Chapter 2
Epidemiology of Prosthetic Joint Infection

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2.1 Incidence of Prosthetic Joint Infections

The joints that are most commonly replaced with a prosthetic implant involve total hip and knee arthroplasties. In addition to hip and knee replacements, shoulder, elbow and ankle arthroplasties are now available. Procedures to replace the wrist, temporomandibular, metacarpophalangeal and interphalangeal joints are less commonly performed. Virtually all extra-axial joints can be replaced with a prosthetic joint.

Total hip arthroplasty is indicated for patients who have failed previous treatment options for deteriorated hip joints but continue to have persistent debilitating pain and significant impairment in the activities of daily living. Displaced femoral neck fractures can also be treated with a prosthetic hip replacement. The indications for hip arthroplasty in the UK are osteoarthritis (93%), osteonecrosis (2%), femoral neck fracture (2%), developmental dysplasia of the hip (2%) and inflammatory arthritis (1%) [1]. The main indication for total knee arthroplasty is for the relief of pain and disability associated with osteoarthritis (primary or secondary) or inflammatory arthritis of the knee in patients who have failed nonoperative treatments [2]. Symptomatic osteoarthritis is the indication for surgery in more than 90% of patients, and its incidence is increasing because of an ageing population and the obesity epidemic in industrialized countries [3]. Osteoarthritis is one of the ten most disabling diseases in developed countries. Worldwide estimates indicate that 10% of men and 18% of women aged 60 years or older have symptomatic osteoarthritis, including moderate and severe forms [4]. Joint replacement surgery is considered the most effective intervention for severe hip and knee osteoarthritis, reducing pain and disability, restoring function and independence and improving the patient’s quality of life [3]. While joint replacement surgery is mainly carried out in people aged 60 or more, it is increasingly performed in those who are younger [3].

An increasing number of joint replacements are being carried out in most of the industrialized countries worldwide, and the incidence of prosthesis implantation is expected to
continue to rise. Procedures are referred to as either primary or revision arthroplasty, according to the number of times that a given joint is replaced. Primary arthroplasty is the first time that a native joint is replaced; revision arthroplasty is a second or subsequent surgical procedure performed when a joint replacement fails and some or all parts of the original prosthesis need to be changed. In 2009, a total of 284,000 primary total hip arthroplasties, 45,000 revision total hip arthroplasties, 619,000 primary total knee arthroplasties and 59,500 revision total knee arthroplasties were performed in the USA [5]. From 2009 to 2010, the total number of procedures increased by 6.0% for primary total hip arthroplasty, 6.1% for primary total knee arthroplasty, 10.8% for revision total hip arthroplasty and 13.5% for revision total knee arthroplasty [5]. The numbers of primary total hip and knee arthroplasty are projected to reach 572,000 and 3.48 million, respectively, by 2030 [6]. According to the Canadian Institute for Health Information, hip and knee arthroplasty rates increased by 16.5% and 21.5%, respectively, in the 5-year period from 2008 to 2013 [7]. The number of hip and knee replacements in most European countries has also increased in recent years, although rates between countries vary considerably [3] (Fig. 2.1). In the USA, primary shoulder and elbow

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**Figure 2.1** Trends in hip (left) and knee (right) replacement surgery, 2000–2014, selected European countries (OECD Health Statistics) (From OECD/EU [3], with permission)
arthroplasty procedures increased at annual rates of 6–13% from 1993 to 2007 [8]. The revision burden increased from approximately 4.5–7% [8]. These numbers are anticipated to escalate further over the next few decades.

Most of the information about the incidence of prosthetic joint infection in the published literature has been hampered by methodological problems. These include a reliance on case series rather than well-designed cohort studies, the lack of explicit or standardized case definitions, incomplete case ascertainment, selection biases and, especially, differences in the length of follow-up [9]. Studies with longer follow-ups will report higher cumulative incidences (a percentage), even when the true incidence is low; failure to account for differences in length of follow-up between groups will lead to wrong conclusions [10]. Consequently, estimates of cumulative risk based on comparison should be made with caution unless the follow-up periods are the same. The denominator for the incidence rate is the prosthetic joint year.

The overall rate of prosthetic joint infections is highest in the first 2 years after surgery; the greatest risk of prosthetic joint infection occurs in the first 6 months after the operation and declines steadily after that [9, 11]; nevertheless, approximately 20–25% of all prosthetic joint infections occur after 2 years [11, 12]. According to a review by researchers from the Mayo Clinic in 2000, the combined incidence of total hip and knee arthroplasty infection was 5.9 (95% confidence interval [CI] 5.3–6.5) infections per 1000 joint years in the first 2 years following implantation and 2.3 (95% CI, 2.1–2.5) in years 2–10 [9]. The rates of late prosthetic joint infection (detected >2 years after the index operation) and of very late prosthetic joint infection (detected >5 years after the operation) for primary hip and knee replacements due to primary osteoarthritis performed between 1998 and 2009 were analysed from nationwide Finnish health registers [12]. The incidence rate of late prosthetic joint infection was 0.069% (95% CI, 0.061–0.078) per prosthesis year and was higher after knee replacement than after hip replacement (0.080 vs. 0.057). The rate of very late prosthetic joint
infection was 0.051% (95% CI, 0.042–0.063) per prosthesis year, 0.058 for knees and 0.944 for hips [12]. The cumulative incidence of infection following primary hip or knee arthroplasty implanted between 1969 and 2007 was 0.5%, 0.8% and 1.4% at 1, 5 and 10 years, respectively, according to a population study in Olmsted County, Minnesota [13]. In the US Medicare population between 1997 and 2006, the incidence of prosthetic joint infection within 2 years of total knee arthroplasty was 1.55% and 0.46% between 2 and up to 10 years [11]. The higher early incidence of infection following implantation of a prosthesis followed by a decrease over time reflects the predominant effect of infection acquired during surgery, variable delays in symptom onset and diagnosis of infection after implantation and the decreasing susceptibility of prostheses to haematogenous seeding over time [9].

The establishment of national and international nosocomial surveillance networks has provided information on rates of surgical site infection after joint replacements. Fourteen European countries participate in the orthopaedic modules within the European Centre for Disease Prevention and Control surgical site infection surveillance network. The latest overall infection rates provided by the network for 2010–2011 were 0.7% for infection within 1 year of a knee replacement (95% confidence interval [CI] 0.7–0.8) (intercountry range 0.2–3.2%) and 1.0% for a hip replacement, including hip hemiarthroplasty (intercountry range 0.4–11.4%), with considerable variation in rates between countries [14]. A similar cumulative incidence of 0.9% (95% CI, 0.85–1.02) for prosthetic joint infections within 2 years of the index surgery was reported from Sweden’s hip arthroplasty register between 2005 and 2008 [15]. European infection rates for hip and knee arthroplasty within the first year of the index surgery are in line with estimates from the National Healthcare Safety Network of the Centers for Disease Control and Prevention in the USA: 0.9% for hip and 1.3% for knee prosthesis from 2006 to 2008 [16]. Data from the Healthcare Infection Surveillance Western Australia shows that the incidence of infection for hip and knee arthroplasty
was 1.4 (95% CI 1.2–1.6) and 1.4 (95% CI 1.2–1.5), respectively, in 2008–2013 [17]. A surveillance study of surgical site infections in patients undergoing surgical procedures from 2005 to 2010, conducted in 30 countries across 4 continents (America, Asia, Africa and Europe), showed infection rates within 1 year of a hip and knee replacement of 2.6% and 1.6%, respectively [18]. A recent review of several national surveillance networks in Europe and the USA reported considerable differences in data collection methods and data quality, mainly in follow-up and post-discharge surveillance [19]. In that review, the cumulative incidence of prosthetic joint infection after total hip arthroplasty ranged from 1.3% to 2.9% and from 0.7% to 3.7% following total knee arthroplasty [19]. Conventional surgical site infection surveillance focuses largely on infections detected at the hospital where the operation was performed. Infections diagnosed and treated at other healthcare facilities may consequently be missed by conventional surveillance, which can lead to varying degrees of underestimation of the infection rate [20]. In a US study, 17% of infections would have been missed using operative hospital surveillance alone [20]. In that study, when infections diagnosed at other centres were included, the cumulative incidence of infection in the year following surgery was 2.3% for total hip arthroplasty and 2% for total knee arthroplasty [20]. Other sources of information on the incidence of prosthetic joint infections are the national arthroplasty registers, although it has also been found that the rate of prosthetic joint infection may be underestimated also in arthroplasty registers [21, 22]. An important weakness of the arthroplasty registers is that they are not designed for registration of infections. In the Nordic arthroplasty registers, the surgeon decides—based on a subjective assessment—whether or not the revision/reoperation is due to an infection. Positive cultures will not be available until 2–7 days after surgery, but once the revision diagnosis is reported to the register, it is probably never changed [22].

In most, but not all, of the studies, the rate of infection for total knee arthroplasty is higher than for hip arthroplasty
The rate of surgical site infection is higher following hip hemiarthroplasty than total hip arthroplasty, ranging between 1.7% and 7.3% [23]. Hip hemiarthroplasty is the emergent surgical procedure indicated for displaced intracapsular femoral neck fractures, which are more frequent in the elderly population compared with total hip arthroplasty which is an elective procedure generally performed in younger people.

Some studies have reported an increasing incidence of prosthetic joint infections in hip and knee arthroplasties. Data extracted from the Nationwide Inpatient Sample in the USA showed that the incidence of prosthetic joint infection for hip arthroplasties increased from 1.99% (CI 95%, 1.78–2.21%) in 2001 to 2.18% (CI 95%, 1.97–2.39%) in 2009; after adjusting for other patient demographic factors, there was a significant year-to-year increase in the risk of hip infection over the study period [24]. The corresponding incidence rates for knee arthroplasties were 2.05% (CI 95%, 1.86–2.23%) in 2001 and 2.18% in 2009 (CI 95%, 1.99–2.37%). A more gradual but, nonetheless, significant increase in the risk of infection over time was found for knee compared to hip arthroplasty from 2001 to 2009 [24]. Similarly, the Nordic Arthroplasty Register Association (Denmark, Finland, Norway and Sweden) found an increase in cumulative 5-year revision rates due to infection in hip arthroplasties, rising from 0.46% (CI 95%, 0.42–0.50) during the period from 1995 to 1999 to 0.71% (CI 95%, 0.66–0.76) from 2005 to 2009 (6); the entire increase in risk of revision due to infection was within the first year of the primary surgery, and the risk increased in all four countries [25]. A population-based study, however, conducted in Olmsted County, Minnesota (USA), from 1969 to 2007, found no increase over the period of the study [13]. A recent study based on the Danish Hip Arthroplasty Register and several other national registers found that the relative risk of prosthetic joint infection in the year following primary total hip arthroplasty implantation did not increase over the 2005–2014 study period (the incidence was 0.53% [95% CI, 0.44–0.63] for 2005–2009 and 0.57% [95% CI, 0.49–0.67] for 2010–2014) [26].
primary hip and knee replacements between 1998 and 2009, the incidence of late prosthetic joint infection (>2 years after the index operation) varied between 0.041% and 0.107% during the years of observation, with no temporal trend, while very late infections (>2 years after the index operation) increased significantly, from 0.026% in 2004 to 0.056% in 2010 [12]. By contrast, several national and international nosocomial surveillance networks have shown decreasing rates of surgical site infection after joint replacement in recent years [14, 17, 27, 28].

There is currently insufficient data to analyse the true incidence of arthroplasty infection at other anatomic locations, since the rates are based mainly on single-centre studies. After a shoulder arthroplasty, the rate of prosthetic infection appears to be similar to those for hip and knee prostheses, ranging from 0.98% to 1.3% in US series [29, 30]. The reported infection rate for elbow arthroplasty has been higher than for other joints: 3.3% in a systematic review [31]. The reasons for this may include an increased number of patients with rheumatoid arthritis (immunocompromised) receiving elbow arthroplasty and the fact that the elbow is a subcutaneous joint with a thin soft tissue envelope.

While it is still unclear whether the incidence of prosthetic joint infection is increasing, the absolute number of cases is growing. A further increase in the absolute number of arthroplasty infections is expected in the future, due to an increasing number of primary implantations carried out on a progressively elderly population with more associated comorbidities, the significant increase in the number of revision procedures, better methods of detection for the microbial biofilms involved in prosthetic joint infections, the increasing prevalence of microorganisms resistant to standard antibiotic prophylaxis and the accumulating number of arthroplasties that stay in place but remain at risk of infection during their implanted lifetime. Late infections occurring many years after prosthesis implantation may become more common, since the number of people living with some kind of joint arthroplasty is also increasing [12].
2.2 The Impact of Prosthetic Joint Infection

Prosthetic joint infections have a significant impact, not only on healthcare resources and economic costs but also on the morbidity, quality of life and mortality of patients. Research continues to quantify the impact of these infections.

2.2.1 Impact on Patient Mortality, Morbidity and Quality of Life

Prosthetic joint infection is widely depicted as a devastating complication with a potential impact on a patient’s mortality and quality of life. Nonetheless, there is very little information in the literature about the quantity and quality of life of these patients.

Berend et al. [32] studied 205 infected total hip arthroplasties treated with a two-stage reimplantation protocol and found that, in spite of the high degree of infection control, there was a 48% mortality rate over the study period (1996–2009). Choi et al. [33] performed the first analysis of septic and non-septic revisions by investigating mortality rates in 93 patients after revision total hip arthroplasty matched to 93 control subjects. They found that the mortality rate in the septic group was 33% (31/93) and 22% (20/93) in the aseptic group at the 5- and 6-year follow-up, respectively. Although this difference was not statistically significant, the septic patients were younger and died 6 years earlier. The same authors performed a similar study focusing on 88 infected total knee arthroplasties and 88 controls [34]. The overall mortality rate following revision total knee arthroplasty was 10.7% after a median follow-up of 4 years but was 6 times higher after septic revision (18%–16/88) than after aseptic revision (3%–3/88) [34]. In order to determine the effect of prosthetic joint infection on mortality, Zmistowski et al. [35] compared the outcomes of 436 infected revisions with 2342 patients undergoing revision arthroplasty for aseptic failure. Prosthetic joint infection was associated with a fivefold
increase in mortality, even after controlling for other variables. Mortality in the prosthetic joint infection cohort was 3.7% at 90 days, 10.6% at 1 year and 25.9% at the 5-year follow-up. These figures compare unfavourably with some of the most commonly dreaded cancers, such as female breast and uterus and male prostate cancer [36]. Of course, the increased risk of mortality is not only due directly to the adverse effect of infection and treatment but also to the fact that prosthetic joint infection often reflects a poorer health status. Nevertheless, these figures should raise awareness of the systemic impact of disease among those doctors involved in the management of these infections and of the need to concentrate on two highly interconnected dimensions when dealing with prosthetic joint infections: infection eradication and general health status.

There is extensive evidence to show that a successful total joint arthroplasty greatly increases the patient’s quality of life in terms of function, pain and mobility, although surprisingly few studies in the literature about quality of life after prosthetic joint infections. Cahill et al. [37] were among the first to address this issue. They compared 62 uncomplicated total joint replacements and 34 cases of prosthetic joint infection, using a visual analogue scale for satisfaction, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Assessment of Quality of Life (AQoL) and the Short-Form 36 (SF-36). They found that infection reduced patient satisfaction and seriously impaired functional health status and health-related quality of life, but provided no information about the influence of infection control on health status. Helwig et al. [38] analysed 58 patients with prosthetic joint infection, applying the Short-Form Health Survey 12 (SF-12) to evaluate physical and mental status according to the outcome of infection, but did not differentiate between those treated with debridement and implant retention and one- or two-stage revision protocols. Surprisingly, when they compared successful and unsuccessful therapies, they found no significant differences on either scale, suggesting that even after a good clinical outcome, patients remained physically and mentally
limited. As expected, when the infected cohort was compared with the general German population, they found that physical status was significantly disadvantaged.

There is some debate about whether one- or two-stage exchange is the best surgical option for chronic prosthetic joint infection. The impact on quality of life would be a major consideration for deciding which is the most appropriate option, although it is not possible to draw definitive conclusions from the available data. One study analysed functional outcome after revision surgery for prosthetic hip infection, and two-stage exchange was the first therapeutic option for more severe infections and patients with more comorbidities [39]. Studies that compare different surgical options with similar patients or in clinical trials should include functional and quality-of-life analysis. At the same time, there is also little information about the functional outcomes of patients treated with open debridement and implant retention, a common surgical strategy for treating acute prosthetic joint infection. Aboltins et al. [40] prospectively collected pre-and post-arthroplasty data of 2134 total joint arthroplasty patients, in which there were 41 prosthetic joint infections. The main conclusion was that prosthetic joint infection cases treated with debridement and implant retention had a similar improvement from pre-arthroplasty to 12 months post-arthroplasty as patients without prosthetic joint infection in terms of quality of life, according to the SF-12 survey. The analysis did not evaluate the potential influence of aetiological microorganisms. Núñez et al. [41] evaluated 24 patients with acute knee prosthetic joint infection who underwent debridement and implant retention and were in remission after 12 months of follow-up. Their health-related quality of life was analysed using WOMAC and SF-36 at baseline (before knee replacement) and at 12 and 24 months after antibiotic treatment ceased. There was a significant improvement in all items from baseline to 48 months after the operation, except for patients infected with Staphylococcus aureus who had significantly worse outcomes, most especially in terms of stiffness and function on the WOMAC index and the
SF-36. Indeed, the only variables independently associated with worse outcomes were *S. aureus*, number of comorbidities and age. *S. aureus* is a virulent microorganism that causes severe soft tissue damage, which is potentially associated with a higher degree of fibrosis and scarring and would explain, at least in part, the worse functional outcomes.

Although more studies are needed to fully clarify the extent of the impact of prosthetic joint infection on a patient’s quality of life, there is no doubt that it should be a concern for professionals involved in the management of these patients. According to the literature, debridement and implant retention for early postoperative prosthetic joint infection is associated with a similar quality of life to subjects who do not have infection except those caused by *S. aureus*. Early diagnosis and treatment would probably improve the results in such cases. Meanwhile, revision surgery for infection has been clearly associated with a significant deleterious impact on health-related quality of life.

### 2.2.2 Economic Impact

Prosthetic joint infection management represents a substantial economic burden for hospitals, healthcare systems and patients alike. Infection is consistently one of the leading causes of total joint revision surgery [42–45]. It is often the first or second most common indication for revision total knee arthroplasty [42, 44] and the third most common for revision total hip arthroplasty after aseptic loosening and dislocation [45]. It is also a leading cause of failure in other prostheses, specifically, shoulder, elbow and ankle prostheses [30].

The real cost of treating an infected joint is not easy to ascertain. It depends on many variables, such as the type of surgery, treatment, patient comorbidities and even bacterial factors, such as the antibiotic susceptibility profile. The full spectrum of economic impact includes not only the most commonly reported direct in-hospital costs but also direct outpatient costs (follow-up visits, rehabilitation, pharmacy),
as well as indirect costs that are virtually impossible to gauge with any accuracy, such as loss of productivity or absence from work by the patient or his caregivers.

Kurtz et al. [24] included over 150,000 prosthetic joint infection cases and found that the average total hospital costs for infected hip revision were $72,700 US dollars (USD) in 2001, and $93,600 USD in 2009. The average charges for infected knee revision were $58,700 USD in 2001 and $74,900 USD in 2009. More recent studies from the USA included not only inpatient costs but also the cost of outpatient services. In 2014, Kapadia et al. [46] identified 21 infected total knee arthroplasties and matched them to 21 non-infected subjects who underwent uncomplicated primary surgery. Patients with prosthetic joint infection had significantly longer hospital stays, more readmissions and more clinic visits. The mean total episode cost (fixed and variable direct costs) for patients with surgical site infections was $116,383 USD (range, $44,416–$269,914), which was significantly higher than the mean $28,249 USD (range, $20,454–$47,957) in the matched group. Just recently, the same authors studied 16 consecutive infected total hip arthroplasties matched to 32 non-infected patients [47]. As before, the mean cost per episode was significantly higher in the infected group, $88,623 USD (range, $44,043–$158,202) than in the matched cohort, $25,659 USD (range, $13,595–$48,631).

The specific cost varies sharply from one setting to another, depending on the type of healthcare system and the corresponding economic standard. Fernandez-Fairen et al. [48] performed a systematic review of the literature and found significant disparities in absolute values between publications, depending on the country of origin. Nonetheless, the cost of a septic revision was consistently around 2–4 times more expensive than primary surgery and 1.5–3 times more expensive than aseptic revision surgery.

Cases of early postoperative and haematogenous prosthetic joint infection can be treated effectively with debridement and implant retention. The specific objective of an Australian study by Peel et al. [49] was to calculate
the cost associated with this strategy. They focused on 21 prosthetic joint infections (12 total hip arthroplasties, 9 total knee arthroplasties) matched to 42 control patients with uneventful primary joint replacements. They included inpatient and also outpatient expenses, including readmissions, follow-up medical and nursing visits, medical imaging, pathology and pharmacy, including dispensed antibiotics. The total cost for patients with infection was $69,414 Australian dollars (AUD), compared with $22,085 AUD for the controls, with significant differences across almost all areas of patient care. The cost of an infection including the index operation and the costs of prosthetic joint infection management was 3.1 times that of an uneventful primary arthroplasty.

In summary, the economic cost of treating a case of prosthetic joint infection is two to four times higher than a primary replacement or aseptic revision.

More studies are needed that not only include a descriptive cost analysis but also take into account outcome measures, such as successful infection eradication, functional results and quality-of-life measurements after treatment. These cost benefit analyses will allow for more informed decision-making in all fields of prosthetic joint infection management. Prevention remains the best way to avoid the dire health-related and economic consequences of infection. Advances in the prevention of prosthetic joint infection will be needed to make an impact on the anticipated increase in the number of infections in the years to come.

2.3 Risk Factors

Several risk factors for the development of a prosthetic joint infection have been described, mainly derived from patients with total hip and knee arthroplasties. Some of the proposed risk factors should however be interpreted with caution because different studies used diverse methods or employed different classifications/scoring systems or focused on only one particular anatomic site [50]. Some studies have suggested
that the risk factors could vary according to the particular anatomic joint [51]. Identifying the current risk factors that predispose patients to prosthetic joint infections after an arthroplasty will help the clinician establish strategies to prevent them. Risk factors for acquiring prosthetic joint infections can be categorized as patient characteristics, perioperative related factors and risk during bacteraemia [50].

2.3.1 Host Risk Factors

Nutritional status (mainly obesity), diabetes mellitus, rheumatic diseases and immunosuppressive therapy are among the most frequently reported risk factors for developing prosthetic joint infections [50, 52]. Smoking, coagulopathy, preoperative anaemia and previous joint surgery, mainly previous arthroplasty, have also been described as risk factors for prosthetic joint infection.

Obesity, defined as weight >20% above the ideal body weight or increased body mass index (BMI), has been associated with and increased risk of infection in several studies [52, 53]. Possible reasons include prolonged operative duration, increased allogenic blood transfusions and the presence of other comorbidities [54, 55]; however, obesity has remained an independent risk factor after adjustment for other covariates in some investigations [55]. In their study, Peel et al. described that for every 1 kg/m² increase in BMI, there was an associated 10% increase in the risk of prosthetic hip infection [51]. It was suggested that the association between obesity and hip arthroplasty could reflect an increase in postoperative dead space and the excellent medium for microbiological growth provided by necrotic fat [51]. Conversely, suboptimal preoperative nutrition with BMI <25 or malnutrition with serum albumin <34 g/L has also been associated with an increased risk of prosthetic joint infection [52, 54, 56, 57].

Diabetes mellitus is a risk factor for infection after general surgical and arthroplasty procedures [52, 58]. Moreover, Mraovic et al. observed that postoperative morning
hyperglycaemia (blood glucose > 200 mg/dL) increased the risk of surgical site infection, even in patients without diabetes [59].

Patients with rheumatoid arthritis are at higher risk for developing prosthetic joint infections, with a relative risk increased approximately two- to fourfold, compared with that of patients without rheumatoid arthritis [9, 52, 60, 61]. This risk increases further in the context of revision arthroplasty or when there has been a previous prosthetic joint infection. It is often difficult to separate the relative contribution of the underlying illness, the accompanying comorbid conditions and the therapy with immunosuppressive or immunomodulating agents used with the patients [55]. New treatment approaches for patients with rheumatoid arthritis, including earlier use of disease-modifying antirheumatic drugs and the advent of biologic drugs, such as antitumour necrosis factor inhibitors, may have significantly increased the risk of prosthetic joint infections in these patients [61]. Until further data is available, the discontinuation of chronic treatment with these drugs should be assessed on a case-by-case basis before undergoing elective orthopaedic surgery. In their study, Peel et al. demonstrated that systemic corticosteroid therapy remained a predictor of infection when controlling for underlying comorbidity; this association may be mediated, at least in part, by impaired wound healing [51].

A systematic review found that smokers were substantially more likely to have postoperative complications following total knee or hip arthroplasty [62]. Current smokers undergoing knee or hip replacement had more often surgical site infections than never smokers. This is likely related to the negative effects associated with vasoconstriction on surgical wound healing [57].

Greenky et al. analysed 15,222 patients who underwent total joint arthroplasties from January 2000 to June 2007. A percentage of 19.6% presented with preoperative anaemia; prosthetic joint infection occurred more frequently in anaemic patients at an incidence of 4.3% compared with 2% in nonanaemic patients (P < 0.01) [63]. The multivariate model confirmed the risk of prosthetic joint infections to be two times higher in anaemic patients vs. nonanaemic patients.
A mean international normalized ratio (INR) greater than 1.5 has been found to be more prevalent in patients who developed postoperative wound complications (such as haematoma) and later prosthetic joint infections [64].

A history of prior arthroplasty on the index joint has consistently been recognized as a risk factor for prosthetic joint infection, increasing the risk of infection by up to eight times compared with patients with primary implantation [56, 60, 65]. The risk increases with the number of previous joint arthroplasties [60]. Prolonged operating times during revision surgery, the presence of unrecognized infection at the time of revision and abnormal surrounding soft tissue could be contributing factors.

*S. aureus* colonization increases the risk of *S. aureus* surgical site infections. The risk for these infections may be decreased by screening patients for nasal carriage of *S. aureus* and decolonizing carriers during the preoperative period [66, 67].

The presence of distant infections previous to the joint replacement has also been related to a higher risk of prosthetic joint infections, presumably due to transient bacteraemia from a distant infection site during this high-risk period [55]. Therefore, it has been recommended to screen for the presence of active infection elsewhere (such as urinary tract infection, respiratory tract infection, active skin infection, abscess or infected ulceration) prior to an elective prosthetic replacement. If asymptomatic pyuria or bacteriuria is associated with the development of prosthetic joint infections is not completely clear [68–70].

### 2.3.2 Perioperative Factors

It is considered that prosthetic joint infection is frequently acquired in the operating room during the arthroplasty procedure [57]. During arthroplasty, 50–67% of surgical gloves are estimated to be perforated, which is associated with increased infection rates. Handwashing, double gloving and changing
gloves at regular intervals during the operation may be preventive strategies [71–73]. Human traffic in the operating room is associated with increased bacterial air counts, while opening and closing the theatre door disrupts the airflow around the patient, allowing microorganisms to enter the airspace around the surgical site [74]. Hypothermia could also facilitate prosthetic joint infection by inducing peripheral vasoconstriction with a substantial reduction of subcutaneous oxygen tension and directly inhibiting the inflammatory response [75]. The use of alcohol-based antiseptic skin preparations, combined with povidone or chlorhexidine, in the operating room [76], skin drapes and clipping hair immediately before surgery rather than the night before are associated with a reduced risk of surgical site infections [77]. A timely and appropriate perioperative antibiotic, according to the current guidelines for antimicrobial prophylaxis, is one of the most effective agents for the prevention of prosthetic joint infection [78]. It is recommended to administer the antimicrobial 1 h prior to surgical incision, with a repeat dose if the operation extends beyond 2 or 3 h, or if there is substantial blood loss [75, 77, 79].

Another independent risk factor predictive of prosthetic joint infection is the duration of the operation. The risk increases significantly when a procedure lasts more than 120 min, which is a reflection of more complex surgery, with prolonged surgical exposure and tissue damage during the procedure [80].

In essence, all wound complications (such as delayed healing, drainage or persistent dehiscence, haematoma, seroma) increase the risk of infection. Several authors have shown that developing a superficial surgical site infection not involving the prosthesis is a significant risk factor for prosthetic joint infection [60, 65, 81]. In Berbari et al.’s study, surgical site infection correlated with a 35.9-fold increase in the risk of infection in multivariate analysis [60]. Several authors have described local haematoma and wound discharge as risk factors for infection [51, 53, 56, 60]. One case-control study with 63 cases observed that drainage tube
implants reduced the risk of subsequent prosthetic knee infections. However, previous studies have found that drainage tubes reduce haematoma formation; they have not shown a reduction in infection [51].

There are risk factors for prosthetic joint infections not primarily associated with the surgical procedure or wound healing. These include developing postoperative atrial fibrillation and myocardial infarction as independent risk factors. One plausible explanation is that all patients with serious cardiac complications receive aggressive anticoagulation with heparin or similar, which has been reported to be an independent risk factor for the development of prosthetic joint infection [53, 64]; also, the patients are generally older and sicker with pre-existing medical conditions that delay wound healing [53].

An association has been reported between allogeneic blood transfusion and infection related to the immunomodulation effect of the transfusion [82]; these patients are 2.1 times more likely to develop prosthetic joint infections, compared to those who do not receive a transfusion [53].

Longer hospital stays are another adjusted independent risk factor for infection. These patients are more likely to be exposed to nosocomial organisms that can lead later to prosthetic joint infection [53]. For this reason, it is important to avoid unnecessary stays in hospital before elective joint implantation.

2.3.3 Risk of Haematogenous Prosthetic Joint Infection

Finally, it is important to remark that an arthroplasty implant is at risk of infection not only in the immediate postoperative period but during their implanted lifetime due to the risk of bacteraemia. Nevertheless, the incidence of haematogenous seeding to a joint from a remote infection is low (0.1%) [83]. The situation is different in the case of *S. aureus*, where the
rate of prosthetic joint infection after *S. aureus* bacteraemia is approximately 35% [84]. This means that if bacteraemia (mainly due to *S. aureus*) occurs, patients with uninfected prosthetic joints should be carefully monitored clinically for the development of prosthetic joint infection. In this situation, early diagnosis may avoid exchange of the prosthesis since infection can be cured with debridement and implant retention.

Along the same lines, the question of whether dental procedures alter the risk of prosthetic hip or knee infection has been actively debated in the last few decades. Recent case-control and cohort studies have finally concluded that the risk of infection in patients with prosthetic joints does not increase after dental procedures and specific antibiotic prophylaxis is not required [85, 86].

### 2.3.4 Risk Scores

The American Society of Anaesthesiologists (ASA) score is a widely used grading system for preoperative health of the surgical patients based in five classes. The ASA score has been associated with an increased risk of prosthetic joint infection in several studies [51–53].

The National Nosocomial Infections Surveillance (NNIS) System surgical score for identifying patients at a high risk of postoperative surgical site infection includes the ASA preoperative assessment score, the duration of the surgical procedure and surgical wound classification of each procedure (classification degree of microbial contamination of surgical wound at time of operation) [87]. The NNIS has been shown to be a better predictor of surgical site infection than individual components of the index. In one large case-control study, an NNIS score $\geq 1$ was a significant risk factor for the development of prosthetic joint infections and an NNIS score of 2 correlated with a 5.2-fold increase in the probability of infection [60]. These findings remained in the multivariate analysis.
Two proposed Mayo prosthetic joint infection risk score models were developed using data from 339 cases and 339 controls of patients undergoing total hip or knee arthroplasty in the same period at a tertiary referral hospital; risk factors were detected using multivariable modelling [56]. The baseline Mayo prosthetic joint infection risk score included BMI (either high or low), a previous operation on the index joint, prior arthroplasty, immunosuppression, ASA score and procedure duration. This score has the potential to help identify high-risk individuals at the time of surgery. The 1-month-post surgery score for risk of prosthetic joint infection contained the same variables, as well as postoperative wound drainage. The last score can be used in the postoperative period as an early workup in patients with early signs or symptoms suggestive of prosthetic joint infection. The two risk score models require external validation before they can be implemented in clinical practice [56].

2.4 Classification Schemes

Several classifications have been proposed for prosthetic joint infections. Their objective is to guide medical and surgical decisions in patients with prosthetic joint infections.

The Zimmerli classification divides prosthetic joint infections into three categories based on time to infection: early-, delayed- and late-onset infections. Early-onset infection occurs in the 3 months following arthroplasty. The microorganisms involved are usually more virulent and are inoculated into the surgical site during implant surgery. In this classification, delayed-onset infection occurs after 3 months and before 12 or 24 months. This type is usually caused by less virulent microorganisms that contaminate the surgical site during arthroplasty. Late infections occur between 1 and 2 years after arthroplasty and are considered to be mainly haematogenous in origin, although some are also caused by slow-growing bacteria acquired during the index surgery [88].
This classification is somewhat similar to an older one by Coventry et al., who defined three stages of prosthetic joint infection. Stage I is acute infection in the first 3 months after surgery; stage II is delayed infection occurring between 3 months and 2 years after arthroplasty and constant chronic pain after the operation; stage III is a haematogenous infection with a previously pain-free period [89].

Another important classification that is frequently used is the Tsukayama classification, which proposes four types of prosthetic joint infection [90]. Early postoperative infection occurs in the first month after arthroplasty. Late chronic infection occurs after this time and is generally associated with a more protracted clinical course. The third type is acute haematogenous infection, which is a late infection with a long, previously asymptomatic period and usually follows a more acute clinical course. The fourth type of prosthetic joint infection is a positive intraoperative culture, found in patients undergoing revision arthroplasty for presumed aseptic failure. This latter category and late chronic infection represent the same clinical scenario: a loosened prosthesis inserted months or years previously, although with the difference that the new prosthesis has already replaced the infected one at the time of diagnosis in the positive intraoperative culture category.

The Zimmerli and Tsukayama classifications are the most frequently used and are similar from a practical point of view. Except for the timing, a positive intraoperative culture and late chronic infection are equivalent to delayed infection in the Zimmerli classification. Tsukayama’s haematogenous category is defined in the same way as Zimmerli’s late category, except for the time limit, set at 2 years. In summary, early postoperative infections and haematogenous infections (Zimmerli’s late type) can be regarded as acute infections, whereas Tsukayama’s late chronic and Zimmerli’s delayed prosthetic joint infections correspond to chronic infections.

Most teams use these classifications for deciding how to manage prosthetic joint infections. Patients with early postoperative and haematogenous infections are candidates for
debridement and implant retention with prolonged antimicrobial therapy in an attempt to cure the infection without removing the implant. Late chronic and delayed infections are frequently managed with a two-stage implant exchange. This approach is based on the possibility of curing acute infections while biofilm is still immature and the difficulty of treating chronic infections with mature biofilms without removing the implant [91].

Other authors have added some useful considerations to prosthetic joint infection classifications. According to Garvin and Hanssen, acute prosthetic joint infections occur in the 4 weeks following surgery and late chronic prosthetic joint infections 4 weeks after surgery with an insidious clinical onset [92]. This insidious clinical onset is useful in daily practice for distinguishing between late chronic and late (acute) haematogenous prosthetic joint infections. Senneville et al. mainly considered the duration of the symptoms and attached less importance to timing with respect to surgery. Their classification proposes acute infection as one with <1 month of symptoms. Other infections with symptoms duration of >1 month are late infections [93].

As some studies on the subject of prosthesis retention have suggested, successful management of prosthetic joint infections depends on factors other than the time when infection occurs [94, 95]. Hence, factors such as the condition of the host, the appearance of the soft tissue around the prosthesis and the virulence of the microorganism causing the infection should be taken into account when deciding on the therapeutic attitude. McPherson et al. categorized prosthetic joint infections not only in terms of timing but also in terms of the systemic status of the host [96]. Their classification included early postoperative infection (stage I), haematogenous infection (stage II) and late chronic infection (stage III). Late chronic infection was considered when symptoms arose 4 weeks or more after the index arthroplasty. Patients were classified, on the basis of age, the presence of neutropenia and low CD4 cell count, as non-compromised (A), compromised (B) or significantly compromised (C). The infection
site was also graded according to the presence of chronic infection, fistula, tissue loss and similar factors, as grade 1, 2 or 3 (uncompromised, compromised and significantly compromised, respectively). The use of this classification for the management of prosthetic joint infections has yielded different results in prognosis [96, 97].

2.4.1 Microbial Aetiology

Much of our current understanding of the microbial aetiology of prosthetic joint infections comes from studies that have limitations due to small sample size, single-centre experiences, lack of uniform or standardized definitions of infection and a variety of selection biases [9, 98]. Most studies have focused on specific categories of infection (mainly early-onset or chronic infections) or on infections treated with particular surgical strategies (largely debridement with retention of the prosthesis or two-stage exchange). Few studies have systematically described the full microbial aetiology of these infections [98].

A wide range of bacterial and fungal microorganisms can cause prosthetic joint infection (see Table 2.1). Aerobic Gram-positive cocci are the most common group of causative microorganisms (65–78%) [9, 55, 98], driven largely by infection with staphylococci, both coagulase-negative staphylococci and S. aureus, which account for 50–65% of all infections [55, 98]. S. aureus is a virulent pathogen and prosthetic joint infection by S. aureus typically presents with acute infection, although chronic infections have also been reported [99]. The group of microorganisms referred to as coagulase-negative staphylococci includes many species, with Staphylococcus epidermidis being the most frequently identified member of this group. Many are ubiquitous members of the skin microbiota. This group of organisms is the most frequent cause of chronic infection. Since much of the literature on prosthetic joint infection tends not to refer to individual species, the role of different species is unclear. Streptococcus and Enterococcus
Table 2.1 Microbiology results for culture-positive prosthetic joint infections (From Benito et al. [98], with permission)

<table>
<thead>
<tr>
<th>Microorganism or microorganism group</th>
<th>Total no. (% [95%CI]) of culture-positive infections (N = 2288)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive cocci</strong></td>
<td>1777 (77.7 [75.9–79.4])a</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci (CNS)</td>
<td>905 (39.6 [37.5–41.6])b</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>532 (23.3 [21.5–25])</td>
</tr>
<tr>
<td><em>S. lugdunensis</em></td>
<td>43 (1.9 [1.3–2.5])</td>
</tr>
<tr>
<td><em>S. capitis</em></td>
<td>35 (1.5 [1–2.1])</td>
</tr>
<tr>
<td><em>S. hominis</em></td>
<td>30 (1.3 [0.8–1.8])</td>
</tr>
<tr>
<td><em>S. warneri</em></td>
<td>19 (0.8 [0.3–1.2])</td>
</tr>
<tr>
<td><em>S. auricularis</em></td>
<td>15 (0.7 [0.3–1])</td>
</tr>
<tr>
<td>Other species of CNS</td>
<td>31 (1.4 [0.9–1.9])c</td>
</tr>
<tr>
<td>CNS without identification at species level</td>
<td>293 (12.8 [11.4–14.2])</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>643 (28.1 [26.2–30])</td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>180 (7.9 [6.7–9])</td>
</tr>
<tr>
<td><em>Streptococcus</em> species</td>
<td>207 (9 [7.9–10.2])d</td>
</tr>
<tr>
<td><em>S. agalactiae</em></td>
<td>65 (2.8 [2.1–3.5])</td>
</tr>
<tr>
<td>Viridans group streptococci without identification at species level</td>
<td>45 (2 [1.4–2.6])</td>
</tr>
<tr>
<td><em>S. mitis</em> group</td>
<td>32 (1.4 [0.9–1.9])e</td>
</tr>
<tr>
<td><em>S. anginosus</em> group</td>
<td>24 (1 [0.6–1.5])f</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>17 (0.7 [0.4–1.1])</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>12 (0.5 [0.2–0.8])</td>
</tr>
<tr>
<td><em>S. dysgalactiae</em></td>
<td>10 (0.4 [0.1–0.7])</td>
</tr>
<tr>
<td>Other species of streptococci</td>
<td>6 (0.3 [0–0.5])g</td>
</tr>
</tbody>
</table>

(continued)
### Table 2.1 (continued)

<table>
<thead>
<tr>
<th>Microorganism or microorganism group</th>
<th>Total no. (% [95%CI]) of culture-positive infections (N = 2288)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus</em> species</td>
<td>182 (8 [6.8–9.1])(^h)</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>158 (6.9 [5.8–8])</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>13 (0.6 [0.2–0.9])</td>
</tr>
<tr>
<td>Other species of <em>Enterococcus</em></td>
<td>6 (0.3 [0–0.5])(^i)</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp. without identification to species level</td>
<td>6 (0.3 [0–0.5])</td>
</tr>
<tr>
<td>Other aerobic Gram-positive cocci</td>
<td>4 (0.2 [0–0.4])(^j)</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative bacilli (GNB)</strong></td>
<td><strong>632 (27.6 [25.8–29.5])(^k)</strong></td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>466 (20.4 [18.7–22])</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>208 (9.1 [7.9–10.3])</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
<td>109 (4.8 [3.9–5.7])(^l)</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>97 (4.2 [3.4–5.1])(^m)</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td>58 (2.5 [1.9–3.2])(^n)</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
<td>43 (1.9 [1.3–2.5])</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>19 (0.8 [0.4–1.2])</td>
</tr>
<tr>
<td>Other <em>Enterobacteriaceae</em></td>
<td>19 (0.8 [0.4–1.2])(^o)</td>
</tr>
<tr>
<td>Non-fermenting GNB</td>
<td>218 (9.5 [8.3–10.8])</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>202 (8.8 [7.6–10])(^p)</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>13 (0.6 [0.2–0.9])(^q)</td>
</tr>
<tr>
<td><em>Ralstonia pickettii</em></td>
<td>4 (0.2 [0–0.4])</td>
</tr>
<tr>
<td>Other non-fermenting GNB</td>
<td>6 (0.3 [0–0.5])(^r)</td>
</tr>
<tr>
<td>Other Gram-negative bacilli</td>
<td>6 (0.3 [0–0.5])(^s)</td>
</tr>
<tr>
<td>Microorganism or microorganism group</td>
<td>Total no. (% [95%CI]) of culture-positive infections (N = 2288)</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive bacilli</strong></td>
<td>54 (2.4 [1.7–3])</td>
</tr>
<tr>
<td>Corynebacterium species</td>
<td>50 (2.2 [1.6–2.8])</td>
</tr>
<tr>
<td>Corynebacterium striatum</td>
<td>17 (0.7 [0.4–1.1])</td>
</tr>
<tr>
<td>Other species of Corynebacterium spp.</td>
<td>12 (0.5 [0.2–0.8])t</td>
</tr>
<tr>
<td>Corynebacterium spp. without identification to species level</td>
<td>21 (0.9 [0.5–1.3])</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>4 (0.2 [0–0.4])</td>
</tr>
<tr>
<td><strong>Anaerobic bacteria</strong></td>
<td>156 (6.8 [5.8–7.9])u</td>
</tr>
<tr>
<td>Anaerobic Gram-positive bacilli</td>
<td>117 (5.1 [4.2–6])v</td>
</tr>
<tr>
<td>Cutibacterium (formerly Propionibacterium) spp.</td>
<td>111 (4.9 [3.9–5.8])w</td>
</tr>
<tr>
<td>Clostridium spp.</td>
<td>7 (0.3 [0.1–0.6])x</td>
</tr>
<tr>
<td>Anaerobic Gram-positive cocci</td>
<td>33 (1.4 [0.9–2])y</td>
</tr>
<tr>
<td>Anaerobic Gram-negative bacilli</td>
<td>21 (0.9 [0.5–1.3])z</td>
</tr>
<tr>
<td>Bacteroides group</td>
<td>16 (0.7 [0.3–1.1])aa</td>
</tr>
<tr>
<td>Other anaerobic Gram-negative bacilli</td>
<td>8 (0.3 [0.1–0.6])ab</td>
</tr>
<tr>
<td>Anaerobic Gram-negative cocci</td>
<td>1ac</td>
</tr>
<tr>
<td><strong>Mycobacterium species</strong></td>
<td>9 (0.4 [0.1–0.7])ad</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>30 (1.3 [0.8–1.8])</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>27 (1.2 [0.7–1.6])ae</td>
</tr>
<tr>
<td>Other fungi</td>
<td>3af</td>
</tr>
</tbody>
</table>

(continued)
Table 2.1 (continued)

Unless stated otherwise, data are number (%) of patients with indicated characteristic.

Files in **bold-italic** show the groups of microorganisms that include the microorganisms in the lines below; that is, they are the main big groups of microorganisms (1. Aerobic Gram-positive cocci 2. Aerobic gram-negative bacilli (GNB) 3. Aerobic gram-positive bacilli 4. Anaerobic bacteria 5. Mycobacterium species 6. Fungi). Each group of these six big groups may include some subgroups of microorganisms. These subgroups cannot be identified in the current table, but they were marked in the original Table because they were placed at the left margin. These subgroups should be identified as the main subgroups belonging to the big groups. So, p.ex. 1. Aerobic Gram-positive cocci includes the next subgroups: 1.1. Coagulase-negative staphylococci (CNS) 1.2. Staphylococcus aureus 1.3. Streptococcus species 1.4. Enterococcus species; 2. Aerobic Gram-negative bacilli (GNB) comprises the next subgroups: 2.1. Enterobacteriaceae 2.2. Non-fermenting GNB, and so on.

Each subgroup of microorganisms can include several microorganisms or sub-subgroup of microorganisms, that are identified in the original Table with indentation respect to the subgroup that they belong. P.ex. 1.1. Coagulase negative staphylococci (CNS) includes: Staphylococcus epidermidis, Staphylococcus lugdunensis.

*a*More than one aerobic Gram-positive coccus was isolated in 232 out of 1777 (13.1%) episodes of prosthetic joint infection where these organisms were identified

*b*More than one species of coagulase-negative staphylococci was identified in 81 out of 905 (9%) episodes of prosthetic joint infection where these microorganisms were involved.

*c*Staphylococcus haemolyticus 10, S. simulans 5, S. saccharolyticus 4, S. schleiferi 4, S. cohnii 3, S. intermedius 3, S. lentus 1, S. saprophyticus 1

d*Two species of viridans streptococci were involved in four prosthetic joint infection cases

*e*Streptococcus mitis 18, S. oralis 7, S. sanguis 5, S. parasanguis 2

*f*Streptococcus anginosus 13, S. intermedius 6, S. constellatus 5

*g*Streptococcus bovis group 3, S. salivarius 2, nutritionally variant (deficient) streptococci 1

*h*Enterococcus faecalis and E. faecium were involved in one episode of prosthetic joint infection

*i*Enterococcus gallinarum 2, E. hirae 1, E. durans 1, E. casseliflavus 1, E. avium 1

*j*Gemella morbillorum 2, Gemella haemolysans 1, Facklamia sp. 1
More than one aerobic Gram-negative bacillus was isolated in 131 (20.7%) episodes of prosthetic joint infection due to these microorganisms:

- *Proteus mirabilis* 101, *P. vulgaris* 2, *P. penneri* 2, *Proteus* spp. 4
- *Enterobacter cloacae* 82, *E. aerogenes* 11, *Enterobacter* spp. 4
- *Klebsiella pneumoniae* 51, *K. oxytoca* 6, *Klebsiella* sp. 1
- *Citrobacter* species 8 (C. koseri 6, C. freundii 2), *Providencia* species 7 (P. stuartii 6, P. rettgeri 1), *Salmonella* species 4
- *Pseudomonas aeruginosa* in all but five cases: *P. stutzeri* P. stutzeri and *P. putida* were identified in one case each and *Pseudomonas* spp. in three cases
- *Acinetobacter baumannii* 12, *A. calcoaceticus* 1
- *Comamonas* spp. 2, *Achromobacter* spp. 2, *Stenotrophomonas maltophilia* 1, *Ochrobactrum anthropi* 1
- Other Gram-negative bacilli include *Pasteurella multocida* 3, *Haemophilus* spp. 2, *Campylobacter fetus* 1
- *Corynebacterium diphtheriae* 6, *C. jeikeium* 4, *C. aquaticum* 1, *C. ulcerans* 1

More than one anaerobic bacterium was involved in eight cases of prosthetic joint infection:

- Two species of anaerobic Gram-positive bacilli were identified in one prosthetic joint infection
- *Cutibacterium acnes* 83, *C. avidum* 6, *Cutibacterium* without identification to species level 22
- *Clostridium perfringens* 3, *C. absonum* 1, *C. ramosum* 1, *C. septicum* 1, *C. sphenoides* 1
- Two patients had more than one species of aerobic Gram-negative bacilli (three species in one case and two species in the other one)
  - *Bacteroides fragilis* 12, *B. stercoris* 2, *B. thetaiotaomicron* 1, *Bacteroides* sp. 1
  - *Prevotella* species 5 (P. bivia 2, P. corporis 1, P. melaninogenica 1, P. buccae 1), *Parabacteroides distasonis* 1, *Porphyromonas asaccharolytica* 1, *Fusobacterium* sp. 1
  - *Veillonella* sp.
  - *Mycobacterium tuberculosis* 5, *M. fortuitum* 4
  - *Candida albicans* 16, *C. parapsilosis* 6, *C. glabrata* 2, *C. tropicalis* 1, *C. famata* 1, *Candida* sp. 1
  - *Aspergillus fumigatus* 2, *Scedosporium apiospermum* 1
species were involved in 9% and 8% of cases, respectively, in a recent large multicentre study [98]. Among the streptococci, *Streptococcus agalactiae* was the species most often isolated. More than 50% of *Enterococcus* species were involved in infections occurring in the first 90 days after prosthesis implantation, and more than 50% of cases were polymicrobial infections [100]. *Enterococcus faecalis* was isolated in more than 85% of enterococcal infections [98, 100]. In most past series, aerobic Gram-negative bacilli were implicated in less than 10% of cases of prosthetic joint infections [9, 55, 88]. Recently, however, studies in different geographical areas have reported higher frequencies of these pathogens, ranging from 17% to 42% [98, 101–106]. The percentage of *Enterobacteriaceae* appears to be increasing, and the most common species isolated (in descending order) are *Escherichia coli*, *Proteus* spp., *Enterobacter* spp. and *Klebsiella* spp. [98, 105]. Anaerobic bacteria were involved in 7% of all cases of prosthetic joint infection in the recent large multicentre study referred to above, with *Cutibacterium* spp. (formerly *Propionibacterium* spp.) being the most commonly identified anaerobic bacterium (5% of all infections) [98]. *Cutibacterium acnes* is a low-virulence microorganism, generally found in the skin microbiota and sebaceous glands. This microorganism can be inoculated at the time of surgery, but most infections have an indolent clinical course and are usually diagnosed months after prosthesis implantation. Less frequently isolated in prosthetic joint infections are aerobic Gram-positive bacilli, such as *Corynebacterium* spp. (2%), fungi (1%) and *Mycobacterium* spp. (<1%) [98]. Even though fungi are not commonly involved in prosthetic joint infections, the proportion of infections has significantly increased in recent years [98]. In decreasing order, the following species are involved in more than 80% of all prosthetic joint infections: *S. aureus*, *S. epidermidis*, *E. coli*, *Pseudomonas aeruginosa*, *E. faecalis* and *P. acnes* (it should be remembered that coagulase-negative staphylococci are not often identified to the species level, so that *S. epidermidis* may be the most common species) [98].

The threat of infection caused by multidrug-resistant organisms is increasing worldwide, yet little is known about
their possible role in prosthetic joint infection. In one recent study, multidrug-resistant bacteria were involved in 14% of these infections, including methicillin-resistant *S. aureus* (8%) and multidrug-resistant Gram-negative bacilli (6%) [98]. The percentage of methicillin-resistant *S. aureus* varies in studies performed in different geographical areas [98, 103, 107]. Of particular concern are data that suggest an increase in the proportion of multidrug-resistant bacteria in recent years, mainly due to the increase in multidrug-resistant Gram-negative bacilli [98]. The significant (almost 18%) and increasing quinolone resistance found in a recent study is of greatest concern because ciprofloxacin is considered a cornerstone of the treatment of prosthetic joint infections caused by aerobic Gram-negative bacilli [108].

Most infections are monomicrobial; usually fewer than 20% of infections are polymicrobial [55, 98]. Aerobic Gram-negative bacilli, enterococci and *S. aureus* are, in decreasing order, the most commonly isolated microorganisms in polymicrobial infections [109]. Polymicrobial infections occur more often as early-onset infections, and they are also more frequent in infected hip hemiarthroplasty than total hip arthroplasty infections.

In 4–12% of cases, no microorganisms are detected [50, 110]. This is related to various factors, which include the use of preoperative antimicrobials; the definition of a positive culture result, whether a positive culture represents contamination; the method of obtaining and transferring culture samples to the laboratory; and the number and type of specimens obtained for microbiological diagnosis [55, 110]. The most important risk factor for culture-negative prosthetic joint infection is antecedent antimicrobial therapy.

Although the most common causative organisms of prosthetic joint infections overall are coagulase-negative staphylococci and *S. aureus*, there are significant differences depending on the category of infection [109]. Early infections are characterized by a preponderance of virulent pathogens (*S. aureus*, aerobic Gram-negative bacilli, mainly *Enterobacteriaceae* and *Pseudomonas aeruginosa*), multidrug-resistant organisms (methicillin-resistant *S. aureus* and multidrug-resistant
Gram-negative bacilli) and polymicrobial infections. Coagulase-negative staphylococci are the leading cause of chronic infections, while *S. aureus* is the most common isolate found in acute haematogenous infection. Gram-negative bacilli and *Enterococcus* spp. are significantly more often found in early postoperative infections than in other categories of infection, while *Streptococcus* spp. are more frequently found in haematogenous infections. The four most commonly involved species in each classification group in a large recent study were (1) chronic infections, *S. epidermidis* (33%), *S. aureus* (20%), coagulase-negative staphylococci not identified at the species level (17%) and *P. acnes* (5%); (2) early post-interventional infections, *S. aureus* (36%), *S. epidermidis* (16%), *E. coli* (15%) and *P. aeruginosa* (15%); and (3) acute haematogenous infections, *S. aureus* (39%), *E. coli* (13%), *S. agalactiae* (11%) and viridans group streptococci (5%) [98].

There are also differences in the relative frequency of the microorganism with respect to the infected joint, although staphylococci predominate in all types of prosthetic joint infection [55]. A large single-institution database from the Mayo Clinic suggests that hip arthroplasty patients have a lower frequency of *S. aureus* than coagulase-negative staphylococcal infection compared to patients with infected knee arthroplasty, where the frequency of the two types of staphylococci is similar [55]. Anaerobic bacteria, including *P. acnes*, seem to be more frequently identified in hip than in knee arthroplasty infections. Among hip arthroplasties, significant differences have been found in the aetiology of infected hemiarthroplasties (an urgent procedure for the treatment of femur fractures) and total hip arthroplasties (usually an elective procedure performed on patients with generative joint diseases) [111–113]. Patients with infected hip hemiarthroplasties are older, have more comorbidities and early infections than patients with infected total hip arthroplasties. Compared to total hip arthroplasty infections, hemiarthroplasty infections are characterized by a greater preponderance of Gram-negative bacilli, multidrug-resistant organisms and polymicrobial infections [111–113]. Shoulder arthroplasty infection is much more commonly caused by *C. acnes*.
than other prosthetic joint infections of other joint types. The notable presence of *C. acnes* may be related to the fact that it is prevalent on the skin of the upper body where there is a high density of sebaceous glands (a well-known habitat of this organism). Coagulase-negative staphylococci are also more frequently involved in shoulder infection than *S. aureus*. *S. aureus* and coagulase-negative staphylococci cause over three quarters of elbow arthroplasty infections [55].

In summary, most prosthetic joint infections are monomicrobial and caused by staphylococci; however, the rate of infection caused by aerobic Gram-negative bacilli seems to have increased in the last few years, as well as the proportion of multidrug-resistant infections, mainly due to the increase of resistant Gram-negative bacilli. These data suggest that empirical and specific antimicrobial therapy for prosthetic joint infections could become more challenging. Reassessing antimicrobial prophylaxis strategies and other preventive measures for patients undergoing joint replacement could be required [66, 104]. Identifying the risk factors for antimicrobial-resistant prosthetic joint infections may help prevent them.

### 2.5 Pathogenesis

In order for microorganisms to initiate an infection, they must be able to reach the implant, which is introduced into a sterile field in the body using an aseptic surgical procedure. Arguably, the most frequent way of reaching the implant is via the contamination of the prosthesis during implant surgery [55, 114, 115]. This is considered the probable origin of the majority of infections. Another mechanism is for infection to progress from a contiguous focus of infection. Infection of the surgical wound in the days following surgery could be the source of a deep infection. In some cases (especially knee surgery), it should be remembered that there is very little soft tissue between the prosthesis and the skin surface, so that a prosthesis-related infection can almost always be suspected when a surgical wound infection appears following knee implant
surgery [116]. The contiguity mechanism can be the source of many acute infections and of a limited number of delayed ones. The last source of infection is haematogenous, when a microorganism gains access to the implant from a distant focus during a bacteraemia episode. This mechanism is possibly the least frequent one, with haematogenous infections comprising around 10% of all prosthetic joint infections in most series [98].

Despite the different routes that microorganisms can take in order to reach the implant, the pathogenic process seems to be common in most of them, characterized, in terms of the theory put forward by A.G. Gristina, as “the race for the surface” [114]. According to this theory, the implantation of a prosthetic device initiates a race between bacteria and host cells to colonize the implant. If the bacteria win the race, they attach to the surface of the implant, start to multiply and prevent the host tissue from integrating with the device. If the host cells win, they cover the surface of the implant, so enhancing tissue integration and preventing bacterial attachment and subsequent infection. Differences between the host tissue and the characteristics of the bacteria can lead to different types of infection, but the bulk of the process is considered to be the same for all of them.

The process of bacterial adhesion is a complex one and can be divided into different stages according to the relationship established between the bacteria and the surface of the device [117, 118]. In the initial stages, long-range forces acting between the microorganism and the surface serve to bring them closer together; the forces are physical ones and include gravity, Van der Waals forces, other electrostatic interactions and Brownian movement. They act when the microorganisms are 100 \( \mu \text{m} \) away from the surface and so relatively weak; the bond that the microorganism establishes with the surface is thus not a strong one, and it is easy to detach the bacteria from the implant during this stage.

When bacteria come closer to the surface (10 \( \mu \text{m} \) or less), a new set of forces starts to act. These are strong forces of a chemical nature that establish a tight bond between the organism and the surface by means of ionic and covalent links. In this part of the process, the molecules present in the bacterial cell are extremely important, because they are the
key to creating the bond mentioned above. These molecules, known as adhesins or MSCRAMMs (microbial surface components recognizing adhesive matrix molecules), vary depending on the bacterial species and so behave differently according to the material [119]. It should however be borne in mind that the surface of the implant is rapidly covered with host molecules (blood and extracellular fluid) during surgery. These host cell proteins act as receptors for most of the adhesins of the different microorganisms, such as the fimbriae or pili of Gram-negative organisms or the family of *Staphylococcus* proteins, which includes protein A, clumping factor A, fibronectin-binding protein A and others [120, 121]. However, microorganisms can also attach to uncovered device surfaces, as many in vitro studies have demonstrated, and differences between species can be found in this setting too [119, 122].

Once attached, the bacteria start to multiply and produce extracellular matrix, which is the main component of a biofilm. In some cases, bacteria produce toxins and other pathogenic factors that trigger an acute inflammatory response with polymorphonuclear leukocytes. In such cases, acute infection appears with a large number of planktonic organisms. However, beneath this process, a biofilm is developing, which may be the cause of delayed infection in the future [123].

Biofilm development is the most important pathogenic factor in infections related to biomaterials, including device-related osteoarticular infection [55, 115, 124]. A biofilm is a superstructure composed of microorganisms and extracellular matrix attached to a surface or associated with an interface, in which the organisms form complex communities and interact with each other, with metabolic processes that trigger differentiation into subpopulations of cells. Biofilm development starts when adhered bacteria start to multiply and produce extracellular matrix. This is the main component of biofilm and includes various proteins, glycopeptides, lipids, DNA and many other molecules in a species-specific composition, although water is the most abundant component in all cases. Extracellular matrix serves to protect its components from external aggression and is also the medium that allows sessile organisms to communicate with each other, a source of nutrients for the different cell populations inside the
structure and the environment in which the various metabolic activities take place [124].

Bacteria are known to communicate with each other using quorum sensing [124]. This involves very small, species-specific molecules that can interact with other individual cells. When the cell density inside the biofilm is high enough (a quorum is reached), this communication becomes general rather than individual and the process of metabolic differentiation inside the structure is initiated, with the activation and deactivation of specific genes. This leads to the development of subpopulations of metabolically inactive organisms, actively multiplying ones, cells designed to detach from the structure in order to find new areas to colonize and the development of “persister” cells. “Persister” cells are of enormous medical interest because they behave like spores (metabolically inactive, extremely resistant to environmental aggressions), whose objective is biofilm survival, even if all other cells are destroyed.

Once it is fully established, the biofilm becomes an extremely important resistance factor against antibiotics and the host immune system by deploying the full range of its various mechanisms, including impermeability, metabolically inactive organisms and persister cells, activation and/or interchange with resistance genes and probably many others [125]. The phenotypic consequence of this is that increased concentration and effort is necessary to eradicate the bacteria inside the biofilms [126]. In many cases, this requires that the infected implant be physically removed in order to eliminate the biofilm [125].

Related to biofilm maturation is another pathogenic event that occurs in prosthetic joint infections: the ability of microorganisms to survive intracellularly. First suggested by Drancourt in 1993 [127], intracellular survival was recently demonstrated in experimental in vivo models [128]. The possible mechanism behind this phenomenon starts when sessile cells differentiate in order to detach themselves from the mature biofilm. Various nonprofessional phagocytes, such as osteoblasts, fibroblasts, epithelial cells and so on, are able to phagocytize these bacteria, which are nevertheless able to survive within the phagocyte. This process has been studied in greater detail for “small colony variants” (SCV) of *S. aureus*
These strains are able to survive intracellularly without destroying the cell because they lack some of the enzymes responsible for cell lysis when usual strains of *S. aureus* are internalized [130]. In those cases where a biofilm is physically removed, the intracellular cells can be regarded as a bacterial reservoir. In this situation, the intracellular organisms could be the source of a new colony on the new prosthesis, with a new biofilm and the development of a new infection (Fig. 2.2).

**Figure 2.2** Pathogenic process of prosthetic joint infections including adherence steps, biofilm development and intracellular bacteria, with the potential relationships between them. 1 Bacterial adherence (weak forces), 2 bacterial adherence (strong forces), 3 biofilm development (bacterial multiplication and production of extracellular matrix); 4 biofilm development (bacterial detachment); 5 intracellular bacteria
The pathogenesis of prosthetic joint infections is a complex procedure that needs to be taken into account in order to establish proper therapy for the patient, because of the important implications of these phenomena for the outcome of the patient.

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