Prophylactic antimicrobial regimens providing adequate drug levels in tissue during surgery and for periods of 24 hours to 14 days are of proven effectiveness in reducing infection rates after joint arthroplasty. Although most surgeons employ short regimens of <24 hours’ duration, their efficacy has not been clearly established for joint replacement in placebo-controlled trials. Careful preparation of the patient before surgery and attention to operating room asepsis are also important. In early postoperative infections, surgical debridement and antibiotic treatment may allow conservation of the prosthetic components. In established infection in which the components have become loose, radical surgical debridement must include removal of all prosthetic material as well as involved bone and soft tissue; reconstruction by exchange arthroplasty has an acceptable success rate. For infections caused by organisms of low virulence, exchange arthroplasty has been successful as a one-stage procedure, but no comparative trial with two-stage exchange has yet been reported.

Prosthetic joint replacement is a powerful tool in the contemporary management of severe disabling arthritis. Deep prosthetic infection impairs function and general health, and its management is difficult and expensive. Some infections are clearly blood-borne from distant sources, but the majority appear to be initiated by operative contamination by organisms from room air (mainly shed from the skin of the operating team) or from the recipient’s own skin. Cost-effective perioperative preventive strategies are therefore critical in reducing the incidence of postsurgical infection [1]. In established infection, the objective is restoration of acceptable function with control of the local and systemic consequences of infection. The infected total joint replacement may be considered as a special case of chronic osteomyelitis, for which there are clearly established principles of management utilizing both surgery and antimicrobial agents.

Coventry’s proposed classification of infection after joint replacement [3] has been widely used. Stage 1 infections were those occurring in the first 3 months after surgery. Stage 2 infections occurred between 3 months and 2 years after surgery. Late infections (stage 3) occurred after 2 years. Schmalzried et al. [4] proposed classification by mode of infection—surgical, hematogenous, or recurrent—but admitted that it is always possible to prove the etiology of deep periprosthetic sepsis. In a recent review [5], ~50% of suspected hematogenously spread infections occurred within 2 years of surgery. A recent classification proposed by Estrada et al. [6, 7] (table 1) reflects the increasing frequency of revision surgery and current management concepts.

**Epidemiology**

** Infecting Organisms

Aerobic gram-positive organisms, particularly staphylococcal species, are the commonest isolates; *Staphylococcus epidermidis* predominated in some series [8] and *Staphylococcus aureus* in others [7]. Gram-negative enteric species may be isolated, and the majority apparently are derived from the genitourinary tract [4]. Multiple isolates from operative specimens have been reported in 25%–40% of cases [7, 9]. Even when single species are identified, ribotyping may indicate that the isolates are not identical [9]. Increasing numbers of multiply resistant isolates of *S. epidermidis* are being recovered [10].

Reported infection rates vary between centers, probably because of differences in the populations presenting for surgery, definition of infection, and intensity of surveillance, as well as the employment of prophylactic measures. Rates of infection have declined since the introduction of total joint arthroplasty. Deep infection rates, although mostly <2.5%, continue to range over an order of magnitude below that level [11].
Table 1. Classification of infected total joint replacements.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Positive intraoperative culture</td>
<td>Two or more intraoperative specimens positive for the same organism</td>
</tr>
<tr>
<td>Early postoperative infection</td>
<td>Apparent within 1 month of surgery</td>
</tr>
<tr>
<td>Late chronic infection</td>
<td>Presenting &gt;1 month after surgery, with an insidious clinical onset</td>
</tr>
<tr>
<td>Acute hematogenous infection</td>
<td>Acute onset of clinical symptoms in a previously well-functioning joint</td>
</tr>
</tbody>
</table>

NOTE. Data are from [6].

Host Factors

Local host factors associated with an increased risk of infection include poor-quality soft tissues, previous local surgery [12, 13], and previous sepsis [14, 15]. However, previous sepsis does not preclude successful joint arthroplasty [16, 17]. In a review of published series of joint replacements in patients with hemophilia, the cumulative infection rate was 9% [5]; the authors hypothesized that recurrent intraarticular bleeding may have had a role.

Systemic factors that have been associated with increased risk of infection include remote infection at the time of surgery [18], diabetes mellitus [19], sickle cell disease [20], and rheumatoid arthritis [5, 21].

Prophylaxis Against Infection After Total Joint Replacement

Preoperative Evaluation and Management

As well as general measures such as cessation of smoking, specific attention to comorbidities is important. Although there are no robust data specifically concerning joint replacement [5], temporary withdrawal of methotrexate may reduce infection rates in susceptible patients [22]. Stabilization of diabetes [19] should be achieved. As a matter of surgical principle, any site of skin infection should be healed before prosthetic surgery is performed. Although hematogenous infection from dental or periodontal sepsis appears to be uncommon [4], it is rational to attempt preoperative control of such infections. As the genitourinary tract is an important source of hematogenous infection [4], urinary tract infection should be identified preoperatively and eradicated. In joint replacement, preoperative lymphocyte counts of <1,500/mm³ and albumin levels of <3.5 g/dL are associated with greater frequency of wound complications [23].

Perioperative Care

Infection after joint replacement is usually a consequence of wound contamination by bacteria from operating room air and from the patient’s own skin [24–27]. Therefore, strategies to reduce the number of contaminated particles are an important component of prophylactic efforts. Routine preoperative skin disinfection over a period of 12–24 hours, although effective in reducing contamination of the superficial layers of the skin, has little effect on the deeper layers, and recontamination occurs rapidly [28]. Therefore, prior to the immediate preoperative skin preparation, good normal hygiene is sufficient. Adhesive drapes are also widely used during surgery, although their value is unclear. Their use may be associated with greater numbers of surface organisms during surgery [29]; they have no confirmed impact on infection rates and contribute to operating room and disposal costs [30].

Good operating room discipline is essential in reducing infection rates in prosthetic surgery. The importance of the shedding of potential pathogen–carrying skin fragments by members of the surgical team and others in the operating room has been clearly established [31]. Reduction of movement within the operating room has proven effectiveness in reducing the number of cfu in the air [32].

Conventional positive-pressure turbulent-ventilation operating theaters contain up to 10⁴ cfu/m³ [33]. For prosthetic surgery, standards aim for particle counts of <5 cfu/m³ [34]. Such counts can be achieved by use of systems combining high filtration efficiency, frequent air change, and directional flow and by use of impermeable clothing or suit ventilation to further reduce shedding by the operating team. Many institutional case-series support the use of these measures, but the evidence from powerful direct-comparative studies is largely confined to the use of obsolescent horizontal laminar-flow systems [33, 35]. Current evidence suggests that although ultraclean air systems do appear to reduce the incidence of infection in total joint replacement, the additional benefit is probably small when antibiotic prophylaxis is also used.

The use of ultraviolet irradiation at 254 nm (UVC) to sterilize the air in operating rooms has been described over several decades [36, 37]. Despite low potential risk to properly protected staff and evidence of potential efficacy in clean orthopedic surgery, its use has not become widespread because attention has been focused on provision of ultraclean air. Recently, an extensive reinvestigation of UVC has been described [38] in which the level of contamination of the surgical environment compared favorably with that achieved in an ultraclean air enclosure. This may be a cost-effective option [39] and deserves further investigation.

Antibiotic Prophylaxis

The agent chosen for antibiotic prophylaxis should be effective against the expected pathogens, have a pharmacodynamic profile that will ensure adequate antimicrobial activity at the site of surgery throughout the procedure, have minimum toxicity or allergenicity, and carry a low risk of inducing resistant bacterial strains. Some confusion has been generated in the past by reports of widely differing abilities of antibiotic agents...
to penetrate bone. These appear to reflect methodological variations. In practice, the concentration in the bone extracellular space at the interface with the prosthesis should equilibrate with the concentration in the blood [40]. Regional perfusion below a tourniquet can provide very high local tissue antibiotic levels [41], but infection rates following use of this technique have not been reported.

The effectiveness of systemic antibiotic prophylaxis in reducing the incidence of deep infection after total joint replacement has been examined in randomized trials. Many of these trials have been small and have individually lacked power to confirm or refute the effectiveness of antimicrobial prophylaxis. Therefore, although there have been differences between studies in the agents tested and in the details of the regimens employed, a meta-analysis of the data is briefly presented. Trials were identified by electronic searching of the databases MEDLINE and EMBASE and were eligible if they evaluated in a randomized design the use of prophylactic antimicrobial agents and the outcome of deep prosthetic infection. Odds ratios and 95% confidence intervals were calculated for each individual study and for the pooled data, with use of the Peto log odds ratio method.

Four randomized controlled trials, carried out between 10 and 25 years ago [42–45], compared antimicrobial administration with a placebo or no prophylaxis. Pooling of the data supports the value of antimicrobial prophylaxis in reducing infection rates after joint replacement (pooled OR, 0.24; 95% CI, 0.15–0.37). These studies employed antimicrobial regimens lasting 24 hours to 2 weeks. Although the efficacy of 8–12-hour prophylactic regimens has not been shown in placebo-controlled trials, most surgeons now use such regimens.

Four trials [46–49] have compared the efficacy of multiple-dose programs of different duration. Only one tested a regimen as short as 12 hours. The data from these studies, considered either individually or pooled, are insufficient to confirm whether shorter regimens are preferable or inferior (pooled OR, 1.12; 95% CI, 0.43–2.92).

The efficacy of single-dose prophylactic regimens is also uncertain. Two trials [50, 51] examined a single preoperative dose of the same agent given for 12–24 hours (pooled OR, 1.58; 95% CI, 0.62–3.98). Such regimens cannot yet be recommended. Single-dose prophylaxis with agents that are more slowly eliminated may be acceptable. Three trials [52–54] compared deep infection rates after a single dose of an agent with a long half-life (≥6 hours) vs. multiple doses of another, shorter-acting agent (pooled OR, 0.69; 95% CI, 0.25–0.98). Since two of these three trials compared agents of different types and antimicrobial activity, the question of optimal duration of prophylaxis remains open.

Many surgical units have reported the use of antibiotic-impregnated polymethylmethacrylate bone cement. Two trials comparing this route of administration with systemic prophylaxis in primary joint replacement have been reported [55, 56]. Deep prosthetic infection occurred more frequently in the group receiving systemic antimicrobials (OR, 2.00; 95% CI, 0.94–4.38), but superficial infections appeared less common in those receiving systemic prophylaxis (OR, 0.45; 95% CI, 0.20–0.99).

Some surgeons believe that antibiotic prophylaxis should be continued until suction drains are removed, but there is no direct evidence that this is necessary. Colonization of drains by skin organisms can certainly occur [57], but in only 10% of cases with positive drain-tip culture does overt infection develop. Further studies that address the role of drains and vascular access sites in postoperative bacteremia after joint replacement are required.

The universal use of antibiotic prophylaxis in joint replacement surgery also has adverse effects. The emergence of resistant strains is a well-established complication [58]. Administration of penicillin carries a risk of anaphylaxis and skin sensitivity. Penicillins are now rarely used in prophylaxis; most units prefer cephalosporins, although these carry a risk of pseudomembranous colitis 40 times that of penicillins [59].

Prophylaxis Against Hematogenous Infection

Experimental studies [60, 61] suggest that infection of a joint implant from bacteremia most readily occurs in the early postoperative period. During this period the main sources are likely to be skin infections, including decubitus ulcers [5], vascular access sites [62, 63], and the urinary tract [64]. Up to 30% of females and 8% of males presenting for total joint replacement have bacteriuria [65, 66]. Although these patients are treated, some will develop urinary tract infection postoperatively, but the bacteria involved may be different [67].

The incidence of bacteriuria increases with the duration of indwelling catheterization [68]. The optimal management of urinary retention after total joint replacement is controversial. Alternatives include routine catheterization for 24 hours [67], since up to half of all total hip replacement recipients require catheterization for urinary obstruction in the early postoperative period. Routine catheterization for 48 hours may not result in higher infection rates than with intermittent catheterization, but normal voiding returns more quickly when intermittent catheterization is begun at the onset of retention [69]. Alpha blockade may reduce the risk of postoperative retention [70].

To prevent late hematogenous infection, prompt treatment of intercurrent bacterial infections is important. Dental treatment and endoscopic investigation or surgery carry a risk of precipitating bacteremia. Although some investigators have recommended that all joint replacement patients undergoing dental work should receive prophylactic antibiotics [71], this may be associated with unacceptable costs and incidence of antibiotic-induced adverse effects in comparison with the very small risks incurred [72]. Modeling indicates the cost-effectiveness of administration of erythromycin [73] or cephalexin [74] for higher-risk cases. Although there are inadequate data at present to confirm these predictions, prophylaxis is recommended in the presence of overt or imminent dental sepsis but
not for all dental procedures, except in cases where systemic or local risk factors are considered to be important.

**Diagnosis and Management of Joint Replacement Infection**

**Early Postoperative Infection**

Early postoperative infection is usually overt and purulent. Diagnosis can usually be readily made with evidence from the history and physical examination, confirmed by simple imaging and laboratory investigations. Ultrasonography is useful to demonstrate the location of an infected hematoma or abscess [75, 76] and to guide diagnostic aspiration. The C-reactive protein level appears to have a higher predictive value for deep sepsis than does the erythrocyte sedimentation rate or WBC count [77, 78]. The C-reactive protein level falls rapidly after the second postoperative day following uncomplicated joint arthroplasty; maintained high levels may indicate possible peri-prosthetic infection. Scintigraphy presently has no important role in this clinical context.

Soft-tissue debridement with antibiotic therapy and retention of the prosthesis is successful in ~70% of cases of early post-surgical infection in both hip [7] and knee [79, 80]. Antibiotics may be administered systemically, by temporary implantation of antibiotic-impregnated cement beads [7] or by implantation of pumps [81]. No rigorous comparative studies of route or duration of administration have so far been reported; such choices should be made on the basis of the individual patient’s condition and the institution’s antimicrobial policy. Tsukayama et al. [7] used 4 weeks of intravenous therapy; in Europe the use of oral regimens, often of rifampin in combination with other agents [82], is quite common.

**Chronic Deep Infection**

Low-grade chronic infection often presents as pain alone and is difficult to distinguish from aseptic prosthetic loosening. The evaluation protocol should include history, physical examination, hematologic screening, imaging, and aspiration.

Hematologic screening has low sensitivity and specificity for chronic prosthetic infection, particularly in patients with rheumatoid arthritis or who are immunosuppressed. Imaging techniques are also of limited value. In established chronic infection, radiological changes are often difficult to distinguish from those of aseptic loosening, although extensive loosening occurring in the first 2 years after implantation is suggestive of chronic infection.

Localized periosteal new-bone formation around the implant is strong evidence of infection but is relatively rarely seen in this clinical context. Scalloped cortical erosions are suggestive of infection but may also be associated with accumulation of sterile polyethylene or methylmethacrylate debris.

Scintigraphic techniques have also proved disappointing. Reports of the sensitivity and specificity of both 99mTc bone scanning and techniques that localize concentrations of inflammatory cells around the implant vary widely. 99mTc bone scanning alone cannot distinguish septic and aseptic painful loose prostheses [83]. 99mTc/gallium scanning, with a high reported specificity but low sensitivity, cannot rule out infection. Indium-labeled leukocyte scans appear to have better sensitivity but poorer specificity than 99mTc/gallium studies [84]. The efficacy of newer techniques such as immunoglobulin labeling remains unclear.

Ultimately, only the identification of an organism or a biopsy confirming the presence of acute inflammatory cells can confirm the diagnosis. Superficial sinus cultures are poor predictors of the active organism [89]. Aspiration should be carried out. Ultrasonography may aid needle placement [90]. Isolation of a microorganism from deep-tissue specimens obtained at surgery can be achieved in >80% of cases. Multiple specimens should be taken for both culture [10] and histopathologic analysis. If a blood culture system is used for specimens from possibly infected joints, care should be taken to avoid the danger of false-positive results [91]. Frozen sections from the prosthetic interface at surgery may confirm the presence of acute inflammation, even if cultures are negative [92–94].

In patients with established infection for whom surgery is contraindicated, medium-term control of infection may be achieved by the use of antimicrobial therapy with oral or injection regimens, but the long-term success rate is poor since prosthetic loosening occurs and eradication of the infection cannot be ensured [95, 96]. No randomized trials have compared either antibiotic suppression with surgical management or different regimens of antibiotic suppression.

Worthwhile results can be obtained with surgical treatment of chronic prosthetic infection, although these results are inferior to those obtained with primary joint replacement and with revision for aseptic loosening. Removal of the loose implant is essential for both eradication of infection and relief of pain. Its replacement by another prosthesis (exchange arthroplasty) is the best method of maintaining acceptable function. This may be combined with debridement in a single procedure or staged in two procedures 4–6 weeks apart. Most experience with one-stage exchange is in total hip arthroplasty [97]. The debridement includes the removal of all implant-associated materials as well as involved bone and soft tissue. Occasionally, when exchange arthroplasty is contraindicated, salvage procedures such as excision arthroplasty in the hip or arthrodesis in the knee are employed.

Although for relatively avirulent infections the differences in outcome between one- and two-stage exchange arthroplasty are probably small, no randomized trials addressing the effectiveness of the two options have so far been reported. Surgical choice remains based on local tradition, personal experience, and the opinion of experts. Few surgeons would consider one-stage exchange for a frankly purulent infection or if the organism were known to be virulent.

Adjuvant antimicrobial therapy is an important element of management. Following the first stage of a two-stage exchange,
Antimicrobial therapy may be administered systemically, locally, or, most commonly, by both routes. Local administration may employ either an implanted pump [81] or an implant of antibiotic-impregnated bone cement. One small randomized trial [98] compared systemic therapy with the use of antibiotic-impregnated cement but lacked power to show even quite large differences between the two methods, both of which appear moderately effective in clinical practice.

Antibiotic-impregnated bone cement implants may take the form of solid spacers [99], beads [7, 100], or temporary arthroplasties that allow some function [101, 102]. Commercially available products include cements with gentamicin and others with combinations of agents. Although it is possible to add some antibiotic preparations to cement, there may be adverse effects on the strength of the cement [103]. If a cemented arthroplasty is chosen for the second-stage exchange procedure, antibiotic-impregnated cement may again be employed; in combination with 6 weeks of systemic antimicrobial therapy, this method has been associated with low rates of recurrence of infection [104].

Neither the minimum necessary period of antimicrobial administration nor the most cost-effective route of administration following exchange arthroplasty is known. Currently, most clinics use long periods of therapy, based on experience or on the stabilization at normal levels of laboratory values such as the erythrocyte sedimentation rate and the concentration of C-reactive protein. Data from well-planned and well-conducted clinical trials are needed.

The costs of managing a primary joint arthroplasty that becomes infected are 8–10 times those of a successful, uninfected arthroplasty [105]. One-stage exchange is clearly less expensive than two-stage exchange, as are the published outcomes, even in cases with sinus formation [106]. The outcomes are sufficiently similar to justify a randomized trial to compare the efficacy of the two regimens.

The functional results of excision arthroplasty of the hip as a salvage procedure after infection are generally poor [107–110]. The procedure is now recommended only when exchange arthroplasty is inappropriate, for example, in nonambulant patients with significant sepsis, in those with major bone loss associated with infection, and perhaps in some with gram-negative or multidrug-resistant staphylococcal infections.

When exchange arthroplasty in the knee fails, the preferred salvage procedure is arthrodesis, which can be achieved in ~80% of cases [111, 112]. Above-knee amputation has been required occasionally [113].

Conclusion

Although current results are better than appeared possible in the early years after the introduction of total joint arthroplasty, the management of established prosthetic joint infection remains difficult and expensive in terms of time and resources. Careful attention to prevention of infection is therefore important, but difficulties and uncertainties remain. The emergence of multiply resistant strains of *S. epidermidis* is a serious concern, as it suggests that currently favored antimicrobial agents will become less effective. Further large trials would be required to identify the most cost-effective prophylactic antimicrobial regimens.

Despite their widespread use, evidence of the cost-effectiveness of ultraclean air systems is surprisingly weak. A randomized trial incorporating incremental cost-effectiveness analysis would be required to confirm the efficacy of contemporary ceiling-mounted laminar-flow systems when used in addition to antimicrobial agents. In management, direct comparative trials of one-stage vs. two-stage exchange arthroplasty in established prosthetic infection are needed.

Joint arthroplasty is overall a cost-effective intervention [114]. Its practice—and in particular the management of its complications—deserves better evidence for the everyday choices being made.

References


