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REVIEW ARTICLE

How We Approach Suppressive Antibiotic Therapy (SAT) Following Debridement, Antibiotics, and Implant Retention for Prosthetic Joint Infection

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The optimal treatment of prosthetic joint infection (PJI) remains uncertain. Patients undergoing debridement, antibiotics, and implant retention (DAIR) receive extended antimicrobial treatment, and some experts leave patients at perceived highest risk of relapse on suppressive antibiotic therapy (SAT). In this narrative review, we synthesize the literature concerning the role of SAT to prevent treatment failure following DAIR, attempting to answer 3 key questions: (1) What factors identify patients at highest risk for treatment failure after DAIR (ie, patients with the greatest potential to benefit from SAT), (2) Does SAT reduce the rate of treatment failure after DAIR, and (3) What are the rates of treatment failure and adverse events necessitating treatment discontinuation in patients receiving SAT? We conclude by proposing risk–benefit stratification criteria to guide use of SAT after DAIR for PJI, informed by the limited available literature.

Keywords. prosthetic joint infection; PJI; DAIR; antibiotic suppression; suppressive antibiotic therapy.

Prosthetic (periprosthetic) joint infection (PJI) is a serious complication of arthroplasty, with 15-year incidences of 1.5–2% and a 5-year mortality exceeding 20% [1]. Current guidelines highlight numerous PJI risk factors but offer limited guidance as to how these should inform PJI management [2]. Surgical approaches to PJI include debridement, antibiotics, and implant retention (DAIR) and exchange arthroplasty. Two-stage exchange arthroplasty remains the US gold standard, but DAIR involves fewer surgeries and is often preferred when feasible. Unfortunately, DAIR has a widely variable success rate, with many studies suggesting failure in the majority of cases [3–5]. These high failure and mortality rates indicate the need for improved PJI treatment, including optimized antibiotic therapy.

For PJI treated with DAIR, the 2013 Infectious Diseases Society of America (IDSA) guidelines recommended 4–6-week antibiotic durations, extended in staphylococcal infections up to 3 months for hips and 6 months for knees [6]. Consideration of chronic suppression was suggested, but with little guidance regarding whom to suppress, which antimicrobials to use, or how long suppression should continue. Below, we synthesize published literature on suppressive antibiotic therapy (SAT) to prevent treatment failure in PJI managed with DAIR. We set to out to answer 3 questions:

Q1: Which patients are at highest risk of treatment failure after DAIR?
Q2: Does SAT reduce the incidence of treatment failure?
Q3: What are the rates of treatment failure or adverse events (AEs) leading to treatment discontinuation in patients receiving SAT for PJI?

METHODS

To identify literature addressing questions Q1–Q3, we searched PubMed from inception through 1 April 2023 for English-language clinical studies (see Supplementary Material for search terms and details); 1 author (N. C.-P.) initially reviewed abstracts to identify manuscripts for full-text review, and all authors collaborated to confirm the selected studies met inclusion/exclusion criteria and performed data extraction. This study was carried out as a narrative rather than as a systematic review, with the limitations that entails (eg, reasons for an individual study's exclusions were not recorded).

We were challenged to distinguish between primary antimicrobial therapy and SAT due to substantial heterogeneity in the literature regarding standard antimicrobial durations (eg, Shah et al reported a benefit of oral SAT following DAIR [7], but defined SAT as any therapy beyond 6 wk; yet, a recent clinical trial

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demonstrated the superiority of 12 to 6 wk of antibiotics following DAIR in the absence of SAT [8]). Ultimately we defined SAT as any antimicrobial therapy beyond 6 months in a patient with PJI managed with DAIR, because this was the longest duration recommended in the IDSA guidelines [6].

For Q1, we included studies of patients managed with DAIR reporting multivariable analyses of treatment failure with odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals. We excluded studies with insufficient reporting of parameters determining DAIR failure or apparent significant overlap of patient populations with other included studies. For Q2, we only included manuscripts reporting outcomes restricted to patients who underwent DAIR for PJI. For both Q2 and Q3, we excluded studies in which not all patients given suppressive antibiotics met our definition of SAT. We performed descriptive statistics using Microsoft Excel (Microsoft Corporation) and generated forest plots with ORs using Review Manager 5.4 (Cochrane).

WHAT PREDICTS TREATMENT FAILURE IN PROSTHETIC JOINT INFECTION MANAGED WITH DEBRIDEMENT, ANTIBIOTICS, AND IMPLANT RETENTION?

We included 33 studies evaluating the risk of failure after DAIR, comprising 31 retrospective cohorts, 1 prospective cohort, and 1 case-control study [3–5, 9–38]. Most (18/33) studies used the Musculoskeletal Infection Society (MSIS) criteria to define PJI [39], but definitions of treatment failure varied substantially (Supplementary Table 1). Given the heterogeneity of outcome definitions and data gathered, the factors associated with failure of DAIR for PJI unsurprisingly varied (Table 1; the proportion of studies finding significant associations for each variable are given in Supplementary Table 2). Because not all adverse treatment outcomes following DAIR are plausibly preventable by SAT (eg, future aseptic failures), in Table 2 we report data from the 14 studies that defined PJI failure only in terms of new or relapsed infection (ie, infection-related reoperation, infection-related death, or recurrent/persistent clinical evidence of infection). Notably, even this subset of studies may not optimally reflect who is likely to benefit from SAT, as many infection-related PJI treatment failures are due to new organisms, for whom the SAT regimen may be ineffective.

In the full analysis, the median sample size was 112 (interquartile range [IQR]: 71–199) and the median reported follow-up was 919 days (IQR: 695–1270 d). Most PJIs occurred less than 90 days postoperatively, and most occurred in knees (60.4%; IQR: 51–80%). Approximately half of cases were due to staphylococci, with smaller proportions of streptococcal, gram-negative, polymicrobial, and culture-negative infections. Specific antimicrobial regimens were infrequently reported, but 10 of 33 studies reported rates of quinolone-rifampin use (median: 30%; IQR: 12–47%) and 12 of 33 reported rates of any rifampin use (median: 48%; IQR: 39–67%). The median treatment failure rate across all studies was 34% (IQR: 27–44%).

Staphylococcal infection, and in particular *Staphylococcus aureus*, was consistently associated with increased failure risk, whereas 1 study found a significantly lower failure rate in culture-negative infections. Cirrhosis, higher initial C-reactive protein values, and bacteremia were also consistently associated with DAIR failure. Multiple studies found that the risk of failure was higher with PJI of a revision versus primary arthroplasty, when fracture was the indication for primary arthroplasty, in late (hematogenous) versus early postoperative infection, when the symptom duration before diagnosis or surgery was prolonged, when more than 1 debridement was initially required, and when surgical source control was suboptimal (eg, arthroscopic vs open DAIR, or not performing polyethylene liner exchange). Contrary to prevailing wisdom, only 1 of 3 studies found the risk of failure to be higher for infected knees versus hips.

Three treatment factors were consistently reported as being protective against failure following DAIR. Receipt of a fluoroquinolone in gram-negative PJI was associated with greater treatment success in all 3 studies examining this association. For staphylococcal PJI, 2 studies found that receipt of rifampin was associated with greater treatment success (1 study examining the specific combination of rifampin plus a fluroquinolone and 1 study examining any receipt of rifampin, the latter's benefit significant in knee PJI only). Two studies found that longer durations of rifampin were associated with greater treatment success. Shorter antibiotic durations were inconsistently associated with failure, but the durations examined varied between studies, limiting comparability. These associations are all likely influenced by confounding by indication and immortal time biases and should be interpreted cautiously.

DOES SUPPRESSIVE ANTIBIOTIC THERAPY REDUCE TREATMENT FAILURE?

Three retrospective cohorts addressed the value of SAT in PJI following DAIR [40–42]. All studies included reoperation for infection in their definition of treatment failure, 2 included PJI-related mortality, and 1 included signs of recurrent or ongoing infection. The mean duration of SAT was reported in 1 study and was 276 (SD: 166) weeks [40].

Characteristics of PJI varied considerably among the 3 studies. The proportion of acute postoperative PJI (infection within 28 d of primary arthroplasty) ranged from 17% to 100% and the proportion of knee PJIs ranged from 0% to 76%. One study only included streptococcal PJI [41]; in the others, staphylococci caused 67% of infections (including *S. aureus* in 42% and methicillin-resistant S. aureus in 15.7%), streptococci 10%, and gram-negative organisms 4.1%, while 8.9% were polymicrobial and 9.5% were culture negative. The SAT regimens

Table 1. Risk Factors for Treatment Failure of DAIR in Prosthetic Joint Infection From Observational Studies With Multivariate Analyses

Variable	Study (N)	OR/ HR	Effect Size	95% CI Lower	95% CI Upper
Antibiotic treatment					
Factors significantly associated with treatment failure following DAIR					
Antibiotic duration (wk)	Bene 2018 (76)	HR	0.99	.982	.998
Antibiotic duration (wk)	Lesens 2018 (137)	HR	0.78	.69	.88
Antibiotic duration <3 mo	Letouvet 2016 (60)	OR	20	2.2	200
Antibiotic duration 3 mo versus 1 y	Tai 2022 (247)	HR	3.5	1.48	8.25
Quinolone use on gram-negative infections	Rodriguez-Pardo 2014 (173)	aHR	0.23	.13	.4
Quinolone use on gram-negative infections	Tornero 2014 JABFM (160)	OR	0.15	.04	.56
Quinolone use on gram-negative infections	Martinez-Pastor 2009 (47)[a]	OR	0.11	.02	.51
Quinolone + rifampin used	El Helou 2010 (101)	HR	0.11	.01	.84
Rifampin use in knees	Tai 2022 (149)	HR	0.4	.2	.79
Rifampin use in knees (6 mo vs 3 mo)	Tai 2022 (149)[b]	HR	0.58	.28	1.2
Rifampin use ≥3 wk (*Staphylococcus aureus*)	Lesens 2018 (137)	HR	0.08	.02	.36
Rifampin use in days	Becker 2020 (79)	HR	0.95	.92	.99
Ineffective empiric antibiotics	Puhto 2015 (113)	HR	3.20	1.40	7.10
Factors not associated with treatment failure following DAIR					
Antibiotic duration (d)	Becker 2020 (79)	HR	1	.99	1.01
Antibiotic duration (6 wk vs 4 wk)	Tai 2022 (247)	HR	1.01	.52	1.94
Antibiotic duration (5 y vs 1 y)	Tai 2022 (247)	HR	1.43	.29	6.98
IV antibiotics <28 d	Byren 2009 (112)	HR	0.49	.18	1.37
Quinolone use for staphylococci	Tai 2022 (247)	HR	0.62	.31	1.24
Quinolone + rifampin use on gram-negative infections	Becker 2020 (79)	HR	0.28	.02	3.83
Rifampin use	El Helou 2010 (101)	HR	0.55	.24	1.26
Any rifampin use	Lesens 2018 (137)	HR	0.5	.2	1.28
Rifampin use in hips	Tai 2022 (247)	HR	1.47	.35	6.15
Rifampin duration in hips	Tai 2022 (247)	HR	0.45	.05	4.01
Rifampin resistance	Shabana 2022 (157)[c]	aOR	5.69	.61	52.75
Combination of antibiotics for gram-negative infections	Rodriguez-Pardo 2014 (173)	aHR	0.52	.25	1.06
Infecting organism					
Factors significantly associated with treatment failure following DAIR					
Staphylococcus aureus	Byren 2009 (112)	HR	2.9	1	8.3
	Letouvet 2016 (60)	OR	9.4	1.6	53.9
	Swenson 2018 (71)	OR	7.1	2.3	25.3
	Zhu 2021 (230)	OR	2.11	1.48	3.22
	Urish 2018 (216)[a]	HR	1.68	1.12	2.51
	Davis 2022 (352)[a]	OR	2.56	1.47	4.55
MSSA	Toh 2021 (106)	OR	4.32	1.53	12.10
MRSA or MRSE	Kim 2015 (28)	OR	12.44	2.01	76.86
MRSA or *Enterococcus* spp.	Soriano 2006 (39)	OR	17.60	1.30	238.3
Staphylococci	Weston 2018 (134)	HR	3.6	1.8	7.2
Gram-negative	Zhu 2021 (230)	OR	1.85	1.07	3.19
Drug-resistant organism[d]	Weston 2018 (134)	HR	1.9	1	3.4
Fluoroquinolone-resistant organism	Shabana 2022 (157)	OR	5.45	1.67	17.83
Polymicrobial	Chen 2021 (106)	HR	2.651	1.412	4.376
	Shohat 2019 (199)	aOR	2.4	1.1	5.2
	Lora-Tamayo 2013 (345)	HR	1.77	1.17	2.7
All intraoperative cultures positive	Tornero 2015 CMI (222)	OR	6.3	1.84	21.53
Culture-negative	Weston 2018 (134)	HR	0.3	.1	.9
Bacteremia	Lora-Tamayo 2017 (462)	HR	1.69	1.19	2.4
	Lora-Tamayo 2013 (345)	HR	1.81	1.12	2.92
	Kuo 2019 (49)	OR	3.94	1.18	13.1
Factors not associated with treatment failure following DAIR					
Staphylococcus aureus	Becker 2020 (79)	HR	2.7	.17	42.1
MRSA	Becker 2020 (79)	HR	2.29	.12	42.1

Table 1. Continued

Variable	Study (N)	OR/ HR	Effect Size	95% CI Lower	95% CI Upper
Gram-negative	Weston 2018 (134)	HR	0.8	.2	2.7
Drug-resistant organism[d]	Shohat 2019 (199)	aOR	1.03	.45	2.37
Polymicrobial	Weston 2018 (134)	HR	0.7	.2	2
% of culture-positive samples	Tornero 2014 JABFM	OR	1.03	.99	1.06
Comorbidities					
Factors significantly associated with treatment failure following DAIR					
Age >60 y	Weston 2018 (134)	HR	2.4	1.2	4.6
Age >80 y	Wouthuyzen-Bakker 2019 (340)	aOR	2.6	1.15	5.91
Body mass index >40 kg/m^2	Katakam 2020 (114)	HR	1.82	1.04	3.18
Male sex	Wouthuyzen-Bakker 2019 (340)	aOR	2.02	1.05	3.89
Chronic kidney disease	Rodriguez-Pardo 2014 (173)	aHR	2.56	1.14	5.77
	Tornero 2015 CMI (222)	OR	5.92	1.47	23.85
Cirrhosis	Tornero 2014 JABFM (160)	OR	12.4	3.1	49.7
	Tornero 2015 CMI (222)	OR	4.46	1.15	17.24
One or more comorbidities	Davis 2022 (352)[a]	OR	2.27	1.32	4.17
Charlson comorbidity index	Shohat 2019 (199)	aOR	1.22	1.01	1.51
Active smoking (tobacco)	Lesens 2018 (137)	HR	3.6	1.09	11.84
Rheumatoid arthritis	Lora-Tamayo 2017 (462)	HR	2.36	1.5	3.72
Immunosuppressive therapy	Lora-Tamayo 2013 (345)	HR	2.23	1.18	4.2
COPD	Bene 2018 (76)	HR	4.112	1.418	11.922
Atrial fibrillation	Bene 2018 (76)	HR	3.33	1.504	7.372
CHF	Wouthuyzen-Bakker 2019 (340)	aOR	5.13	1.08	24.34
Diabetes	Chen 2021 (106)	HR	2.375	1.07	4.024
Major depression or generalized anxiety	Katakam 2020 (114)	HR	2.09	1.17	3.74
Factors not associated with treatment failure following DAIR					
Age (y)	Kim 2015 (28)[e]	OR	0.9	.8	1
Age (y)	Rodriguez-Pardo 2014 (173)	aHR	1.01	.13	1.04
Age >70 y	Shabana 2022 (157)	aOR	0.97	.24	2.05
Body mass index >40 kg/m^2	Weston 2018 (134)	HR	1.3	.7	2.4
Body mass index >30 kg/m^2	Shabana 2022 (157)	aOR	0.71	.25	3.9
Male sex	Weston 2018 (134)	HR	1.6	.9	2.9
Male sex	Kim 2015 (28)	OR	2.81	.38	20.45
ASA score 3+	Shabana 2022 (157)	aOR	1.03	.35	3.05
ASA score	Becker 2020 (79)	HR	2.67	.55	13
ASA score	El Helou 2010 (101)	HR	0.91	.53	1.77
Presence of comorbidity	Byren 2009 (112)	HR	1.81	.55	5.9
Charlson comorbidity index	Becker 2020 (79)	HR	1.26	.87	1.84
Charlson comorbidity index	Kim 2015 (28)	OR	0.5	.22	1.05
Chronic kidney disease	Shabana 2022 (157)	aOR	1.48	.31	7.22
Chronic kidney disease	Lora-Tamayo 2017 (462)	HR	1.55	.97	2.48
Diabetes	Becker 2020 (79)	HR	0.8	.08	8.38
HTN	Wouthuyzen-Bakker 2019 (340)	aOR	2.9	.99	8.68
CAD	Wouthuyzen-Bakker 2019 (340)	aOR	1.76	.59	5.35
Oral anticoagulation	Wouthuyzen-Bakker 2019 (340)	aOR	0.53	.17	1.63
Active smoking (tobacco)	Becker 2020 (79)	HR	2.69	.25	28.7
Laboratory values					
Factors significantly associated with treatment failure following DAIR					
CRP (mg/dL)	Bene 2018 (76)	HR	1.003	1.001	1.005
CRP (<5 mg/dL vs 5–12 vs >12 mg/dL)	Tornero 2014 JABFM (160)	OR	1.06	1	1.11
CRP >6.5 mg/dL	Zhu 2021 (230)	OR	1.79	1.08	2.95
CRP >11.5 mg/dL	Tornero 2015 CMI (222)	OR	12.308	4.56	33.19
CRP >15 mg/dL	Wouthuyzen-Bakker 2019 (340)	aOR	2	1.04	3.86
	Martinez-Pastor 2009 (47)	OR	3.57	1.05	12.50
CRP at diagnosis (per 10 mg/dL)	Lora-Tamayo 2013 (345)	HR	1.22	1.03	1.43

Table 1. Continued

Variable	Study (N)	OR/ HR	Effect Size	95% CI Lower	95% CI Upper
ESR >107	Toh 2021 (106)	OR	6.60	2.29	19.00
ESR per unit increase	Kim 2015 (28)	OR	1.02	1	1.05
WBC >10 000 cells per mL	Puhto 2015 (113)	HR	3.70	1.90	7.30
>15 WBC/hpf on pathology	Bene 2018 (76)	HR	5.552	1.523	20.246
Hematocrit <32.1 (%)	Swenson 2018	OR	6.7	2.2	22.4
Albumin (higher vs lower)	Davis 2022 (352)[a]	OR	0.95	.91	.99
Factors not associated with treatment failure following DAIR					
CRP per unit increase	Kim 2015 (28)	OR	1	.99	1.01
CRP >11.5 mg/dL	Shao 2022 (104)	HR	1.37	.51	3.7
WBC >15 000/mL	Wouthuyzen-Bakker 2019 (340)	aOR	0.96	.45	2.05
Presenting symptoms					
Factors not associated with treatment failure following DAIR					
Temperature >38.5°C	Wouthuyzen-Bakker 2019 (340)	aOR	1.84	.84	4.03
Physical signs of inflammation	Wouthuyzen-Bakker 2019 (340)	aOR	1.81	.74	4.45
Surgery					
Factors significantly associated with treatment failure following DAIR					
Fracture (vs osteoarthritis) as indication for primary arthroplasty	Berqkvist 2016 (35)	OR	8.30	1.50	44.90
Fracture (femoral neck) versus primary arthroplasty as indication for surgery	Tornero 2015 CMI	OR	4.39	1.16	16.62
Cemented versus not-cemented prosthesis	Tornero 2015 CMI	OR	8.71	1.95	38.97
Revision versus primary arthroplasty	Byren 2009 (112)	HR	3.1	1.2	8.3
	Tornero 2014 CMI (222)	OR	4.34	1.34	14.04
	Letouvet 2016 (60)	OR	6.3	1.8	22.3
	Berqvist 2016 (35)	OR	0.10	.01	.90
	Shohat 2019 (199)	aOR	2.55	1.22	5.32
Knee versus hip PJI	Wouthuyzen-Bakker 2019 (340)	aOR	5.39	1.42	20.46
Need for multiple debridements	Lora-Tamayo 2013 (345)	HR	1.63	1.03	2.59
Need for >1 debridement	Vilchez 2011 (65)	OR	4.61	1.86	11.4
Polyethylene liner exchange	Lora-Tamayo 2017 (462)	HR	0.6	.44	.81
	Lora-Tamayo 2013 (345)	HR	0.65	.44	.95
	Kim 2015 (48)	OR	0.07	.007	.68
	Zhu 2021 (230)	OR	0.51	.32	.81
Arthroscopy versus open debridement	Byren 2009 (112)	HR	4.2	1.5	12.5
Factors not associated with treatment failure following DAIR					
Revision versus primary arthroplasty	Wouthuyzen-Bakker 2019 (340)	aOR	0.96	.49	1.89
	Lora-Tamayo 2017 (462)	HR	1.37	.98	1.9
Knee versus hip PJI	Tatarelli 2021 (21)	aOR	3.13	.3	32.41
	Shohat 2019 (199)	aOR	0.89	.44	1.8
Need for multiple debridements	Lora-Tamayo 2017 (462)	HR	1.38	.96	1.99
Intraoperative purulence	Rodriguez-Pardo 2014 (173)	aHR	1.64	.91	2.98
Polyethylene liner exchange	Shao 2022 (104)	HR	0.6536	.32776	1.297
Fracture as a reason for arthroplasty (vs osteoarthritis or avascular necrosis)	Shabana 2022 (157)	aOR	2.2	.59	8.23
Fracture as a reason for arthroplasty	Wouthuyzen-Bakker 2019 (340)	aOR	1.21	.6	2.45
Cemented versus not-cemented prosthesis	Shabana 2022 (157)	aOR	3.23	.49	21.39
Timing of infection					
Factors significantly associated with treatment failure following DAIR					
Late versus early PJI	Tatarelli 2021 (21)	aOR	12.51	1.21	129.63
Late versus early PJI	Davis 2022 (352)	aOR	2.99	1.57	5.71
Late versus early PJI	Lora-Tomayo 2017 (462)	HR	2.2	1.51	3.2
Sinus tract present	Marculescu 2006 (99)	HR	2.84	1.48	5.44
Symptoms for >7 d	Marculescu 2006 (99)	HR	1.77	1.02	3.07
Symptoms for ≥10 d	Shao 2022 (104)	HR	8.49	1.16	62.21
Symptom duration <3 wk	Davis 2022 (352)	OR	0.16	.05	.50
Symptom duration (2–4 wk vs <1 wk)	Urish 2018 (216)	HR	1.68	1.07	2.65
Symptom duration (>4 wk vs <1 wk)	Urish 2018 (216)	HR	2.35	1.42	3.87

Table 1. Continued

Variable	Study (N)	OR/HR	Effect Size	95% CI Lower	95% CI Upper
Acute hematogenous infection	Shohat 2019 (199)	aOR	2.36	1.16	4.81
Hematogenous infection	Vilchez 2011 (65)	OR	2.57	1.02	6.51
Factors not associated with treatment failure following DAIR					
>90 d after arthroplasty	Byren 2009 (112)	HR	1.1	.31	3.8
Time from arthroplasty to PJI (mo)	Kim 2015 (28)	OR	1.05	.98	1.11
Months from arthroplasty to DAIR	Kim 2015 (28)	OR	1.02	.98	1.07
Acute hematogenous versus early postoperative infection	Shao 2022 (104)	HR	1.61	.61	4.29
Chronic versus early postoperative infection	Shao 2022 (104)	HR	1.76	.83	3.7
Months from symptoms to DAIR	Kim 2015 (28)	OR	3.51	.19	63.73
Acute postoperative infection	Weston 2018 (134)	HR	1.3	.7	2.6
Symptoms for >10 d	Wouthuyzen-Bakker 2019 (340)	aOR	1.21	.54	2.74
Symptoms for <15 d	Weston 2018 (134)	HR	0.7	.2	2.3
Symptoms for <3 d	Weston 2018 (134)	HR	1	.5	2

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ASA, American Society of Anesthesiology; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CMI, clinical microbiology and Infection; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DAIR, debridement, antibiotics, and implant retention; ESR, erythrocyte sedimentation rate; hpf, high-power field; HR, hazard ratio; HTN, hypertension; IV, intravenous; MRSE, methicillin-resistant *S. epidermidis*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; OR, odds ratio; PJI, prosthetic joint infection; WBC, white blood cell count.

[a]HR or OR was recalculated due to reporting as success instead of failure due to the parameter being used as a reference for comparison, or to match the format of accompanying references reporting the same risk factor.

[b]Tai et al note that, due to nonlinearity, the overall test of association is significant, even though the CI does not exclude HR = 1.

[c]Rifampin resistance in Shabana et al trended toward significance, although it was rare in both groups (12.9% in failures and 3.4% in successes) and may have reached significance with a larger sample size.

[d]Drug-resistant organism was defined as either vancomycin-resistant enterococcus, methicillin-resistant *S. aureus*, or methicillin-resistant *S. epidermidis* in Shohat et al, and went undefined in Weston et al.

[e]The 95% upper CI of this association reached 1.0 exactly, with a *P* value of .72, so was considered nonsignificant.

varied, with 47.2% of patients receiving oral beta-lactams overall (range: 38–92% per study) versus 39.5% (range: 4–47%) for tetracyclines and 12.2% (range: 0–15%) for trimethoprim-sulfamethoxazole.

Twenty-one PJIs occurred in 138 patients receiving SAT (15.2%) and 111 PJIs occurred in 173 patients not receiving SAT (64.2%), indicating that receipt of SAT was associated with lower odds of recurrent PJI (OR: .22; 95% confidence interval: .12, .42) (Figure 1). The mean time to failure was reported in 1 study and was 27.8 weeks [42].

These data suggest that SAT reduces PJI treatment failure following DAIR, but they have limitations. First, the actual duration of SAT was only specified in 1 study, and both studies that only included DAIR patients did not specify the mean duration of SAT. Therefore, it is not clear how different the total antibiotic duration was for these patients versus those receiving the typical 6-month course for staphylococcal knee infection recommended by current guidelines, or how much of the apparent effect of SAT was due to immortal time bias. Second, none of the studies were randomized or had propensity score adjustment for the likelihood of receiving SAT, meaning that these data likely suffer from selection bias. Third, there was great heterogeneity in study outcome definitions, patient populations, causes and types of PJI, and surgical and antimicrobial management.

Critically, these data do not demonstrate whether SAT prevents or merely delays subsequent PJIs, and we lack long-term comparisons between indefinite SAT and time-restricted SAT strategies. In the studies supplying Kaplan-Meier curves, failure-free survival continued to wane in both the SAT and non-SAT groups throughout follow-up, albeit perhaps more slowly in the SAT groups [40, 41]. Byren et al [5] found that the risk of PJI treatment failure increased 4-fold after antimicrobials were stopped regardless of the initial antibiotic duration, with most failures occurring in the first 4 months afterward. This suggests that lengthening antibiotic therapy may simply postpone, rather than prevent, treatment failure. Clinicians should consider whether SAT truly prevents recurrent PJI because the adverse effects of antimicrobials (eg, *Clostridioides difficile* colitis and difficult-to-treat pathogens in subsequent PJIs) accrue regardless [43–45]. Furthermore, delaying an inevitable treatment failure may be harmful if it means that infection recurs when the patient is a poorer surgical candidate.

HOW OFTEN DOES SUPPRESSIVE ANTIBIOTIC THERAPY FAIL OR PRODUCE ADVERSE EVENTS NECESSITATING TREATMENT DISCONTINUATION?

We identified 9 articles assessing the failure rate and tolerability of SAT, including 7 retrospective cohorts, 1 observational prospective cohort, and 1 case-control study (Supplementary Table 3) [40–42, 46–51]. The median sample size was 32

Table 2. Risk Factors for Treatment Failure of DAIR in Prosthetic Joint Infection From Observational Studies With Multivariate Analyses and Reporting Infection-Related Treatment Outcomes

Variable	Study (N)	OR/HR	Effect Size	95% CI	
				Lower	Upper
Antibiotic treatment					
Factors significantly associated with treatment failure following DAIR					
Antibiotic duration (wk)	Bene 2018 (76)	HR	0.99	.982	.998
Antibiotic duration < 3 mo	Letouvet 2016 (60)	OR	20	2.2	200
Antibiotic duration 3 mo versus 1 y	Tai 2022 (247)	HR	3.5	1.48	8.25
Quinolone use on gram-negative infections	Tornero 2014 JABFM (160)	OR	0.15	.04	.56
Quinolone use for gram-negative infections	Martinez-Pastor 2009 (47)[a]	OR	0.11	.02	.51
Rifampin use in knees	Tai 2022 (149)	HR	0.4	.2	.79
Rifampin use in knees (6 mo vs 3 mo)	Tai 2022 (149)[b]	HR	0.58	.28	1.2
Factors not associated with treatment failure following DAIR					
Antibiotic duration (6 wk vs 4 wk)	Tai 2022 (247)	HR	1.01	.52	1.94
Antibiotic duration (5 y vs 1 y)	Tai 2022 (247)	HR	1.43	.29	6.98
Quinolone use for staphylococci	Tai 2022 (247)	HR	0.62	.31	1.24
Rifampin use in hips	Tai 2022 (247)	HR	1.47	.35	6.15
Rifampin duration in hips	Tai 2022 (247)	HR	0.45	.05	4.01
Rifampin resistance	Shabana 2022 (157)[c]	aOR	5.69	.61	52.75
Infecting organism					
Factors significantly associated with treatment failure following DAIR					
Staphylococcus aureus	Letouvet 2016 (60)	OR	9.4	1.6	53.9
	Swenson 2018 (71)	OR	7.1	2.3	25.3
MRSA or *Enterococcus* spp.	Soriano 2006 (39)	OR	17.60	1.30	238.3
Fluoroquinolone-resistant organism	Shabana 2022 (157)	OR	5.45	1.67	17.83
Polymicrobial	Shohat 2019 (199)	aOR	2.4	1.1	5.2
Bacteremia	Kuo 2019 (49)	OR	3.94	1.18	13.1
Factors not associated with treatment failure following DAIR					
Drug-resistant organism[d]	Shohat 2019 (199)	aOR	1.03	.45	2.37
% of culture-positive samples	Tornero 2014 JABFM	OR	1.03	.99	1.06
Comorbidities					
Factors significantly associated with treatment failure following DAIR					
Body mass index >40 kg/m^2	Katakam 2020 (114)	HR	1.82	1.04	3.18
Cirrhosis	Tornero 2014 JABFM (160)	OR	12.4	3.1	49.7
Charlson comorbidity index	Shohat 2019 (199)	aOR	1.22	1.01	1.51
COPD	Bene 2018 (76)	HR	4.112	1.418	11.922
Atrial fibrillation	Bene 2018 (76)	HR	3.33	1.504	7.372
Major depression or generalized anxiety	Katakam 2020 (114)	HR	2.09	1.17	3.74
Factors not associated with treatment failure following DAIR					
Age >70 y	Shabana 2022 (157)	aOR	0.97	.24	2.05
Body mass index >30 kg/m^2	Shabana 2022 (157)	aOR	0.71	.25	3.9
ASA score 3+	Shabana 2022 (157)	aOR	1.03	.35	3.05
Chronic kidney disease	Shabana 2022 (157)	aOR	1.48	.31	7.22
Laboratory values					
Factors significantly associated with treatment failure following DAIR					
CRP (mg/dL)	Bene 2018 (76)	HR	1.003	1.001	1.005
CRP (<5 mg/dL vs 5–12 vs >12 mg/dL)	Tornero 2014 JABFM (160)	OR	1.06	1	1.11
	Martinez-Pastor 2009 (47)	OR	3.57	1.05	12.50
>15 WBC/hpf on pathology	Bene 2018 (76)	HR	5.552	1.523	20.246
Hematocrit <32.1 (%)	Swenson 2018	OR	6.7	2.2	22.4
Factors not associated with treatment failure following DAIR					
CRP >11.5 mg/dL	Shao 2022 (104)	HR	1.37	.51	3.7
Surgery					
Factors significantly associated with treatment failure following DAIR					
Revision versus primary arthroplasty	Letouvet 2016 (60)	OR	6.3	1.8	22.3
	Shohat 2019 (199)	aOR	2.55	1.22	5.32
Factors not associated with treatment failure following DAIR					

Table 2. Continued

Variable	Study (N)	OR/HR	Effect Size	95% CI Lower	95% CI Upper
Knee versus hip PJI	Tatarelli 2021 (21)	aOR	3.13	.3	32.41
	Shohat 2019 (199)	aOR	0.89	.44	1.8
Polyethylene liner exchange	Shao 2022 (104)	HR	0.6536	.32776	1.297
Fracture as a reason for arthroplasty (vs osteoarthritis or avascular necrosis)	Shabana 2022 (157)	aOR	2.2	.59	8.23
Cemented versus not-cemented prosthesis	Shabana 2022 (157)	aOR	3.23	.49	21.39
Timing of infection					
Factors significantly associated with treatment failure following DAIR					
Late versus early PJI	Tatarelli 2021 (21)	aOR	12.51	1.21	129.63
Sinus tract present	Marculescu 2006 (99)	HR	2.84	1.48	5.44
Symptoms for >7 d	Marculescu 2006 (99)	HR	1.77	1.02	3.07
Symptoms for ≥10 d	Shao 2022 (104)	HR	8.49	1.16	62.21
Acute hematogenous infection	Shohat 2019 (199)	aOR	2.36	1.16	4.81
Factors not associated with treatment failure following DAIR					
Acute hematogenous versus early postoperative infection	Shao 2022 (104)	HR	1.61	.61	4.29
Chronic versus early postoperative infection	Shao 2022 (104)	HR	1.76	.83	3.7

Abbreviations: aOR, adjusted odds ratio; ASA, American Society of Anesthesiology; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DAIR, debridement, antibiotics, and implant retention; hpf, high-power field; HR, hazard ratio; JABFM, journal of applied biomaterials & functional materials; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; PJI, prosthetic joint infection; WBC, white blood cell count.

[a]HR or OR was recalculated due to reporting as success instead of failure due to the parameter being used as a reference for comparison, or to match the format of accompanying references reporting the same risk factor.

[b]Tai et al note that, due to nonlinearity, the overall test of association is significant, even though the CI does not exclude HR = 1.

[c]Rifampin resistance in Shabana et al trended toward significance, although it was rare in both groups (12.9% in failures and 3.4% in successes) and may have reached significance with a larger sample size.

[d]Drug-resistant organism was defined as either vancomycin-resistant enterococcus, methicillin-resistant *S. aureus*, or methicillin-resistant *S. epidermidis*.

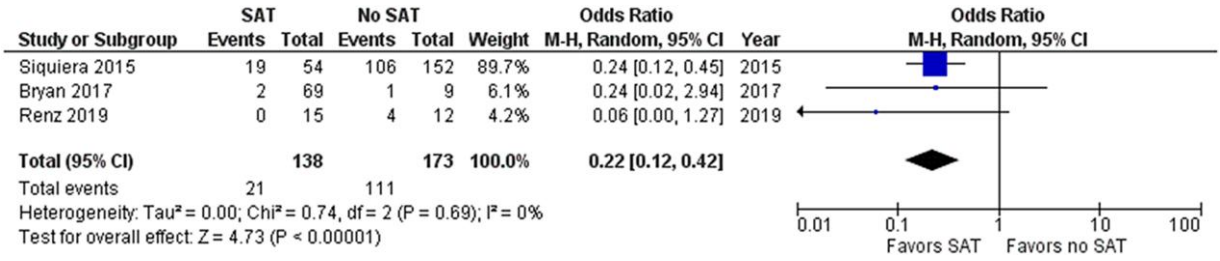

Figure 1. Receipt of SAT is associated with reduced probability of treatment failure following PJI managed with DAIR. Abbreviations: CI, confidence interval; DAIR, debridement, antibiotics, and implant retention; M-H, mantel-haenszel; PJI, prosthetic joint infection; SAT, suppressive antibiotic therapy.

(IQR: 14–45), the median duration of SAT was 161.2 (IQR: 96.5–275.9) weeks, and the median failure rate was 16.7% (IQR: 8.45–30.6%). Only 5 studies reported how often AEs led to SAT cessation. Across those studies, AEs were reported in a median of 8.3% (IQR: 0.0–23.1%) of patients, leading to cessation of SAT in a median of 3.1% (IQR: 0.0–15.4%). No study categorized AEs by grade.

As with the previous questions discussed above, drawing firm conclusions from such low-quality and heterogenous literature is difficult. Importantly, 4 studies did not limit their enrollment to patients who had undergone DAIR, and while these 9 studies collectively enrolled 336 patients treated with SAT following a PJI, only 82% had actually undergone DAIR. Confounding by indication makes the outcome of SAT in PJIs managed with DAIR versus exchange procedures difficult to compare retrospectively. While failure rates of SAT were stratified by surgical procedure for each of the 4 studies, most other data points, such as duration of treatment with SAT, choice of antibiotic, and the frequency of AEs, were not.

In the 5 more recently published studies, widely accepted diagnostic criteria were used to define PJI: the MSIS 2011 criteria in 2 studies and the MSIS 2013 criteria, the IDSA criteria, and the European bone and joint infection society criteria in 1 study each. The 4 older studies each devised their own definitions based on a combination of clinical, radiographic, laboratory, and/or histologic findings [46–49]. Moreover, many of these studies

Table 3. Factors We Suggest Guide Prescription of Suppressive Antibiotic Therapy Following DAIR

Factors strongly suggesting benefit from SAT after DAIR (the authors would offer SAT to most patients with at least 1 of these factors)
• Limited options for arthroplasty revision (ie, recurrent infection would require amputation, arthrodesis, or difficult wound coverage and likely result in a substantially worse functional outcome)a
• Recurrent PJI/prior PJI treatment failureb
• Infection with difficult-to-treat pathogens (*S. aureus*b and possibly othersa, eg *Pseudomonas aeruginosa* or Candida)
• Severe immunocompromise (ie, solid-organ or stem cell transplant, active chemotherapy, chronic systemic steroid therapy, TNF-inhibitor therapy, advanced HIV)a
• Underwent arthroscopy instead of open DAIR, or polyethylene liner was not exchangedb
Factors that may suggest benefit from SAT after DAIR (the authors would consider SAT in patients with at least 1 of these factors)
• Major end-organ disease predisposing to poor outcome (ie, cirrhosis, ESRD, or heart failure)b
• Age >75 y b or estimated life expectancy <10 ya
• Late hematogenous infection (onset >2 y after initial arthroplasty), particularly if associated with active bacteremiab
• Gram-negative infection that cannot be treated with a fluoroquinoloneb
• Patient strongly values the potential benefits of SAT over the potential risks after both have been explained in an informed shared-decision-making conversationa
Factors suggesting little benefit from SAT (the authors would not offer SAT to most patients with these factors)
• Completion of >6 wk of adjunctive rifampin for susceptible, monomicrobial coagulase-negative *Staphylococcus* spp. infection (as part of a minimum 3–6 mo total antibiotics)b
• Completion of a fluoroquinolone-based regimen for a gram-negative infectionb
• Culture-negative infectionb

Abbreviations: DAIR, debridement, antibiotics, and implant retention; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; PJI, prosthetic joint infection; SAT, suppressive antibiotic therapy; TNF, tumor necrosis factor.

[a]Based on the consensus opinion of the authors, but not directly supported by the data identified in this review.

[b]Based on retrospective data identifying this as a risk factor for treatment failure.

evaluated only a specific subset of PJIs. For example, several limited enrollment to patients with acute PJI (although the definition of "acute" also varied among the studies), 1 study was limited to late acute-onset infections, and another was limited to chronic PJI. Only 1 study occurred at an institution where all patients undergoing DAIR were systematically offered SAT; in the other 8 studies, treatment with SAT was limited to patients determined to be subjectively at higher risk of relapse, introducing selection bias. Finally, the only definition of treatment failure adhered to among all 9 studies was the need for revision surgery while on SAT, with many studies expanding this definition to include clinical findings as markers of SAT failure such as persistent pain, formation of a sinus tract, or death, as well as more subjective endpoints, such as "any outcome other than the absence of signs of infection" or simply "clinical signs of infection."

Determining the efficacy of SAT has been an elusive research goal, and these 9 studies illustrate how the many permutations of variables known to impact PJI prognosis confound attempts to isolate the impact of a single intervention. Small study sizes, the marked heterogeneity of the populations evaluated, use of different diagnostic criteria, different treatment approaches, and use of different endpoints in these studies were also major limitations. While the combined failure rate of 16.7% in these 9 studies is considerably better than what is typically reported as the failure rate following DAIR, providing some optimism that SAT may be beneficial, these data do not provide a definitive answer.

HOW WE SUGGEST PRACTICING BASED ON THESE DATA

Despite the paucity of literature supporting its utility, SAT is commonly used following DAIR in clinical practice, including by experienced Orthopedic Infectious Diseases specialists. Decisions to initiate and continue SAT should be based on multiple considerations. A risk versus benefit assessment should account for the perceived failure risk based on patient and infection factors known to predict treatment failure, whether further surgical intervention is feasible based on anatomic and implant conditions, whether the patient would be agreeable to future surgery (ie, the consequences of treatment failure), and the possible AEs related to antimicrobial therapy. The risks associated with long courses of antibiotics include allergic reactions, end-organ damage such as nephropathy and neuropathy, *C. difficile* infection, cost, and emergence of difficult-to-treat antimicrobial-resistant organisms (affecting both society and the individual patient); that said, AE profiles vary substantially between antibiotic classes, and patients who have already tolerated several months of a drug with a favorable long-term safety profile (eg, cefadroxil or doxycycline) often continue to do so. Because SAT is unlikely to be effective without good adherence and because unfavorable outcomes remain possible with or without SAT, the decision to pursue SAT should always be accompanied by comprehensive, transparent, shared decision making between the patient and clinician.

We propose risk–benefit stratification criteria (Table 3) to inform the use of chronic antibiotic suppression following DAIR for PJI, which are based on the limited literature identified in this review and reflect our consensus practice. These criteria facilitate decision making informed by the individual patient's risk of recurrent infection, the potential consequences of such a failure, and values and preferences. We suggest that SAT is most reasonable in patients at the highest risk of failure (eg, those with limited surgical source control, recurrent PJI, and/or difficult to treat pathogens) and those in whom further

failure is likely to have catastrophic functional impact due to limited remaining surgical options. On the other hand, in a modern randomized controlled trial, 3 months of antimicrobial therapy following DAIR without antimicrobial suppression led to durable cure in approximately 85% of cases, suggesting that most patients without multiple or strong risk factors for treatment failure (Table 1) may not benefit from indefinite SAT, as long as the initial antimicrobial therapy is optimal [8]. Limited durations of SAT may also be reasonable in patients for whom a delay in recurrent infection would be particularly valuable (eg, someone who needs a period of physical therapy to recover from serious deconditioning, or who has a trip overseas, family reunion, or other major life event scheduled in the months following the planned end of therapy). Finally, we acknowledge that research on patient preferences and values surrounding SAT for PJI is scant, making a single patient-centered approach to SAT difficult to define.

Once a patient begins SAT, the determination to continue or discontinue therapy should be reassessed on a regular basis. While earlier literature did not establish a period beyond which SAT ceases to delay or prevent infection, 2 modern retrospective cohort found no difference in treatment failure among patients with PJI who received 1 year versus longer durations of oral antimicrobial suppression following DAIR, suggesting that most of the benefit of SAT likely accrues in the initial months and that defined-duration SAT may be as effective as lifelong SAT [7, 12]. Rather than setting the expectation with patients initiating SAT that it must be continued lifelong, we suggest telling patients that whether to continue SAT should be revisited at the 1-year mark and that, in most cases, choosing to discontinue SAT at that point is reasonable. Careful monitoring of SAT via regular outpatient visits (typically, annual or biannual after an initial period of closer follow-up) should include assessment for symptoms and laboratory studies that could indicate an adverse reaction to the antimicrobial agent as well as a relapse or reinfection. Signs and symptoms of worsening infection or antibiotic-related AEs should be reviewed with the patient, along with anticipatory guidance about signs of recurrence. When SAT is pursued with a goal of suppressing infection to preserve and maintain functionality without the expectation of definitive cure, it is important to manage patient expectations and ensure that the patient understands the reasoning behind the decision to continue SAT as well as the potential risks and benefits.

CONCLUSIONS

We identified patient-, infection-, and treatment-related factors consistently associated with failure after DAIR for PJI, helping to define the subpopulation of patients with PJI most likely to benefit from chronic antimicrobial suppression. We propose risk–benefit stratification criteria to inform the use of SAT following DAIR for PJI. The biggest risk factors we identified included prior PJI treatment failure, difficult-to-treat pathogens, immunocompromising conditions, and suboptimal surgical or antimicrobial therapy (eg, shorter antimicrobial durations and nonreceipt of polyethylene liner exchange, open surgery, or specific agents such as quinolones and rifampin). Prospective randomized studies with long-term follow-up and standardized criteria for surgery, SAT, and treatment outcome are needed to determine if and for whom SAT truly prevents PJI treatment failure. Previous research has established risk-scoring tools predicting PJI treatment failure, such as KLIC and CRIME80; however, these have been inconsistently associated with treatment outcome in validation studies [52–54]. The data we have aggregated present the opportunity to develop more effective risk-scoring tools to identify patients likely to benefit from SAT following DAIR.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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