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

David A George, Lorenzo Drago, Sara Scarponi, Enrico Gallazzi, Fares S Haddad, Carlo L Romano

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 (11.2%) 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
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.

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 healthcare service. The treatment of PJI is costly to the healthcare 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. 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, systemic infections, and immunocompromise.

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.

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George DA et al. Lower limb PJI risk factors

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.

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) |            |                |
| Berbari et al[10]     | 1998 | 462          | 462                     | OR, CI, P  | Both           |
| Lai et al[10]         | 2007 | 51           | -                       | OR, CI, P  | Both 84        |
| Parviz et al[10]      | 2007 | 78           | 156                     | OR, CI, P  | Both           |
| Pulido et al[10]      | 2008 | 63           | 9182                    | OR, CI, P  | Both 72        |
| Malinak et al[10]     | 2009 | 43           | 8451                    | OR, CI, P  | Both 192       |
| Ong et al[10]         | 2009 | 887          | 39042                   | OR, CI, P  | Hip 108       |
| Berbari et al[10]     | 2010 | 339          | 339                     | OR, CI, P  | Both           |
| Peel et al[10]        | 2011 | 63           | 126                     | OR, CI, P  | Both           |
| Bozic et al[10]       | 2012 | -            | -                       | OR, CI, P  | Hip 12        |
| Janssen et al[10]     | 2012 | 52           | 7129                    | OR, CI, P  | Both 12       |
| Bozic et al[10]       | 2012 | -            | -                       | OR, CI, P  | Kne 12        |
| Dale et al[10]        | 2012 | 2778         | 429390                  | RR, CI, P  | Hip 60        |
| Greenky et al[10]     | 2012 | 389          | 15333                   | OR, CI, P  | Both 108      |
| Namba et al[10]       | 2013 | 404          | 55812                   | OR, CI, P  | Both 124      |
| Sonnay et al[10]      | 2013 | 5            | 254                     | OR, CI, P  | Both 12        |
| Coelho et al[10]      | 2013 | 339          | 339                     | OR, CI, P  | Both 2        |
| Mazo et al[10]        | 2014 | 47           | 3625                    | OR, CI, P  | Hip 12        |
| Gómez-Lesmes et al[10]| 2014 | 32           | 1299                    | OR, CI, P  | Knee 3        |
| Yi et al[10]          | 2014 | 126          | 375                     | OR, CI, P  | Both 3        |
| Wu et al[10]          | 2014 | 45           | 252                     | OR, CI, P  | Both 144      |
| Sousa et al[10]       | 2014 | 43           | 2454                    | OR, CI, P  | Both 1        |
| Jiang et al[10]       | 2014 | -            | -                       | OR, CI, P  | Kne 6         |
| Duchman et al[10]     | 2015 | 802+         | 70129+                  | OR, CI, P  | Both 120      |
| Chrestil et al[10]    | 2015 | -            | -                       | OR, CI, P  | Both 12       |
| Croye et al[10]       | 2015 | 26           | 3393                    | OR, CI, P  | Both 1        |
| Debreuve-Theresette et al[10] | 2015 | 45 | 90 | OR, CI, P | Both |
| Bohl et al[10]        | 2015 | -            | -                       | OR, CI, P  | Both 1        |

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

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
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: (1) 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.

### 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, immunocompromised concomittent systemic infection, cardiovascular and gastroenterology disorders, high ASA (American Society of Anesthesiologists) grade and malnutrition.

Patient demographics also have been shown to have an impact upon risk of PJI, including age, rural residence, race, male gender, and alcohol use. Previous operations to the joint (excluding revisions arthroplasty as this was excluded from analysis) increased the risk of PJI.

### 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         | Retrospective | No          | 2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint     |
| Lai et al             | Retrospective | No          | 2 or more cultural examination positive for the same microorganism; clinical diagnosis                                     |
| Parvizi et al         | Prospective  | No          | Criteria based upon 3 of 5 features                                                                                     |
| Pulido et al          | Retrospective | Yes         | Criteria based upon 3 of 5 features                                                                                     |
| Malinzak et al        | Retrospective | No          | Unknown                                                                                                                  |
| Ong et al             | Retrospective | Yes         | Diagnostic code in Medicare database                                                                                    |
| Berbari et al         | 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            | Prospective  | Yes         | Criteria based upon 3 of 5 features                                                                                     |
| Bozic et al           | Retrospective | Yes         | Diagnostic code in Medicare database                                                                                    |
| Jämsen et al          | Prospective  | Yes         | CDC definition of surgical site infection                                                                                 |
| Bozic et al           | Retrospective | Yes         | CDC definition of surgical site infection                                                                                 |
| Dale et al            | Retrospective | Yes         | Clinical as reported by the surgeon after surgery                                                                          |
| Greenky et al         | Retrospective | No          | Criteria based upon 3 of 5 features                                                                                     |
| Namba et al           | Retrospective | Yes         | CDC definition of surgical site infection                                                                                |
| Sonnayai et al        | Retrospective | No          | Criteria based upon 3 of 5 features                                                                                     |
| Coelho-Prabhoo et al  | Retrospective | Yes         | 2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint     |
| Maoz et al            | Retrospective | Yes         | CDC definition of surgical site infection                                                                                |
| Gómez-Lesmes et al    | Prospective  | Yes         | Criteria based upon 3 of 5 features                                                                                     |
| Yi et al              | Retrospective | No          | Criteria based upon 3 of 5 features                                                                                     |
| Wu et al              | Retrospective | Yes         | MSIS definition                                                                                                           |
| Sousa et al           | Retrospective | No          | Criteria based upon 3 of 5 features                                                                                     |
| Jiang et al           | Retrospective | Yes         | Diagnostic code in Medicare database                                                                                    |
| Duchman et al         | Prospective  | Yes         | Criteria based upon 3 of 5 features                                                                                     |
| Chrastil et al        | Retrospective | No          | CDC definition of surgical site infection                                                                                |
| Crowe et al           | Retrospective | Yes         | CDC definition of surgical site infection                                                                                |
| Debreuve-Theret et al | Retrospective | No          | CDC definition of surgical site infection                                                                                |
| Bohl et al            | Prospective  | Yes         | American College of Surgeons National Surgical Quality Improvement Program definition                                  |

1Refers 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. 2Musculoskeletal Infection Society (MSIS) definition; 3Defined as (1) deep infection; (2) purulent drainage; (3) dehiscence; (4) fever; and (5) localized pain. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.
## Table 3 Host-related risk factors

| Ref. | Statistical parameter | HR  | OR  | RR  | 95%CI       | P value | Site        |
|------|-----------------------|-----|-----|-----|-------------|---------|-------------|
|      |                       |     |     |     |             |         |             |
| General |                       |     |     |     |             |         |             |
| Age: 65-75 yr (compared to 45-65) | [26] | 3.36 | 1.30-8.69 | 0.013 | Hip/knee |
| Coronarities (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] | 3.40 | 1.23-9.44 | 0.029 | Hip/knee |
|                         | [32] | 3.91 | 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] | 1.90 | 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 | Hip |
| 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]  | 4.00 | 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 |
|                         | [13] | 1.40 | 0.90-2.10 | 0.06 | Hip/knee |
|                         | [5]  | 1.80 | 1.20-2.80 | 0.006 | Hip/knee |
|                         | [13] | 3.10 |             | 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] | 1.60 | 1.32-1.93 | 0.009 | Hip |
|                         | [16] | 1.74 | 1.38-2.20 | 0.0044 | Hip |
|                         | [4]  | 1.26 | 1.02-1.57 | 0.033 | 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 | 1.05-2.47 | 0.0369 | Knee |
| Tumour 5 yr before implant | [5] | 3.10 | 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 |
|                         | [4]  | 1.15 | 1.01-1.31 | 0.039 | Knee |
|                         | [5]  | 1.13 | 1.01-1.27 | 0.038 | Knee |
|                         | [16] | 1.44 | 1.24-1.68 | 0.0032 | Hip |
| Gastroenterology disorders |                       |     |     |     |             |         |             |
| Liver cirrhosis | [28] | 5.40 |             | < 0.001 | Hip |
|                         | [28] | 3.40 |             | < 0.001 | Knee |
| Hepatitis B virus (amongst males) | [44] | 4.32 | 1.85-10.09 | < 0.001 | Knee |
|                         | [22] | 2.80 | 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 | 1.13-1.71 | 0.0028 | Knee |
| Renal function (mL/min) | [15] | 1.09 | 0.90-1.00 | 0.05 | Hip |
| Rheumatoid arthritis |                       |     |     |     |             |         |             |
| Rheumatoid arthritis | [15] | 3.30 | 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 |
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\(^5\), 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\(^{18}\), 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\(^{11,19,15}\). 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\(^{26}\)), 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 18 (OR = 6.00, 95%CI: 1.2-30.9, \(p = 0.033\))\(^{21}\), diabetes (OR = 5.47, 95%CI: 1.77-16.97, \(p = 0.003\))\(^{23}\), 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 pre-operatively 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         |    |    |    |         |         |            |
| [5]  | Antibiotic surgical prophylaxis | 0.5 | 0.30-0.80 | 0.003 | Hip/knee |
| [20] | Antibiotic irrigation | 0.67 | 0.48-0.92 | 0.014 | Knee     |
|      | Surgical technique     |    |    |    |         |         |            |
| [20] | Exposure requiring quadriceps release | 4.76 | 1.18-19.21 | 0.029 | Knee     |
| [15] | Use of wound drain tube | 0.09 | 0.01-0.80 | 0.03  | Knee     |
|      | Side of surgery        |    |    |    |         |         |            |
| [12] | Simultaneous bilateral surgery | 5.85 | 2.50-13.90 | < 0.0001 | Hip/knee |
| [20] | Single side (compared to bilateral) | 0.51 | 0.31-0.83 | 0.007 | Knee     |
| [13] | Exposure requiring quadriceps release | 3.1 | 0.01-0.80 | 0.0024 | Hip/knee |
| [13] | Use of wound drain tube | 4   | 0.01-0.80 | 0.009 | Knee     |
|      | Cement                 |    |    |    |         |         |            |
| [20] | Antibiotic-laden cement | 1.53 | 1.18-1.98 | < 0.001 | Knee     |
| [8]  | Non-antibiotic cement  | 1.5 | 1.30-1.80 | < 0.001 | Hip     |
| [8]  | Hybrid (compared to uncemented) | 1.6 | 1.40-1.80 | < 0.001 | Hip     |
|      | Operative duration     |    |    |    |         |         |            |
| [23] | Length of operation (> 115 min) | 3.38 | 1.23-9.28 | 0.018 | Hip     |
| [14] | (> 210 min)             | 1.78 | 1.40-2.26 | < 0.0001 | Hip     |
| [5]  | (> ≥ 240 min)           | 2.7 | 1.50-5.00 | 0.002 | Hip/knee |
|      | Hospital factors        |    |    |    |         |         |            |
| [20] | Hospital volume < 100 (vs > 200/yr) | 0.33 | 0.12-0.90 | 0.03  | Knee     |
| [14] | Medicare buy-in         | 1.34 | 0.01-0.80 | 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    |    |    |         |         |            |
| [15] | Intensive care length of stay (d) | 0.5 | 0.20-1.00 | 0.06  | Knee     |
|      | Haematological         |    |    |         |         |            |
| [12] | Blood transfusion      | 2.11 | 1.10-3.90 | 0.02  | Hip/knee |
| [15] |                         | 2.1 | 1.00-4.20 | 0.04  | Hip/knee |
| [1]  |                         | 1.63 | 1.14-2.33 | 0.007 | Hip/knee |
| [24] | Transfusion if RBCs stored > 14 d | 5.9 | 2.60-13.20 | < 0.001 | Knee |
| [15] | Perioperative blood loss (via drain tube) | 1 | 1.00-1.01 | 0.008 | Hip     |
|      | Cardiac                |    |    |         |         |            |
| [12] | Postoperative atrial fibrillation | 6.22 | 1.40-28.5 | 0.02  | Hip/knee |
| [12] | Postoperative myocardial infarction | 20.4 | 2.10-199.9 | 0.009 | Hip/knee |
|      | Hospital factors        |    |    |         |         |            |
| [12] | Longer hospital stay   | 1.09 | 1.00-1.10 | 0.0003 | Hip/knee |
| [23] | Non same-day surgery   | 4.16 | 1.44-12.02 | 0.008 | Hip     |
|      | Wound complications    |    |    |         |         |            |
| [11] | All wound complications | 27 | 11.00-91.6 | 0.0002 | Hip/knee |
| [5]  | Wound discharge        | 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] | Haematoma              | 32.2 | 8.7-119.17 | < 0.001 | Hip/knee |
| [5]  | Surgical site infection | 35.9 | 8.30-154.6 | < 0.01 | Hip/knee |
| [15] | Superficial incisional SSI | 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 |
| [9]  | NNIS risk index 2      | 3.9 | 2.00-7.50 | < 0.01 | Hip/knee |
|      | Urinary                |    |    |         |         |            |
| [12] | Postoperative urinary infection | 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.
Systemic steroids
21
-5.47
OR
1.89
-1.4
[4,31]
3.55
12.76
OR
1.22
5.1
4.13
Ref.
OR
1.18
4.34
OR
Diabetes
2.25
OR
8.24
[23,32]
3.3
Statistical parameter
5.4
2.6
[20,31]
4.76
OR
HR
[15,26]
3.3
HR
13.2
OR
3.3
HR
16-times.
4.76
Non-modifiable
Pre-operative BM
1.4
5.47
OR
15,26,27
Liver cirrhosis
3.3
OR
4,15,16
Rheumatoid arthritis
2.25
-17
Male
4.34
OR
[4,31]
BMI > 40
1.22
4.13
OR
[23]
BMI < 20
Coronary artery disease
1.22
4.34
OR
[4,31]
Nasal MRSA infection
-824
OR
[31]
Tobacco use
3.4
12.76
OR
[23,32]
Systemic steroids
3.3
21
OR
[15,21]
Ref. 50
of high alcohol intake
BMI
57x60
a patient’s risk of systemic infection, and has widely
50
impairing a patient’s immunity, as demonstrated from high
57x120
ratios
toward immune response
57x168
systemic response to infection. Cardiac dysfunction
57x192
renal failure
57x216
anaemia
57x249
and coagulopathy
57x282
have all been shown to increase the risk of infection. This may
57x282
be directed through specific cellular pathways
57x318
, but may demonstrate the insult the surgical procedures has
57x318
in causing a secondary inflammatory insults, worsening
57x318
multiple organ dysfunction
57x351
. Derangements in renal function, with progressively higher
57x351
poor glomerular filtration rate (GFR) in either the acute or
57x351
chronic stages, reduces the ability to remove unwanted
57x351
and hazardous chemicals from the blood, and places the
57x351
patient at a higher risk. Lieberman et al
57x385

demonstrated
57x421
little is known about the interaction between, or synergistic effect,
of specific patient risk factors
57x421
, as it is likely they have a multiplicity effect, rather than additive
57x421
risk, as shown by Tomás
60
. In their cohort if a patient
57x421
had two (or more) significant factors the probability of
57x421
infection development was 14-times higher, whereas having
57x421
three (or more) factors the probability was increased 16-times.
57x421
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.
57x469
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.
57x513
Infection response
57x513
While not directed specifically to immunosuppression, other co-morbidities have a role in reducing the patients systemic response to infection. Cardiac dysfunction
57x546
renal failure
57x580
anaemia
57x613
and coagulopathy
57x646
have all been shown to increase the risk of infection. This may be directed through specific cellular pathways
57x682
, but may demonstrate the insult the surgical procedures has in causing a secondary inflammatory insults, worsening multiple organ dysfunction
57x716
. Derangements 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
57x750
demonstrated
57x783
infection development was 14-times higher, whereas
57x816
have been documented in arthroplasty patients. Ragni et al
57x849
immunodeficiency virus-positive hemophilicacs with CD4 counts of 200 mm² or less undergoing orthopaedic surgery. Post-operative infection occurred in 10 (15.1%) of 66 patients
57x882
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
57x916
.
57x950
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             | OR                    | [17]   |
| Non-modifiable Diabetes | 1.4              | 5.47             | OR                    | [15,26]|
| Liver cirrhosis      | -                 | 5.4              | HR,OR                 | [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.

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
4,15,16, 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
407
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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\(^\text{[43]}\).

**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 preoperative confirmation of a genitourinary infection\(^\text{[10,27]}\), nasal S. Aureus and MRSA infections\(^\text{[31]}\), or other distant organ infections\(^\text{[5]}\), such as hepatitis B\(^\text{[4]}\).

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\(^\text{[6-18]}\) with known high rates of pneumonia, peripheral vascular disease\(^\text{[6,16]}\) with high risk of skin ulceration and introduction of skin contaminates, and recent oesophagastroduodenoscopy (EGD) with biopsy\(^\text{[22]}\), 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\(^\text{[11,2-15]}\), 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\(^\text{[45,46]}\). 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\(^\text{[47,48]}\).

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 20 000 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\(^\text{[49]}\).

**Antibiotic use**

The use of antibiotic-impregnated cement was shown by Dale et al\(^\text{[16]}\) to protect against revisions due to infection, whereas Namba et al\(^\text{[20]}\) 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\(^\text{[45-47]}\), whereas the Norwegian Arthroplasty Register has demonstrated a synergistic effect of systemic and cement antibiotics\(^\text{[5]}\). However there is a general consensus that antibiotic-impregnated cement has a greater role in revision cases\(^\text{[32]}\), and is recommended as standard practice in these high-risk cases\(^\text{[32]}\).

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\(^\text{[31,54]}\).

**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\(^\text{[28]}\). 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\(^\text{[36]}\), while other studies have shown no difference between the two\(^\text{[56]}\).

Furthermore, the use of a drain post-operatively has been shown by Peel et al\(^\text{[15]}\) 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\(^\text{[57,58]}\).

**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)\(^\text{[59,60]}\), antibiotic impregnated cement or bone graft\(^\text{[61,62]}\), or other novel therapies\(^\text{[63]}\) 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\(^\text{[64]}\). 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 who based the data on their cohort of patients at baseline and at one month. Bozic et al. developed a risk calculator using data from 11 years worth of Medicare claims. A similar tool has been developed in the Chinese population.

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.

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.

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