a high mortality rate of 20%.

The aims of the study are to: i) report the microbiological findings of patients with PJI admitted to the ICU, ii) compare the clinical data between DTT PJI and non-DTT PJI and iii) identify risk factors for mortality.

Materials and Methods

This retrospective, observational, single-center study was performed in a 13-bed surgical ICU of a tertiary healthcare center in Germany. It has been approved by the local ethics committee (no. of approval 18-6260-BR). Included were all patients with acute or chronic PJI of the hip, knee or both who need ICU treatment after hip or knee replacement surgery between January 1, 2012 and December 31, 2016. Patients with PJI were identified using the international classification of diseases, 10th revision (ICD-10) codes T84.5, T84.6, T84.7, T84.8 and T84.9. The decision for admission to ICU after surgery were made by the anesthesiologist based on their assessment or by the leading intensivist. The ICU is accompanied by a stand-alone Intermediate Care Unit (IMC). The resources and therapeutic repertoire of the IMC include standard ICU monitoring, non-invasive ventilation, and continuous vasopressor-administration. The IMC is intensivist-led and provides 24-hour coverage by residents experienced in intensive care. The majority of surgical PJI-patients were admitted to the IMC and were not included in our study.

The demographic and clinical data of the included 124 patients were recently published.[13] As published before, severity of illness were detected using the Simplified Acute Physiology Score II (SAPS II),[14] the American Society of Anaesthosiologists Score (ASA)[15] and the Charlson Comorbidity Index (CCI).[16]

PJI were defined according to the European Bone and Joint Infection Society[17] and Musculosceletal Infection Society[18] (Table 1). Acute or chronic PJI were classified according to the defintion as described by Li *et al*.[19]

For diagnosis of a PJI, joint aspiration and periprosthetic tissue samples such as

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Key words Difficult-to-treat; intensive care unit; mortality; periprosthetic joint infection.

Contributions: The authors contributed equally.

Conflict of interest: The authors declare no conflicts of interest.

Acknowledgments: We acknowledge support by the DFG Open Access Publication Funds of the Ruhr-University Bochum, Germany.

Ethics: This study has been approved by the local ethics committee (Ruhr-University Bochum, Germany, grant number of approval 18-6260-BR). We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Funding: See acknowledgments.

Availability of data and materials: Data and materials are available within the text.

Received for publication: 26 August 2020
Accepted for publication: 22 October 2020.

Orthopedic Reviews 2020;12:8867
doi:10.4081/or.2020.8867

sonication fluid of the retrieved implant were analyzed after an incubation time of 14 days. Two or more positive microbial culture pathogens were necessary to diagnose PJI. The intra-operative detected pathogens of the patients PJI were classified into DTT or non-DTT pathogens. DTT pathogens included rifampin-resistant staphylococci, vancomycin-resistant enterococci, ciprofloxacin-resistant Gram negative bacteria, and Candida spp.[3,4] The outcome measurements were: i) to report the microbiological findings of PJI in patients admitted to the ICU, ii) compare the clinical data between DTT PJI and non-DTT PJI and iii) identify risk factors for mortality.

Statistical analysis

Power analysis was done with G*Power® Version 3.1 (Heinrich-Heine University of Dusseldorf, Germany) and showed a sample size of n=28 for a power of 0.95 with an alpha error of 0.05 and an average effect size of 0.3. The post hoc analysis showed for our study sample size with 124 patients a power of 1.0 with an average effect size of 0.3 and an alpha error of 0.05. Further statistical analysis were performed using Microsoft® Office Excel® for Mac 2019 (Microsoft Corporation, Redmond, Washington, USA) and IBM® SPSS® Statistics Version 26 2019 (IBM Corporation, Armonk, New York, USA). The data are presented as mean and standard deviation or as absolute numbers and percentage. Categorial data were testet using the Chi-square test or Fisher´s exact test. Continouous data were compared using Student´s t test or Mann-Whitney U test. All significant univariate trends were entered into a multivariate (binary logistic) analysis to identify risk factors for mortality. Significance was set at $p \leq 0.05$.

Results

A total of 169 microbial pathogens were detected in 124 ICU-patients with isolated Gram positive bacteria in 73.3%, Gram negative bacteria in 23.6% and Candida spp. in 2.9% of all patients. The most common bacterium was *Staphyloccous aureus* (26.6%), followed by *Staphyloccus epidermidis* (12.4%), *Enterococci* ssp. and *Escherichia coli* (respectively 9.4%). A monomicrobial PJI was found in 93 patients (74.9%) and a polymicrobial PJI in 30 patients (24.2%). A negative culture was only seen in one patient with PJI (0.8%). These data are listed in detail in Tables 2 and 3. Gram positive and Gram negative microbial pathogens were found in 15 cases (15.3%) of polymicrobial PJI, multiple Gram positive in 6 cases (4.8%) and Gram positive and Candida in 5 cases (4%). Eighteen patients showed a polymicrobial PJI with 2 microbial pathogens (60%), 8 patients with 3 microbial pathogens (16.6%), 2 patients with 4 microbial pathogens (6.6%) and one patient had a PJI with 5 microbial pathogens (3.3%).

DTT PJI was diagnosed in 28 patients (22.6%) with 10 monomicrobial PJI (35.6%) and 18 polymicrobial PJI (64.3%). The main pathogens of DTT PJI were *Staphylococus epidermidis* (14.5%), *Eschericia coli* (12.7%), *Staphylococcus aureus* and *Candida* spp. (respectively 9.1%). As shown in Table 3, a total of 41 different microbial pathogens were detected in polymicrobial DTT PJI with 21 DTT pathogens and 20 associated non-DTT Co-pathogens.

Fourteen out of 16 patients (87.5%) with

Table 1. Criteria for PJI.

European Bone Joint Infection Society criteria[17]	Musculoskeletal Infection Society criteria[18]
A PJI is diagnosed if at least one of the following criteria is fulfilled: 1) Clinical: sinus tract (fistula) or purulence around prosthesis 2) Cell count in joint aspiration: > 2000/µl leukocytes or >70% polymorphonuclear granulocytes (PMN) 3) Histology: inflammation in periprosthetic tissue (type 2 or 3 after Krenn and Morawietz) 4) Microbial growth in synovial fluid or ≥ 2 tissue samples (in cases of high virulent microbes like Staphylococcus aureus one sample is considered sufficient) or sonication fluid ≥ 50 CFU/ml	Definition of Periprosthetic Join Infection According to the International Consensus Group. This Is an Adaptation of the Musculoskeletal Infection Society Definition of PJI. PJI Is Present When One of the Major Criteria Exists or Three Out of Five Minor Criteria Exist Major Criteria: Two positive periprosthetic cultures with phenotypically identical organisms, OR A sinus tract communicating with the joint, OR Minor Criteria 1) Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR) 2) Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test stri 3) Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) 4) Positive histological analysis of periprosthetic tissue KRENN?? 5) A single positive culture

Abbreviations: PJI periprosthetic joint infection.

Table 2. Microbial findings in 124 patients with PJI.

	All PJI, n=124 (%)	DTT PJI, n=28 (%)	Non-DTT PJI, n=95 (%)
Monomicrobial PJI	93 (74.9)	10 (35.6)	83 (87.3)
Gram-positive bacteria	72 (58)	6 (21.4)	66 (69.4)
Staphylococcus spp.	53 (42.7)	6 (21.4)	47 (49.4)
Staphylococcus aureus	31 (25)	1 (3.5)	30 (31.5)
Staphylococcus epidermidis	16 (12.9)	5 (17.8)	11 (11.5)
Coagulase-negative *staphylococci*	6 (4.8)	-	6 (6.3)
Streptococcus spp.	9 (7.2)	-	9 (9.4)
Enterococcus spp.	4 (3.2)	-	4 (4.2)
Other[1]	6 (4.8)	-	6 (6,3)
Gram-negative bacteria	21 (16.9)	4 (14.3)	17 (17.9)
Escherichia coli	10 (8)	4 (14.3)	6 (6,3)
Enterobactericaceae spp.[2]	9 (7.2)	-	9 (9.4)
Pseudomonas aeruginosa	2 (1.6)	-	2 (2.1)
Polymicrobial PJI	30 (24.2)	18 (64.3)	12 (12.6)
Negative culture	1 (0.8)	-	-

Data presented as absolute Number (Percentage). Abbreviations: PJI periprosthetic joint infection, DTT difficult-to-treat. [1]Including *Corynebacterium* spp. (n=3), *Micrococcus* spp. (n=2), *Pediococcus* spp. [2]Including *Enterobacter* spp. (n=4), *Klebsiella* spp. (n=3), *Citrobacter* spp., *Serratia marcescens.*

multidrug resistant pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), multiresistant Gram negative bacteria that are not susceptible to 3 specific groups of antibiotics (3MRGN) and Vancomycin-Resistant *Enterococci* (VRE) as the reason for PJI showed DTT pathogens.

The demographic and clinical data of the included 124 patients were recently published.[13] In univariate analysis, polymicrobial PJI [18 (64.3%) vs. 12 (12.5%); p=0.001], number of pathogens [2±0.9 vs. 1.2±0.6; p=0,001], ICU stay [17.8±18 vs. 10.6±13.1; p=0.05] and mortality [11 (39.2%) vs. 15 (15.6%); p=0.007] were found to be significantly different between DTT PJI and non-DTT PJI (Table 4). Multivariate logistic regression identified prolonged ICU stay

Table 3. Microbial findings in 30 patients with polymicrobial PJI.

	All, n=76 (%)	DTT, n=45		Non-DTT (n=31)
		DTT, n=21 (%)	Non-DTT, n=24 (%)	
Gram-positive bacteria	52 (68.4)	9 (42.8)	20 (83.3)	23 (74.2)
Staphylococcus spp.	30 (39.4)	7 (33.3)	11 (45.8)	12 (38.7)
Staphylococcus aureus	14 (18.4)	4 (19)	5 (20.8)	5 (16.1)
Staphylococcus epidermidis	7 (9.2)	3 (14.3)	2 (8.3)	2 (6.4)
Coagulase-negative *staphylococci*	9 (11.8)	-	4 (16.6)	5 (16.1)
Streptococcus spp.	6 (7.9)	-	3 (12.5)	3 (9.6)
Enterococcus spp.	12 (15.8)	2 (9.5)	5 (20.8)	5 (16.1)
Other[1]	4 (5.2)	-	1 (4.1)	3 (9.6)
Gram-negative bacteria	19 (25)	7 (33.3)	4 (16.6)	8 (25.8)
Escherichia coli	6 (7.9)	3 (14.3)	-	3 (9.6)
Enterobacteriaceae spp.[2]	6 (7.9)	1 (4.7)	2 (8.3)	3 (9.6)
Pseudomonas aeruginosa	5 (6.6)	2 (9.5)	1 (4.1)	2 (6.4)
Proteus mirabilis	1 (1.3)	1 (4.7)	-	-
Other[3]	1 (1.3)	-	1 (4.1)	-
Candida spp.	5 (6.6)	5 (23.8)	-	-

Data presented as absolute Number (Percentage). Abbreviations: DTT difficult-to-treat. [1]Including *Bacillus* spp., *Corynebacterium* spp., *Leuconostoc*, *Proprionbacterium* spp. [2]Including *Klebsiella* (n=3), *Acinetobacter* spp. *Citrobacter* spp., *Enterobacter* spp. [3]*Aeromonas* spp.

Table 4. Clinical findings in 124 patients with PJI.

	DTT PJI, n=28 (%)	Non-DTT PJI, n=96 (%)	P value
Male gender	11 (39.2)	41 (42.7)	0.71
Age	77.7±10.9	74.4±12.4	0.2
BMI	27.1±10.9	29±7.5	0.31
Location of the PJI			
Hip	20 (71.4)	65 (67.7)	0.76
Knee	6 (18.1)	27 (28.1)	0.52
Hip and knee	2 (7.1)	4 (4.1)	0.52
No. of patients with previous septic revisions since TA	20 (71.4)	61 (63.5)	0.47
No. of previous septic revision since TA	3.3±3.8	2.9±3.3	0.55
No. of surgeries during hospitalization	2.8±1.6	2.1±1.8	0.07
Reasons for ICU admission			
Unplanned surgical	9 (32.1)	34 (35.4)	0.59
Medical	3 (10.7)	16 (16.6)	0.59
Scheduled surgical	16 (57.1)	46 (47.9)	0.59
CCI	4.6±2.1	3.1±2.5	0.09
ASA Score	3.1±0.6	3±0.5	0.4
SAPS II Score	25.3±13.2	23.7±15.7	0.62
Invasive ventilation	12 (42.8)	25 (26)	0.09
Hours of ventilation	109.1±124.1	123.9±254.7	0.85
RRT	4 (14.2)	11 (11.4)	0.74
Acute PJI	4 (14.2)	15 (15.6)	0.55
Polymicrobial PJI	18 (64.2)	12 (12.5)	≤0.001
No. of pathogens	2±0.9	1.2±0.6	≤0.001
LOS ICU	17.8±18	10.6±13.1	0.05
LOS hospital	54±28.8	46±39	0.31
Mortality	11 (39.2)	15 (15.6)	*0.007*

Data presented as mean±standard deviation or as absolute numbers (percentage). Significant results are in italics. Abbreviations: BMI body mass index, No. number, TA total arthroplasty, CCI Charlson Comorbidity Index, ASA Score American Association of Anesthesiologist Score, SAPS II Score Simplified Acute Physiology Score II, RRT renal replacement therapy, LOS length of stay, ICU Intensive Care Unit, DTT difficult-to-treat.

(OR, 1.05; 95% CI, 1.01-1.09; p=0.01) and DTT PJI (odds ratio [OR], 3.35; 95% confidence interval [CI], 1-11.21; p=0.049) as risk factors for mortality (Table 5).

After discharge from the ICU, 98 out of 124 patients (79%) survived the in-hospital stay and were discharged to rehabilitation (21.4%), nursing home (25.5%) or home (53.1%).

Discussion

We analyzed a large cohort of 124 ICU-patients with the treatment of PJI at a tertiary healthcare center. To our best knowledge, this is the first study showing the microbial findings and clinical data of patients with DTT PJI admitted to the ICU.

The first finding of our study is that the distribution of involved pathogens in ICU-patients with PJI was in accordance with that reported in the literature. The most common microbial pathogens were Staphyloccous aureus and Staphylococcus epidermidis, as noted previously in studies with large cohorts of patients with PJI.[20-22] The proportions of Gram negative bacteria and *Candida* spp. were also similar to our findings.[11,21]

However, only one negative culture was found in our series, which seems to be very low compared to other studies with a rate up to 21%.[22] The main reason for that may be the high number of septic revisions in our cohort with repeated samples of periprosthetic tissue, synovial fluid and the use of sonication to improve the likelihood of detecting microbial pathogens, as recommended before.[23]

Polymicrobial PJI were detected in 24.2% of all critically ill patients in our study. Allthough there were several factors like an age older than 65 years, higher ASA scores and CCI as well as multiple revisions surgeries that are associated with polymicrobial PJI in our findings, we found no higher rates of polymicrobial PJI than previously published.[24-26]

Currently, only one study has investigated the microbial findings of patients with PJI in an ICU.[12] Maaloum *et al.* described the clinical spectrum and outcome of 41 critically ill patients suffering from PJI in a retrospective, observational study in 2013. Their microbial spectrum was also nearly similar to our findings, with a proportion of 76% Gram positive and 20% Gram negative bacteria and polymicrobial PJI in 24% of all patients. The only difference of Maaloum *et al.* to our microbial spectrum was the detection of anaerobe bacteria and no detection of *Candida* spp.

Our second finding is that patients with DTT PJI showed more polymicrobial PJI with a higher number of microbial pathogens and a poorer outcome compared to non-DTT PJI. The role of DTT pathogens in patients with PJI is controversely discussed in the current literature. Some authors hypothesized that the treatment of DTT PJI is more challenging than non-DTT PJI with worse outcome.[4,27] DTT pathogens were first described as rifampin-resistant staphylococci, ciprofloxacin-resistant Gram negative bacteria, *enterococci* and fungi (mainly *Candida* spp.).[4,28]

Renz *et al.* showed a treatment success of 84% in enterococcal PJI, suggesting that enterococci were not DTT.[8] According to the current recommendation of the PRO-IMPLANT foundation only vancomycin-resistant enterococi were defined as DTT next to rifampin-resistant staphylococci, ciprofloxacin-resistant Gram negative bacteria and *Candida* spp.[3] This revised definition of DTT pathogens was used in our study, too.

We found DTT pathogens in 22.6% of all ICU-patients with PJI, especially in polymicrobial PJI (64.2%). Rifampin-resistant *Staphylococcus* spp. were responsible as the microbial agens for DTT PJI in 12 patients (42.8%), Ciprofloxacin-resistant Gram negative bacteria for DTT in 11 patients (39.3%) and *Candida* spp. for DTT PJI in 5 patients (17.8%).

Akgün *et al.* found a rate of 18.4% DTT pathogens in 163 patients with PJI of the hip or knee.[9] Main DTT pathogens were enterococci, followed by rifampin-resistant *Staphylococcus epidermidis* and fungi. The rate of polymicrobial PJI in patients with DTT pathogens was 53.3%. No ciprofloxacin-resistant Gram negative bacteria were detected. These findings were also shown in a study by Faschingbauer *et al.*[10] DTT pathogens were present in 6.3% of all cases, but only 2.1% of PJI were polymicrobial.

These studies showed a significantly longer LOS in the hospital, longer prosthetic-free intervals, longer duration of antibiotic treatment and higher numbers of septic revisions compared to patients with non-DTT PJI.[9,10] Interestingly, the treatment success at Follow Up (FU) of 24 months was not different between DTT and non-DTT PJI. We found no differences in LOS in hospital or in the number of revision surgeries in our ICU-patients with DTT or non-DTT PJI.

However, both studies with DTT PJI used the first described classification of DTT pathogens[4,28] and reported no results of ICU-patients, which limits the ability to compare our results significantly.[9,10] Moreover, FU of less than 24 months after hip or knee replacement was an exclusion criteria in these studies and the mortality rate was also not listed.

Despite these limitations, we confirm the findings of Akgün *et al.* that DTT pathogens are more common in polymicrobial PJI.[9] In addition, we suggest that ciprofloxacin-resistent Gram negative bacteria might play an important role in the setting of DTT PJI in critically ill patients and might be more often the cause of DTT PJI, than previously has been published.[9,10]

The last finding of our study is that prolonged ICU stay and DTT PJI are risk factors for mortality in patients with PJI. As previously published, overall mortality of our cohort was 21%.[13] This rate was similar to the findings of Maaloum *et al.*[12] Acute infection of less than 4 weeks duration, renal replacement therapy (RRT), a high SAPS II Score and a high ASA Score were associated with a high mortality rate in their study. No differences could be found regarding age or type of bacteria. However, the term of DTT pathogens was not used in their study to compare this subgroup with our data.

We found a mortality rate of nearly 40% in patients with DTT PJI compared to 16%

Table 5. Multivariate logistic regression of risk factors for mortality.

	OR	95% CI	p value
LOS ICU	1.05	1.01-1.09	*0.01*
DTT PJI	3.35	1.00-11.21	*0.049*
Polymicrobial PJI	5.4	0.44-66.34	0.18
Number of pathogens	0.25	0.04-1.36	0.11

Data presented as odds ratio with 95% confidence interval. Significant results are in italics. Abbreviations: DTT difficult-to-treat, PJI periprosthetic joint infection, LOS length of stay, ICU intensive care unit, OR odds ratio, CI confidence interval.

in patients with non-DTT PJI. Amazingly, no differences could be found in age, SAPS II Score, ASA Score, CCI, RRT, mechanical ventilation or number of revision surgeries between both groups. Due to our large cohort, we were able to perform a multivariate logistic regression of risk factors for mortality significantly associated with DTT PJI in univariate analysis. Our study identified a prolonged ICU stay and DTT PJI as risk factors which are associated with a poor outcome.

Several studies demonstratred that patients with prolonged critical illness have an increased hospital and 1-year mortality.[29,30] We were able to confirm these findings. However, once ICU care was finished, no patient with DTT or non-DTT PJI died in the IMC or general ward and 79% were discharged from hospital. These findings suggest a good outcome after surviving the initial stage of critical illness.

Some authors found a similar reccurence rate and no differences between DTT PJI and non-DTT PJI in the outcome at final FU after 24 months and noted that a classification in DTT and non-DTT pathogens is useful, but should not be overstated.[9,10] In spite of these literature we could find DTT PJI as a risk factor for mortality. Based on our findings we suggest, that the term of DTT pathogens is useful for the intensivist to assess the clinical outcome in ICU-patients with PJI. In addtion, we also believe that the treatment of patients with DTT PJI in the ICU is more challenging than non-DTT PJI with worse outcome, as published before.[4,27] However, we found no studies in the available literature to compare our results in DTT PJI patients admitted to the ICU.

Limitations

The current study has several limitations. First, it is a retrospective, observational, single-center study with missing data on follow-up after hospital discharge. Some patients may still develop an infection or may have a bad functional outcome. Second, detailed informations of the surgical and antibiotic treatment of PJI are not presented. Third, there are heterogenous definitions of PJI, DTT pathogens or of acute and chronic PJI and the available literature is lacking in comparable studies. Fourth, the number of patients with DTT PJI were small in our ICU cohort. Therefore, conclusion based on our results should be drawn carefully.

However, this study is the first to report the microbial findings of a large ICU cohort with special emphasis on DTT PJI treated in a tertiary healtcare center. The frequently number of patients with DTT PJI permit the analyses of risk factors for mortality.

Conclusions

In summary, the treatment of patients with PJI, especially DTT PJI, admitted to the ICU is complex and represents an ongoing challenge for surgeons and intensivists. The microbial spectrum of PJI in ICU-patients is in accordance with that reported in the literature. However, a high proportion of Ciprofloxacin-resistant Gram negative bacteria was noticed in ICU-patients with DTT PJI. ICU-patients with DTT PJI showed a higher proportion of polymicrobial PJI with higher numbers of pathogens, longer ICU stay and a higher mortality than patients with non-DTT PJI in univariate analysis. In multivariate analysis, prolonged ICU stay and DTT PJI were risk factors for hospital mortality so that the term of DTT pathogens may be useful for the intensivist to assess the clinical outcome in ICU-patients with PJI. Further studies need to investigate the role of DTT PJI in patients admitted to the ICU to emphasize the current findings.

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