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SYSTEMATIC REVIEWS

Predicting lower limb periprosthetic joint infections: A review of risk factors and their classification

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Abstract

AIM

To undertook a systematic review to determine factors that increase a patient's risk of developing lower limb periprosthetic joint infections (PJI).

METHODS

This systematic review included full-text studies that reviewed risk factors of developing either a hip or knee PJI following a primary arthroplasty published from January 1998 to November 2016. A variety of keywords were used to identify studies through international databases referencing hip arthroplasty, knee arthroplasty, infection, and risk factors. Studies were only included if they included greater than 20 patients in their study cohort, and there was clear documentation of the statistical parameter used; specifically *P*-value, hazard ratio, relative risk, or/and odds ratio (OR). Furthermore a quality assessment criteria for the individual studies was undertaken to evaluate the presence of record and reporting bias.

RESULTS

Twenty-seven original studies reviewing risk factors relating to primary total hip and knee arthroplasty infections were included. Four studies (14.8%) reviewed PJI of the hip, 3 (11.21%) of the knee, and 20 (74.1%) reviewed both joints. Nineteen studies (70.4%) were retrospective and 8 (29.6%) prospective. Record bias was identified in the majority of studies (66.7%). The definition of PJI varied amongst the studies but there was a general consensus to define infection by previously validated methods. The most significant risks were the use of preoperative high dose steroids (OR = 21.0, 95%CI: 3.5-127.2, $P < 0.001$), a BMI above 50 (OR = 18.3, $P < 0.001$), tobacco use (OR = 12.76, 95%CI: 2.47-66.16, *P*

= 0.017), body mass index below 20 (OR = 6.00, 95%CI: 1.2-30.9, *P* = 0.033), diabetes (OR = 5.47, 95%CI: 1.77-16.97, *P* = 0.003), and coronary artery disease (OR = 5.10, 95%CI: 1.3-19.8, *P* = 0.017).

CONCLUSION

We have highlighted the need for the provider to optimise modifiable risk factors, and develop strategies to limit the impact of non-modifiable factors.

Key words: Periprosthetic joint infection; Risk factor; Predictive; Hip arthroplasty; Knee arthroplasty

Core tip: This systematic review determines the most statistically significant factors that increase a patient's risk of developing lower limb periprosthetic joint infections. Reviewing all relevant papers until November 2016 through international databases, we have included 27 original studies. The results include multiple factors relating to the patient and the Institute, as well as post-operative predictors and causes of infection. This ultimately reiterates the importance of optimising the patients pre-operatively by addressing modifiable risk factors (such as their immunosuppression, nutrition, diabetes, and smoking), and develops strategies to limit the impact of non-modifiable factors.

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INTRODUCTION

Chronic periprosthetic joint infections (PJI) have received increasing interest in the medical literature as the profession has acknowledged the real-life implications to the patient and the health service[1,2]. The treatment of PJI is costly to the health service with strain upon limited resources as multiple operations and trials of antibiotic therapy may be attempted. But the cost to the patient is greatest, with loss or reduced joint function, deterioration in their physical and psychological health, and loss in trust with the profession.

Prevention is key. Despite improved outcomes following the various treatment modalities for treating established infections today, the patient has to endure the consequences of the infection[3]. Prior to the initial surgery it is imperative the patient is medically optimised and any reversible risk factors be corrected. Such risk factors are well known such as diabetes[4], systemic infections[5], and immunocompromise[6].

However, risk factors vary and are dependent upon the patient cohort, and often findings from isolated studies are not transferable. Therefore, we undertook a systematic review of the literature to determine overall predictive factors that increase a patient's risk of developing a lower limb PJI, and determine which risk factors are most predictive of infection.

In this review, we categorised risk factors in order to better understand the relative role of the host, of the healthcare provider, and of post-surgical conditions, the latter acting more as prognostic factors since the surgical procedure has already taken place. To this aim, we have subdivided known risk factors for PJI in three groups: (1) those relating to the host (host-related risk factors); (2) those that are related to the treatment provider and to the surgical environment (provider-related risk factors); and (3) those that arise from clinical interventions, increasing the patient's inherent risk (post-surgical risk factors). We have then compared the absolute number of risk factors in each main category, scored them according to their relative weight and divided in "modifiable" and "non-modifiable" risk factors.

MATERIALS AND METHODS

This systematic review included full-text studies that reviewed risk factors of developing either a hip or knee PJI following a primary arthroplasty published from January 1998 to November 2016. These were identified through international databases, such as EMBASE, PubMed/MEDLINE, MEDLINE Daily Update, MEDLINE In-Process, Google Scholar, SCOPUS, CINAHL, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.

A variety of keywords were used either alone or in combinations to identify the studies. This included references to hip infections (total hip replacement; THR; periprosthetic hip infection, hip arthroplasty infection), knee infections (total knee replacement; TKR; periprosthetic knee infection, knee arthroplasty infection), general joint infections (PJI, PPI), and "risk factors". We did not use specific keywords to search for individual risk factors, such as diabetes, *etc*.

Studies were only included if the risk factors were calculated by involving greater than 20 patients in their study cohort, and there was clear documentation of the statistical parameter used, and were only included if the P-value was quoted and one or more of the following; hazard ratio (HR), relative risk (RR), or/and odds ratio. Studies were excluded if they referred to recurrent infection following a revision procedure, hip or knee fracture, and a risk factor was excluded if the *P*-value was greater than 0.05. Results from combined studies, as seen in meta-analysis, were also excluded.

Two investigators, DAG and CLR, independently searched and reviewed the literature and determined if the study should be included based on their title and abstract. Once the two lists were compared, if the same material was presented in more than one study, only the most recent one was included.

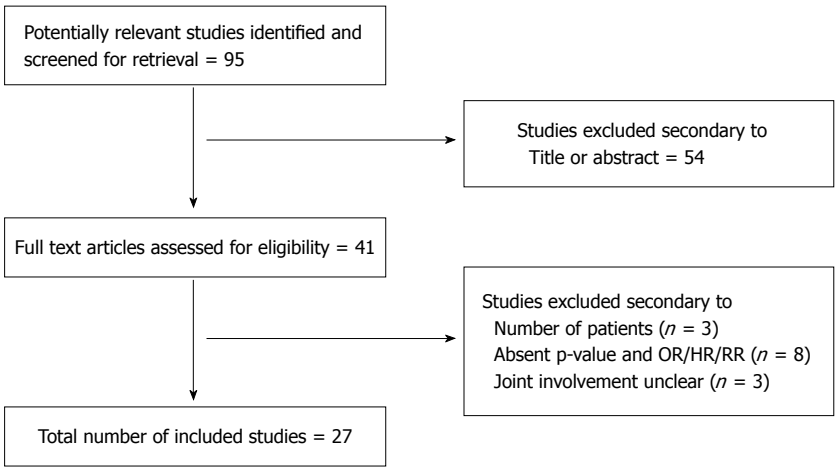

Figure 1 Flowchart summarizing the results of the literature search. RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 1 Study characteristics including number of patients, statistical method used, site (hip, knee or both), and duration of patient follow-up

Ref.	Year	Patients (*n*)			Statistical method used	Site	Follow-up (mo)		
		Infected (cases)	Non-infected (controls)	Total			Min	Max	Mean
Berbari *et al*[9]	1998	462	462	924	OR, CI, *P*	Both	-	-	-
Lai *et al*[10]	2007	51	-	-	OR, CI, *P*	Both	-	84	-
Parvizi *et al*[11]	2007	78	156	234	OR, CI, *P*	Both	-	-	-
Pulido *et al*[12]	2008	63	9182	9245	HR, CI, *P*	Both	12	72	43
Malinzak *et al*[13]	2009	43	8451	8494	OR, *P*	Both	24	192	74.4
Ong *et al*[14]	2009	887	39042	39929	OR, *P*	Hip	-	108	-
Berbari *et al*[5]	2010	339	339	678	OR, CI, *P*	Both	-	-	-
Peel *et al*[15]	2011	63	126	189	OR, CI, *P*	Both	-	-	-
Bozic *et al*[16]	2012	-	-	40919	HR, CI, *P*	Hip	12	-	-
Jämsen *et al*[17]	2012	52	7129	7181	HR, CI, *P*	Both	0	12	12
Bozic *et al*[4]	2012	-	-	83011	OR, CI, *P*	Knee	12	-	-
Dale *et al*[18]	2012	2778	429390	432168	RR, CI, *P*	Hip	0	60	60
Greenky *et al*[19]	2012	389	15333	15722	OR, CI, *P*	Both	36	108	62.4
Namba *et al*[20]	2013	404	55812	56216	HR, CI, *P*	Knee	-	-	-
Somayaji *et al*[21]	2013	5	254	259	OR, CI, *P*	Both	12	124	24
Coelho-Prabhu *et al*[22]	2013	339	339	678	OR, CI, *P*	Both	2	24	-
Maoz *et al*[23]	2014	47	3625	3672	OR, CI, *P*	Hip	12	48	24
Gómez-Lesmes *et al*[24]	2014	32	1299	1331	OR, CI, *P*	Knee	-	3	-
Yi *et al*[25]	2014	126	375	501	OR, CI, *P*	Both	3	-	-
Wu *et al*[26]	2014	45	252	297	OR, CI, *P*	Both	12	144	28
Sousa *et al*[27]	2014	43	2454	2497	OR, CI, *P*	Both	1	12	12
Jiang *et al*[28]	2014	-	-	306946	HR, *P*	Hip	6	-	-
	2014	-	-	573840	HR, *P*	Knee	6	-	-
Duchman *et al*[29]	2015	8062+	70129+	78191	OR, CI, *P*	Both	-	-	-
Chrastil *et al*[30]	2015	-	-	13272	HR, CI, *P*	Both	24	120	-
Crowe *et al*[31]	2015	26	3393	3419	OR, CI, *P*	Both	-	12	-
Debreuve-Theresette *et al*[32]	2015	45	90		OR, CI, *P*	Both	-	-	-
Bohl *et al*[33]	2015	-	-	49603	RR, CI, *P*	Both	-	1	-

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

The quality assessment criteria for the inclusion of the individual studies was adapted from George *et al*[7]. to reflect the information we expect to be present in each study. Therefore we evaluated the presence of (1) record bias reflecting the source of data, and whether the analysis was retrospective or prospective; and (2) reporting bias; each study's definition of PJI (the measured outcome).

Figure 1 demonstrates the overall selection process according to the Prisma model[8]. DAG, CLR, SS and EG compared the overall findings and any discrepancies were solved by reclassification as mutually agreed.

RESULTS

Included studies

In all, 27 original studies reviewing risk factors relating to primary total hip and knee arthroplasty infections were included. The number of risk factors identified ranged from 1 to 18. Four studies (14.8%) reviewed PJI on the hip, 3 (11.21%) on the knee, and 20 (74.1%) reviewed both joints. The statistical methods used to determine significance are also shown in Table 1[4,5,9-33].

The quality of the included studies is demonstrated in Table 2. Nineteen studies (70.4%) were retrospective

Table 2 Paper quality, defined by presence of record and reporting bias

Ref.	Design	Record bias	Reporting bias (outcome measure); definition of infection
Berbari *et al*[9]	Retrospective	No	2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint
Lai *et al*[10]	Retrospective	No	2 or more cultural examination positive for the same microorganism; clinical diagnosis
Parvizi *et al*[11]	Prospective	No	Criteria based upon 3 of 5 features[1]
Pulido *et al*[12]	Retrospective	Yes	Criteria based upon 3 of 5 features[1]
Malinzak *et al*[13]	Retrospective	No	Unknown
Ong *et al*[14]	Retrospective	Yes	Diagnostic code in Medicare database
Berbari *et al*[5]	Prospective	Yes	2 or more cultural examination positive for the same microorganism; acute inflammation on histopathological examination; sinus tract; purulence around the prosthesis/joint
Peel *et al*[15]	Prospective	Yes	Criteria based upon 3 of 5 features[1]
Bozic *et al*[16]	Retrospective	Yes	Diagnostic code in Medicare database
Jämsen *et al*[17]	Prospective	Yes	CDC definition of surgical site infection[3]
[1]Bozic *et al*[4]	Retrospective	Yes	Diagnostic code in Medicare database
Dale *et al*[18]	Retrospective	Yes	Clinical as reported by the surgeon after surgery
Greenky *et al*[19]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Namba *et al*[20]	Retrospective	Yes	CDC definition of surgical site infection[3]
Somayaji *et al*[21]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Coelho-Prabhu *et al*[22]	Retrospective	Yes	2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint
Maoz *et al*[23]	Retrospective	Yes	CDC definition of surgical site infection[3]
Gómez-Lesmes *et al*[24]	Prospective	Yes	Criteria based upon 3 of 5 features[1]
Yi *et al*[25]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Wu *et al*[26]	Retrospective	Yes	MSIS definition[2]
Sousa *et al*[27]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Jiang *et al*[28]	Prospective	Yes	Diagnostic code in Medicare database
Duchman *et al*[29]	Prospective	Yes	Criteria based upon 3 of 5 features[1]
Chrastil *et al*[30]	Retrospective	Yes	Diagnostic code in Medicare database
Crowe *et al*[31]	Retrospective	Yes	CDC definition of surgical site infection[3]
Debreuve-Theresette *et al*[32]	Retrospective	No	CDC definition of surgical site infection[3]
Bohl *et al*[33]	Prospective	Yes	American College of Surgeons National Surgical Quality Improvement Program definition

[1]Refers to 3 of 5 of the following criteria: (1) abnormal serology (ESR > 30 mm/h; CRP > 1 mg/dL); (2) strong clinical and radiographic suspicion for infection; (3) positive joint aspiration culture for infection; (4) evidence of purulence during the subsequent surgical intervention; and (5) positive intraoperative culture; [2]Musculoskeletal Infection Society (MSIS) definition; [3]Defined as (1) deep infection; (2) purulent drainage; (3) dehiscence; (4) fever; and (5) localized pain. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

and 8 (29.6%) prospective. Record bias was identified in the majority of studies (66.7%). The definition of PJI varied amongst the studies but there was a general consensus to define infection by previously validated methods.

This included the presence of 2 or more cultural positive results for the same microorganism (plus other features on infection) in 4 studies (14.8%), the CDC definition in 5 studies (18.5%), the Medicare code for infection in 5 studies (18.5%), and 9 studies (33.3%) based their definition on patients meeting 3 of the following 5 features; (1) abnormal serology (ESR > 30 mm/h; CRP > 1 mg/dL); (2) strong clinical and radiographic suspicion for infection; (3) positive joint aspiration culture for infection; (4) evidence of purulence during the subsequent surgical intervention; and (5) positive intraoperative culture.

One study used the MSIS criteria, which includes: (1) a sinus tract; (2) positive culture results from 2 or more tissue or fluid samples; and (3) 4 of the following 6 criteria are present: (Ⅰ) elevated CRP/ESR; (Ⅱ) elevated synovial WCC; (Ⅲ) high synovial PMN leukocyte percentage; (Ⅳ) presence of purulence in the joint; (Ⅴ) positive culture result from one sample from the affected joint; and (Ⅵ) PMN leukocyte count of more than 5 per high-powered field in 5 high-powered fields on histologic analysis at 400 × magnification[34].

Host-related risk factors

Risk factors relating to the host have been shown in Table 3, and are the most abundant group of risk factors identified. The majority of the risk factors are systemic referring to patient co-morbidities that are negatively associated with patient outcome following a primary THR or TKR, such as presence of diabetes mellitus[4,9,17,20,26], immunocompromised[5,15,21], concomitttent systemic infection[5,10,27,31], cardiology[4,16,21] and gastroenterology disorders[22,28], high ASA (American Society of Anesthesiologists) grade[12,15,20] and mal-nutrition[13,17,21,23,25,26,33].

Patient demographics also have been shown to have an impact upon risk of PJI, including age[16], rural residence[16], race[20], male gender[14,18,20,31], and alcohol[26] or tobacco use[23,29,31,32]. Previous operations to the joint (excluding revisions arthroplasty as this was excluded from analysis) increased the risk of PJI[5,32].

Table 3 Host-related risk factors

	Ref.	Statistical parameter					Site
		HR	OR	RR	95%CI	*P* value	
General							
Age: 65-75 yr (compared to 45-65)	[26]		3.36		1.30-8.69	0.013	Hip/knee
Comorbidities (total number)	[10]		1.35		1.10-1.66	0.005	Hip/knee
Charlson index + 5 (compared to 0)	[14]		2.57		1.96-3.37	< 0.001	Hip
Place of residence (rural)	[26]		2.63		1.13-6.10	0.025	Hip/knee
Hispanic race (compared to White)	[20]	0.69			0.49-0.98	0.038	Knee
Alcohol abuse	[26]		2.95		1.06-8.23	0.039	Hip/knee
Tobacco use	[29]		1.47		1.21-1.78	0.001	Hip/knee
	[31]		3.4		1.23-9.44	0.029	Hip/knee
	[32]	3.91	3.4		1.19-12.84	0.032	Hip/knee
Tobacco use (S aureus colonization)	[23]		12.76		2.47-66.16	0.017	Hip
Gender							
Female	[14]		0.83			0.009	Hip
Male	[18]			1.9	1.80-2.10	< 0.001	Hip
	[20]	1.89			1.54-2.32	< 0.001	Knee
	[31]		3.55		1.60-7.84	0.002	
Endocrine disorders							
Diabetes mellitus	[4]		1.19		1.06-1.34	0.0025	Knee
	[26]		5.47		1.77-16.97	0.003	Hip/knee
	[22]	1.46			1.27-1.68	0.0007	Hip
	[9]		4		1.13-14.18	0.032	Hip/knee
	[20]	1.28			1.03-1.60	0.025	Knee
	[17]	2.31			1.12-4.72	< 0.001	Hip/knee
	[15]		1.4		0.90-2.10	0.06	Hip/knee
	[5]		1.8		1.20-2.80	0.006	Hip/knee
	[13]		3.1			0.02	Hip/knee
	[44]		2.21		1.34-3.64	0.001	Knee
Pre-op BM > 6.9 mmol/L	[17]	2.25			0.60-8.50	0.073	Hip/knee
Pre-operative hyperglycemia	[30]	1.44			1.09-1.89	0.008	Hip/knee
Psychiatric disorders							
Depression	[4]		1.28		1.08-1.51	0.0035	Knee
	[16]	1.6			1.32-1.93	0.0039	Hip
Psychosis	[16]	1.74			1.38-2.20	0.0044	Hip
	[4]		1.26		1.02-1.57	0.0331	Knee
Haematological disorders							
Preoperative anaemia	[16]	1.36			1.15-1.62	0.0005	Hip
	[19]		1.95		1.41-2.69	< 0.001	Hip/knee
	[4]		1.26		1.09-1.45	0.0014	Knee
Coagulopathy	[16]	1.58			1.24-2.01	0.0002	Hip
Malignancy							
Metastatic malignancy	[4]		1.59		1.03-2.47	0.0369	Knee
Tumour 5 yr before implant	[5]		3.1		1.30-7.20	< 0.01	Hip/knee
Cardiovascular disorders							
Congestive heart failure	[4]		1.28		1.13-1.46	< 0.0001	Knee
	[16]	1.57			1.33-1.84	0.0409	Hip
Cardiac arrhythmia	[16]	1.48			1.30-1.70	0.0012	Hip
Coronary artery disease	[21]		5.10		1.30-19.8	0.017	Hip/knee
Valvular disease	[4]		1.15		1.01-1.31	0.039	Knee
Peripheral vascular disease	[4]		1.13		1.01-1.27	0.0381	Knee
	[16]	1.44			1.24-1.68	0.0032	Hip
Gastroenterology disorders							
Liver cirrhosis	[28]	5.4				< 0.001	Hip
	[28]	3.4				< 0.001	Knee
Hepatitis B virus (amongst males)	[44]		4.32		1.85-10.09	< 0.001	Knee
OGD with biopsy	[22]		2.8		1.10-7.10	0.03	Hip/knee
Respiratory disorders							
Chronic pulmonary disease	[4]		1.22		1.10-1.36	< 0.0001	Knee
	[31]		4.34		1.28-14.70	0.041	Both
Pulmonary circulation disorders	[4]		1.42		1.06-1.91	0.0205	Knee
Renal disorders							
Renal disease	[4]		1.38		1.11-1.71	0.0038	Knee
Renal function (mL/min)	[15]		1		0.90-1.00	0.05	Hip
Rheumatoid arthritis							
Rheumatoid arthritis	[15]		3.3		0.80-13.90	0.09	Hip/knee
	[4]		1.18		1.02-1.37	0.0277	Knee
	[16]	1.71			1.42-2.06	< 0.0001	Hip

ASA grade						
ASA score	[15]		2.2	1.30-4.00	0.006	Hip/knee
Mean score	[11]		2.07	1.08-1.97	0.03	Hip/knee
3 (compared to 1 or 2)	[20]	1.65		1.33-2.00	< 0.001	Knee
> 4	[12]	1.95		1.00-3.70	0.04	Hip/knee
Body mass index						
Obesity	[4]		1.22	1.03-1.44	0.0219	Knee
	[16]	1.73		1.35-2.22	< 0.0001	Hip
BMI (kg/m^2)	[15]		1.1	1.00-1.10	0.05	Hip
	[12]	3.23		1.60-6.50	0.001	Hip/knee
< 20	[21]		6	1.20-30.9	0.033	Hip/knee
25-30	[5]		0.4	0.30-0.70	< 0.001	Hip/knee
⩾ 28 (compared to 18.5-28)	[26]		2.77	1.20-6.40	0.017	Hip/knee
31-39	[5]		0.5	0.30-0.70	< 0.001	Hip/knee
35 (compared to < 35)	[20]	1.47		1.17-1.85	0.001	Knee
	[32]	1.84		1.11-3.05	0.007	Both
> 40	[23]		4.13	1.30-12.88	0.01	Hip
	[13]		3.3		0.045	Knee
	[17]	6.41		1.67-24.59	< 0.001	Hip/knee
> 50	[13]		18.3		< 0.001	Hip/knee
Malnutrition	[25]		2.3	1.50-3.50	< 0.001	Hip/knee
Serum albumin < 3.5 g/dL	[33]		2	1.50-2.80	< 0.001	Hip/knee
Immunocompromise						
Immunocompromise	[5]		2.2	1.60-3.00	< 0.001	Hip/knee
Inflammatory disease	[18]		1.4	1.10-1.70	0.001	Hip
Prednisone dose exceeds 15 mg/d	[21]		21	3.50-127.2	< 0.001	Hip/knee
Systemic steroid therapy	[15]		3.3	0.80-13.90	0.09	Hip/knee
Infection						
Distant organ infection	[5]		2.2	1.50-3.25	< 0.001	Hip/knee
Nasal *S. Aureus* Infection	[31]		3.95	1.80-8.71	< 0.001	Hip/knee
Nasal MRSA Infection	[31]		8.24	3.23-21.02	< 0.001	Hip/knee
Asymptomatic bacteriuria	[27]		3.23	1.67-6.27	0.001	Hip/knee
Genitourinary infection	[10]		2.8	1.01-7.77	0.048	Hip/knee
Operative indication						
Hip fracture	[18]		2.1	1.90-2.40	< 0.001	Hip
Post-traumatic osteoarthritis	[20]	3.23		1.68-6.23	< 0.001	Knee
Prior operation on the index joint	[5]		1.9	1.30-2.60	< 0.001	Hip/knee
Per additional surgery	[32]		2.88	1.45-5.80	0.018	Hip/knee
Avascular necrosis	[18]		1.7	1.40-2.10	< 0.001	Hip

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Provider-related risk factors

Risk factors relating to the provider are shown in Table 4. Prolonged operative duration of greater than 115 minutes in hip arthroplasty is a strong predictor of infection[5,14,23], as is non-same day surgery[23]. During knee arthroplasty, exposure to the joint requiring quadriceps release significantly increases the risks of infection[20].

Protective measures include the use of antibiotic surgical prophylaxis systemically[5] and locally as irrigation[20], but antibiotic impregnated cement may or may not be protective[18,20]. In addition, bilateral procedures during the same operation have been shown by some studies to increase the risk[12], whilst in others decrease it[20].

Post-surgical risk factors

Post-operatively patients may present with a superficial infection to the joint with a warm, cellulitic, and sometimes discharging wound, which is a high predictor of an underlying PJI[5,11,9,15]. Table 5 demonstrates other factors that have a high correlation with a PJI, including receiving a blood transfusion[11,12,15] (especially if the blood has been stored for greater than 14 d[24]), post-operative urinary tract infection (UTI)[5,12], and onset of cardiac arrhythmias[12].

Risk factor impact

Several risk factors were shown to have greater significance than others, and a vast majority of the risk factors were directly related to the patient (host-factors). The most significant risks were the use of preoperative high dose steroids (OR = 21.0, 95%CI: 3.5-127.2, $P < 0.001$)[21], a BMI above 50 (OR = 18.3, $P < 0.001$)[13], tobacco use (OR = 12.76, 95%CI: 2.47-66.16, $P = 0.017$)[23], BMI below 20 (OR = 6.00, 95%CI: 1.2-30.9, $P = 0.033$)[21], diabetes (OR = 5.47, 95%CI: 1.77-16.97, $P = 0.003$)[26], and coronary artery disease (OR = 5.10, 95%CI: 1.3-19.8, $P = 0.017$)[21].

Modifiable risk factors

We further categorised the resultant risk factors into whether or not they were modifiable, reflecting the opportunity of the surgeon to optimise their patient preoperatively and to reduce the risk of developing a PJI (Table 6).

DISCUSSION

It is extremely difficult to predict if a patient will develop a

Table 4 Provider-related risk factors

	Ref.	Statistical parameter					Site
		HR	OR	RR	95%CI	*P* value	
Antibiotic use							
Antibiotic surgical prophylaxis	[5]		0.5		0.30-0.80	0.003	Hip/knee
Antibiotic irrigation	[20]	0.67			0.48-0.92	0.014	Knee
Surgical technique							
Exposure requiring quadriceps release	[20]	4.76			1.18-19.21	0.029	Knee
Use of wound drain tube	[15]		0.09		0.01-0.80	0.03	Knee
Side of surgery							
Simultaneous bilateral surgery	[12]	5.85			2.50-13.90	< 0.0001	Hip/knee
	[20]	0.51			0.31-0.83	0.007	Knee
Single side (compared to bilateral)	[13]		3.1			0.0024	Hip/knee
	[13]		4			0.009	Knee
Cement							
Antibiotic-laden cement	[20]	1.53			1.18-1.98	< 0.001	Knee
Non-antibiotic cement	[8]			1.5	1.30-1.80	< 0.001	Hip
Hybrid (compared to uncemented)	[8]			1.6	1.40-1.80	< 0.001	Hip
Operative duration							
Length of operation (> 115 min)	[23]		3.38		1.23-9.28	0.018	Hip
(> 210 min)	[14]		1.78		1.40-2.26	< 0.0001	Hip
(≥ 240 min)	[5]		2.7		1.50- 5.00	0.002	Hip/knee
Hospital factors							
Hospital volume < 100 (*vs* > 200/yr)	[20]	0.33			0.12-0.90	0.03	Knee
Medicare buy-in	[14]		1.34			0.005	Hip

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 5 Post-surgical risk factors

	Ref.	Statistical parameter				Site
		HR	OR	95%CI	*P* value	
Anaesthetic factors						
Intensive care length of stay (d)	[15]		0.5	0.20-1.00	0.06	Knee
Haematological						
Blood transfusion	[12]	2.11		1.10-3.90	0.02	Hip/knee
	[15]		2.1	1.00-4.20	0.04	Hip/knee
	[11]		1.63	1.14-2.33	0.007	Hip/knee
Transfusion if RBCs stored > 14 d	[24]		5.9	2.60-13.20	< 0.001	Knee
Perioperative blood loss (*via* drain tube)	[15]		1	1.00-1.01	0.008	Hip
Cardiac						
Postoperative atrial fibrillation	[12]	6.22		1.40-28.5	0.02	Hip/knee
Postoperative myocardial infarction	[12]	20.4		2.10-199.9	0.009	Hip/knee
Hospital factors						
Longer hospital stay	[12]	1.09		1.00-1.10	0.0003	Hip/knee
Non same-day surgery	[23]		4.16	1.44-12.02	0.008	Hip
Wound complications						
All wound complications	[11]		27	11.00-91.6	0.0002	Hip/knee
Wound discharge	[5]		18.7	7.40-47.2	< 0.001	Hip/knee
	[15]		6.3	1.30-30.7	0.02	Knee
	[15]		5.4	2.00-15.0	0.001	Hip
	[15]		5.7	2.40-13.3	<0.001	Hip/knee
	[11]		32.2	8.7-119.17	< 0.0001	Hip/knee
Haematoma	[5]		3.5	1.30-9.50	0.01	Hip/knee
Surgical site infection	[1]		35.9	8.30-154.6	< 0.01	Hip/knee
Superficial incisional SSI	[15]		3.7	1.10-11.9	0.03	Knee
	[15]		5	1.60-15.9	0.007	Hip
	[15]		4.3	1.90 - 9.90	0.001	Hip/knee
NNIS risk index 2	[9]		3.9	2.00-7.50	< 0.01	Hip/knee
Urinary						
Postoperative urinary infection	[12]	5.45		1.00-8.70	0.04	Hip/Knee
	[5]		2.7	1.04-7.10	0.04	Hip/Knee

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 6 Classification of risk factors and probability of infection (main factors)

	Risk factor	Minimum increase	Maximum increase	Statistical parameter	Ref.
Host-related risk factors					
Modifiable	Systemic steroids	3.3	21	OR	[15,21]
	Tobacco use	3.4	12.76	OR	[23,32]
	Nasal MRSA infection	-	8.24	OR	[31]
	BMI < 20	-	6	OR	[21]
	Coronary artery disease	-	5.1	OR	[21]
	COPD	1.22	4.34	OR	[4,31]
	BMI > 40	-	4.13	OR	[23]
	Pre-operative BM	-	2.25		[17]
Non-modifiable	Diabetes	1.4	5.47	OR	[15,26]
	Liver cirrhosis	-	5.4	HR	[28]
	Male	1.89	3.55	HR,OR	[20,31]
	Age	-	3.36	OR	[26]
	Rheumatoid arthritis	1.18	3.3	OR	[4,15]
	Malignancy	-	3.1	OR	[5]
Provider-related risk factors					
Modifiable	Quadriceps release (TKR)	-	4.76	HR	[20]
	Non-same day procedure	-	4.16	OR	[23]
	Prolonged operation	1.78	3.38	HR	[14,23]
Non-modifiable	Prolonged storage of blood	2.6	13.2	OR	[24]

BMI: Body mass index; RR: Relative risk; HR: Hazard ratio; OR: Odds ratio; COPD: Chronic obstructive pulmonary disease; TKR: Total knee replacement.

post-operative infection following lower limb arthroplasty. Multiple prospective and retrospective studies have reviewed the risks associated with their patient cohort developing such infections. This paper was undertaken to combine these risks and determine if there was a consensus to which factors puts a patient at highest risk, and categorise them if they related directly to the host (patient), provider (the surgical team and their Institute), or occurred during the post-operative period.

Little is known about the interaction between, or synergistic effect, of specific patient risk factors[35], as it is likely they have a multiplicity effect, rather than additive risk, as shown by Tomás[6]. In their cohort if a patient had two (or more) significant factors the probability of infection development was 14-times higher, whereas having three (or more) factors the probability was increased 16-times.

Several themes have emerged following this systematic review of the literature, specifically the patient's immunological and systematic responses to infection, other sources of infection, antibiotic use, and provider factors.

Immunological response

The most frequently quoted risk factor was diabetes mellitus[4,9,17,20,22,26], which had one of the highest odds ratios[26]. Almost all the other highest odds ratio, or hazard ratio, also belonged to medical conditions ultimately impairing a patients immunity, as demonstrated from high dose pre-operative steroids[21], malnutrition (reflective of high alcohol intake[26], BMI below 20[21] and above 50[13]), and tobacco use[23]. Malignancy[4,5], rheumatoid arthritis[4,15,16], and liver cirrhosis[28] can also impair a patient's immunity.

Immunosuppression has long been known to increase a patient's risk of systemic infection, and has widely been documented in arthroplasty patients. Ragni *et al*[36] demonstrated this in human immunodeficiency virus-positive hemophiliacs with CD4 counts of 200 mm^3 or less undergoing orthopaedic surgery. Post-operative infection occurred in 10 (15.1%) of 66 patients[36]. Local steroid injection causing focal immunosuppression about the joint has also been shown to increase the risk, compared to those that have not received any joint injections in hip arthroplasty cases[37].

In rheumatoid patients treated with immunosuppressive drugs (including biologic agents) undergoing all orthopeadic procedures, a statistically significant higher risk of infection was seen in this patient cohort compared to a degenerative/post-traumatic group (OR = 2.58, 95%CI: 1.91-3.48, $P < 0.001$)[38]. Furthermore this risk was significantly increased in patients taking multiple disease-modifying antirheumatic drugs (DMARDs) ($P = 0.036$) or tumor necrosis factor α (TNFα) inhibitors ($P = 0.032$), especially if the last dose of TNFα inhibitor was given < 1 administration interval before surgery[38].

Infection response

While not directed specifically to immunosuppression, other co-morbidities have a role in reducing the patients systemic response to infection. Cardiac dysfunction[4,16,21], renal failure[4,15], anaemia[4,9,16] and coagulopathy[16] have all been shown to increase the risk of infection. This may be directed through specific cellular pathways[39], but may demonstrate the insult the surgical procedures has in causing a secondary inflammatory insults, worsening multiple organ dysfunction[40,41].

Deranges in renal function, with progressively higher poor glomerular filtration rate (GFR) in either the acute or chronic stages, reduces the ability to remove unwanted and hazardous chemicals from the blood, and places the patient at a higher risk. Lieberman *et al*[42] demonstrated

a high rates of infection in patients on chronic renal dialysis (19%), however in a separate patient series no significant increase in infection risk was seen[43].

Infection source

We believe that if a patient is known to have systemic infection, or a localised infection but distant to the operative joint, the risk of haematological spread of infection to the implant is highly likely. We have demonstrated a statistically significant increased risk of PJI in patients with a pre-operative confirmation of a genitourinary infection[10,27], nasal *S. Aureus* and *MRSA* infections[31], or other distant organ infections[6], such as hepatitis B[44].

Conditions that further increase this risk are those that may make the patient more susceptible for the introduction of a new pathogen, such as chronic pulmonary disease[4,31] with known high rates of pneumonia, peripheral vascular disease[4,16] with high risk of skin ulceration and introduction of skin contaminates, and recent oesophagogastroduodenoscopy (EGD) with biopsy[22], risking the introduction of gut flora to the blood system.

Furthermore, perioperative blood transfusion increases the risk of PJI in both hip and knee arthroplasty[11,12,15], and allogeneic blood transfusion has been shown to instigate a detrimental immunomodulation reaction, and decreases T-cell-mediated immunity, and may enhance the acute inflammatory response[45,46]. Stored blood can cause a significant increase in inflammatory cytokine release from the stored neutrophils, and superoxide release results in delaying neutrophil apoptosis and risks cytotoxicity[47,48].

This has been confirmed in a recent systematic meta-analysis of 6 studies demonstrating the association between allogeneic blood transfusion and an increased risk for a SSI after total hip and knee arthroplasty. Data was included from over 20000 patients, and the blood transfusion group had a significantly higher frequency of infection (pooled OR = 1.71, 95%CI: 1.23-2.40, P = 0.002) compared to the non-exposed group[49].

Antibiotic use

The use of antibiotic-impregnated cement was shown by Dale *et al*[18] to protect against revisions due to infection, whereas Namba *et al*[20] identified an increased risk. Such conflicting outcomes are common in the literature regarding the use of antibiotic-impregnated cement in primary procedures. A prospective randomized study with 2948 cemented total knee arthroplasties failed to see an improvement of PJI rates by using bone cement loaded with erythromycin and colistin compared to controls[50], whereas the Norwegian Arthroplasty Register has demonstrated a synergistic effect of systemic and cement antibiotics[51]. However there is a general consensus that antibiotic-impregnated cement has a greater role in revision cases[52], and is recommended as standard practice in these high-risk cases[53].

Systemic antibiotics given at anaesthetic induction are generally the standard of care, and continued post-operatively for a further two doses in the United Kingdom, and for two days in Italy (authors experience). The choice of antibiotic varies in each Institute to reflect the prominent pathogen and patient cohort. Multiple studies have demonstrated the benefits of antibiotics given during the procedure to reduce the risk of post-operative infection[51,54].

Provider factors

Concerning the relative impact of the hospitals yearly volume of procedures, we found only one retrospective review of joint registry data, that suggests that the fewer total knee arthroplasties undertaken per year will result in a lower rate of infection[20]. This particular finding needs, in our opinion, further validation, since it contradicts other reports demonstrating better outcomes from greater volumes of surgery and greater experience of the surgeons, as exemplified by the Hospital for Special Surgery, New York[55], while other studies have shown no difference between the two[56].

Furthermore, the use of a drain post-operatively has been shown by Peel *et al*[15] to reduce the risk of PJI following knee arthroplasty, however multiple meta-analyses and prospective, randomised, controlled trials have demonstrated no significant difference in post-operative infections between the wounds treated with a drain and those without[57,58].

Modifiable risk factors

When the risk factors were further categorised into modifiable or not, the vast majority of factors were non-modifiable. Many risk factors increased a patient's risk by less than 5 times (OR < 5), and very few increased the risk by more than 10 times.

However, the presence of non-modifiable risk factors still requires attention, and may be more important than modifiable ones. Alternate methods should be adopted to reduce the patient's burden and may include a combination of implant modifications (such as silver or disposable microbiological coatings)[59,60], antibiotic impregnated cement or bone graft[61,62], or other novel therapies[63] to provide a personalized and more effective prophylaxis.

It is the responsibility of the operating team to act upon these, and modify or optimise the patient prior to surgery. For example, intensive insulin therapy, maintaining tight blood glucose concentrations between 80 and 110 mg/dL, has been shown to decrease infection-related complications and mortality[64]. Normal renal function should be sought, nutrition improved, cardiac investigations and interventions should be offered, local and systemic infections appropriately treated, as should chronic anaemia, and patients should be informed to withhold DMARDs and stop tobacco smoking and alcohol use preoperatively.

Risk-analysis tools

Indeed, determining individual patients risks is an important step in personalized informed consent. Surgeons may quote published rates or their own, but the risk

is individual and should reflect all the aforementioned factors, which may have consequences in the medico-legal evaluation in case of damage evaluation after PJI.

Previous attempts to combine such measures in a scoring system have been attempted by The Mayo Clinic[65] who based the data on their cohort of patients at baseline and at one month. Bozic *et al*[35] developed a risk calculator using data from 11 years worth of Medicare claims. A similar tool has been developed in the Chinese population[26].

The main disadvantage of such tools is the calculations relate to a specific set of patients, and may not reflect the general public risks, as they have not been externally validated. In addition the data is unlikely to appreciate advances in perioperative care over the time period, and may not capture patients with late onset PJI if follow-up is short.

Limitations

A wide variety of studies were included in this systematic review, which gives an overview of risk factors for hip and knee PJI but the quality of each study is generally poor. As previously discussed, only 8 studies (29.6%) were prospective, and one third of studies demonstrated record bias. Reporting bias was also seen amongst the studies, as a variety of diagnostic criteria were used. This is common amongst studies reviewing PJI as there is no gold standard measure to determine presence of infection, nor an agreement to the medical, or surgical management, for these patients[53].

Our search criteria only highlighted studies with "risk factor" in the title, and therefore we did not search for studies looking at individual risk factors. Therefore studies, some of high quality, may not have met our inclusion criteria. Furthermore, we were unable to undertake a meta-analysis due to the heterogeneity of the data.

In conclusion, as demonstrated, current data is conflicting as the influence of the risk factors vary widely, and we believe more emphasis is required regarding the multiplicity effects of risk factors. We need larger studies and novel tools to investigate single and combined risk factors, and to identify key areas of improvement and modification for these patients.

The literature has demonstrated significant variation in the number and type of risk factors that places a patient at higher risk of developing a PJI, which is heavily weighted towards the patient. However the provider has a role in addressing the modifiable risk factors pre-operatively to optimise their patient, and develop new strategies to limit the impact of non-modifiable factors.

COMMENTS

Background

Several studies have previously shown the impact of various risk factors on the probability of developing an infection after joint replacement. The heterogeneity of the available data notwithstanding, in this systematic review a detailed analysis of the respective weight of known risk factors, classified as host-, provider- or post-surgical-related, is performed; moreover, a further distinction in modifiable or not-modifiable risk factors is proposed.

Research frontiers

A classification and ranking of known risk factors may open new frontiers in prevention and control of peri-prosthetic infections. Furthermore, it can be helpful to improve the information to the patient prior to surgery, to drive personalised prophylaxis and to better evaluate the cost-to-benefit ratio of new technologies, like antibacterial coatings, designed to reduce bacterial adhesion on implanted biomaterials.

Innovations and breakthrough

This systematic review sheds new lights on the relative impact of various risk factors that increase a patient's risk of developing lower limb periprosthetic joint infections (PJI). This ultimately reiterates the importance of optimising the patients pre-operatively by addressing modifiable risk factors (such as their immunosuppression, nutrition, diabetes, and smoking), and develops strategies to limit the impact of non-modifiable factors.

Applications

The data obtained in this systematic review may form the basis for the development of specific software, like the "PJI Risk App", an application for smartphones, specifically designed to calculate the risk of developing a peri-prosthetic infection in a given patient. This in turn may be useful for surgeons and their patients to understand the specific risk of undergoing joint replacement and eventually to better tailor antibiotic prophylaxis.

Peer-review

In this manuscript authors reviewed provider risk factors of chronic PJI. This study is interesting and the objective very clear.

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