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Clinical guidelines in the management of prosthetic joint infection

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Clinical practice guidelines for the diagnosis and management of prosthetic joint infection have been produced by a range of organizations. Guidelines stress the importance of multi-disciplinary working and of adopting a methodical approach. This includes careful assessment of the patient's surgical, medical and psychosocial problems, rational investigation, a decision-making framework for surgery and targeted, sometimes prolonged, use of intravenous or highly bioavailable oral antibiotics. Despite limited high-quality evidence, adoption of clinical guidelines can improve practice by reducing variation and by establishing conditions for the subsequent conduct of multicentre studies or systematic reviews.

Keywords: multi-disciplinary, guidelines, management, consensus

The need for and use of guidelines

The significant challenges posed by prosthetic joint infection (PJI) have stimulated demand for clinical practice guidelines and consensus definitions. Ideally, these would allow best practice to be adopted universally, but even in the worst case, where the evidence is inconclusive, guidelines can catalyse the consistent and widespread application and audit of specific clinical protocols. Widespread guideline adherence allows much more effective and rapid comparison and pooling of outcome data within and across centres, and hence the development and testing of new and improved consensus strategies, even if initial recommendations are later changed. Given that in some published series the success rates are claimed to be as low as 50% or as high as 100%, there is a pressing need, for patients, to eliminate the avoidable variation in outcomes that is currently created by differing approaches to case management. Clinical guidelines aim to do that by setting out optimal diagnostic and treatment algorithms, paving the way for auditable clinical standards and benchmarked outcomes that can guide patient choice and the commissioning decisions of funding bodies.

The usefulness and use of guidelines have recently been discussed,[1] recognizing that the individualism of physicians may make some reluctant to follow published guidelines. To improve adherence to recommendations, it has been suggested that it is necessary to facilitate prediction of which patients are at risk of harm, recommend evidence-based treatments, ensure that these are delivered to the target patients and assess clinical response to those interventions.

Guidelines for the diagnosis and management of PJI

This brief review will focus on clinical practice guidelines recently produced by the Infectious Diseases Society of America (IDSA) in 2013[2] (for which two of the authors were panel members) and on the recent International Consensus on Periprosthetic Infection, concluded at a meeting in Philadelphia,[3] for which one of our authors led the oral antibiotic workgroup. Although other guidance has previously been produced by both the Société de Pathologie Infectieuse de Langue Française (jointly with 10 other French specialty societies in a 69 author guideline)[4] and the Italian Society of Infectious and Tropical Diseases,[5] the IDSA guidance and the International Consensus have the advantage of being the more contemporary and accessible, of having a multinational authorship and being specific to PJI. Like the French guideline group, the IDSA panel was multi-disciplinary in composition, though with a very strong bias towards infectious diseases specialists with bedside and laboratory backgrounds. For the interested reader, the French guidelines do provide valuable additional perspectives, covering the whole scope of device-related osteoarticular infection, giving considerable detail of different surgical techniques and encompassing psychosocial, preventive and medico-legal aspects. The International Consensus had a large, global membership organized into multiple workgroups responsible for different sections, with the whole consensus reviewed by the entire group.

Methodology

As is common in most clinical guidelines, particularly those produced under the auspices of professional specialty societies, the IDSA guideline was developed and written by clinicians with an expert interest in PJI. The literature was initially reviewed by the chair and vice-chair of the panel, searching multiple databases for publications produced between 1966 and April 2011 and including both multiple electronic search terms and hand searches of bibliographies. Consistent with the requirements set out by IDSA at the time of development, the results were not presented as a

formal systematic review, but as guidance that went through an iterative process of discussion and consensus, weighting the quality of evidence and the strength of recommendation, and written as a response to a number of key management questions.

By contrast, the International Consensus statement was produced under the auspices of the Musculoskeletal Infection Society of America. A total of 342 delegates from 80 different countries and over 50 different societies were involved, including clinical experts in orthopaedic infection, related medical disciplines and scientists with an interest in orthopaedic infection. The process culminated in a consensus assembly where a voting process was conducted. Voting was based on evidence, wherever present, as well as standard practices and expert opinion. It involved agreement, disagreement with the consensus statement or abstention from voting. The strength of the consensus was judged by the following scale: (i) simple majority: no consensus (50.1%–59% agreement); (ii) majority: weak consensus (60%–65% agreement); (iii) super majority: strong consensus (66%–99% agreement); and (iv) unanimous: 100% agreement.

The two approaches differ in that the IDSA specifically grades each level of recommendation based on the quality of evidence underpinning it, whereas the International Consensus presents a detailed discussion of the evidence accompanying each question, but concludes with a consensus statement and does not explicitly grade the evidence base of the recommendation given. Rather, the focus is on the strength of the consensus.

Recommendations for diagnosis and treatment of PJI

The IDSA guidelines are structured as responses to a series of questions that capture key management decision points when dealing with cases of PJI. These are:

(i) What pre-operative evaluation and intraoperative testing should be performed to diagnose PJI and what is the definition of PJI?
(ii) What different surgical strategies should be considered for the treatment of a patient with PJI?
(iii) What is the medical treatment for a patient with PJI following debridement and retention of the prosthesis?
(iv) What is the medical treatment for a patient with PJI following resection arthroplasty with or without staged reimplantation?
(v) What is the medical treatment for a patient with PJI following one-stage exchange?
(vi) What is the medical treatment for a patient with PJI following amputation?

Taken together, these six key questions result in 56 graded statements underpinning 39 key recommendations. Of these, a recommendation that 'monitoring of outpatient intravenous antimicrobial therapy should follow published guidelines' is made six times to cover all the different treatment scenarios (culture-positive and culture-negative), since the individual questions above are each meant to be answered separately. In consequence, there are in effect 51 independent graded statements underpinning 34 separate and specific recommendations.

The evidence and recommendation grading scheme is set out in Table 1, with the numbers of statements at each strength of recommendation mapped into the definition table. A detailed understanding of the strength of the recommendations highlights an important message from the guideline development process to date, namely the paucity of high-quality evidence, the extent to which best practice is currently defined by clinical experience, and the published clinical outcomes from a number of expert referral centres.

It is evident from Table 1 that while the panel considered there was good evidence for 13 of the 48 graded statements (9 of the 34 key recommendations contain at least one grade A recommendation), the panel was also unable to grade the majority of the recommendations above 'moderate' or 'poor' in strength. These recommendations were justified only by published descriptive studies, clinical experience and expert opinion. Even within the

Table 1. Strength of recommendations and quality of evidence for 51 statements (48 allowing for repeated statements regarding rifampicin combination therapies) regarding the diagnosis and treatment of prosthetic joint infections

Strength of recommendation	Definition of strength of recommendation	Quality of evidence[a]	Number of recommendations in guideline
A	good evidence to support a recommendation for or against use	I	3[b]
		II	9[c]
		III	4
B	moderate evidence to support a recommendation for or against use	I	0
		II	3
		III	19
C	poor evidence to support a recommendation	I	0
		II	0
		III	13

[a]Criteria for grading quality of evidence: I, evidence from at least one properly randomized, controlled trial; II, evidence from more than one well-designed clinical trial, without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), from multiple time-series or from dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
[b]Strictly, two recommendations; an A-I recommendation to pair rifampicin with ciprofloxacin appears twice.
[c]Strictly, seven recommendations; A-II recommendations to pair rifampicin with levofloxacin or with co-trimoxazole each appear twice.

grade A recommendations, there were very few that were based on properly randomized controlled trials, a salutary reminder of the historical difficulties in designing and undertaking appropriately powered studies in this relatively uncommon, yet complex, condition.

Within these constraints, the IDSA guidelines nevertheless articulate a set of principles and practices that are a consensus between expert practitioners from two centres in the USA, one in the UK and two in Switzerland. For simplicity, the summary algorithms used in the guidelines are reproduced as Figures 1–4, with the evidence gradings annotated on them.

The International Consensus is more comprehensive in its ambition, making 206 recommendations covering multiple areas, including prevention, diagnosis and treatment. There are similar constraints with respect to the quality of evidence underpinning the recommendations and there was a unanimous vote for only one recommendation—that operative room traffic should be kept to a minimum. Despite this, 202 questions received a super majority (strong consensus), two questions had weak consensus and only two questions did not achieve any consensus.

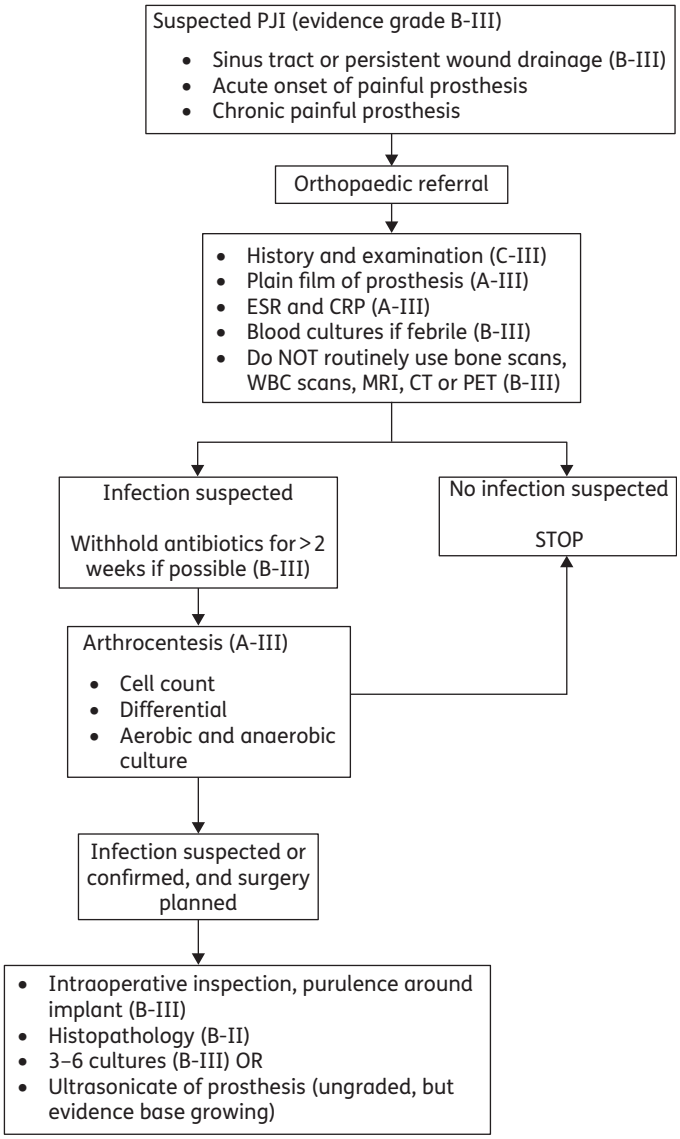

Figure 1. Diagnostic pathway. Adapted with permission from Osmon *et al.*[2]

Narrative summary of the IDSA guidance and comparison with the International Consensus

The key features of the guidelines can be summarized, in effect, into a care pathway for PJI. Multiple measures should be taken to prevent PJI, but, if suspected, it should be managed by a consultant orthopaedic surgeon with multi-disciplinary support from specialties including infectious diseases, plastic surgery, internal medicine, pathology and musculoskeletal imaging. Infection should be suspected whenever there is a sinus tract or a persistent wound over a joint replacement, when there is acute pain in a prosthetic joint or when the joint is chronically painful (especially if the joint was 'never right' or having a history of wound healing problems or prior infection) (B-III, and see Figure 1).

History and clinical examination (C-III) should elicit details and timings of primary implantation, revisions, washouts and other interventions, and courses of antibiotics given. In addition, the patient's symptoms, signs, level of function, mood, social circumstances and expectations must be elicited, as must medical comorbidities, medications and allergies. An elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), taken together, are considered useful if infection is not clinically obvious (A-III). A plain radiograph helps in assessment of loosening and surgical planning (A-III), but other forms of imaging are not routinely recommended (B-III).

Diagnostic arthrocentesis (aspiration for microscopy and culture) is recommended unless surgery is planned and/or the test result is not expected to alter management (A-III). Evidence supports not only anaerobic and aerobic culture, but also total cell count and differential white cell count (A-III). When the patient is stable, antimicrobials should be withheld for at least 2 weeks to maximize recovery of organisms (B-III). Blood cultures are advised in patients with fever or other features suggesting bacteraemia (B-III).

Antibiotics should also be withheld, if possible, for at least 2 weeks prior to surgery (A-II). A sinus tract communicating with the prosthesis, or purulence around the implant with no other cause, is considered definitive macroscopic evidence of infection (B-III). Highly suggestive microscopic evidence is considered to be the presence of acute inflammation in peri-prosthetic tissue (B-II). At operation, five or six independent samples should be obtained for culture (B-II), and infection is considered proven if two or more of these grow the same organism, and possible with other microbiological results according to the clinical circumstances. Clinical judgement is still considered to be important in synthesizing a working diagnosis based on the results of all the available information (B-III).

The IDSA guidelines stress the importance of the orthopaedic surgeon in making the ultimate decisions about surgical strategy (C-III) while also advocating multi-disciplinary consultation. Debridement, antibiotics and implant retention (DAIR) is advised when a patient presents with a well-fixed implant and no sinus tract within 30 days of implantation and <3 weeks of onset of symptoms (A-II; see summary Figure 2). The International Consensus produces a similar recommendation on the indication for DAIR (88%, strong consensus). While there is an acceptance that some patients who do not meet these criteria may

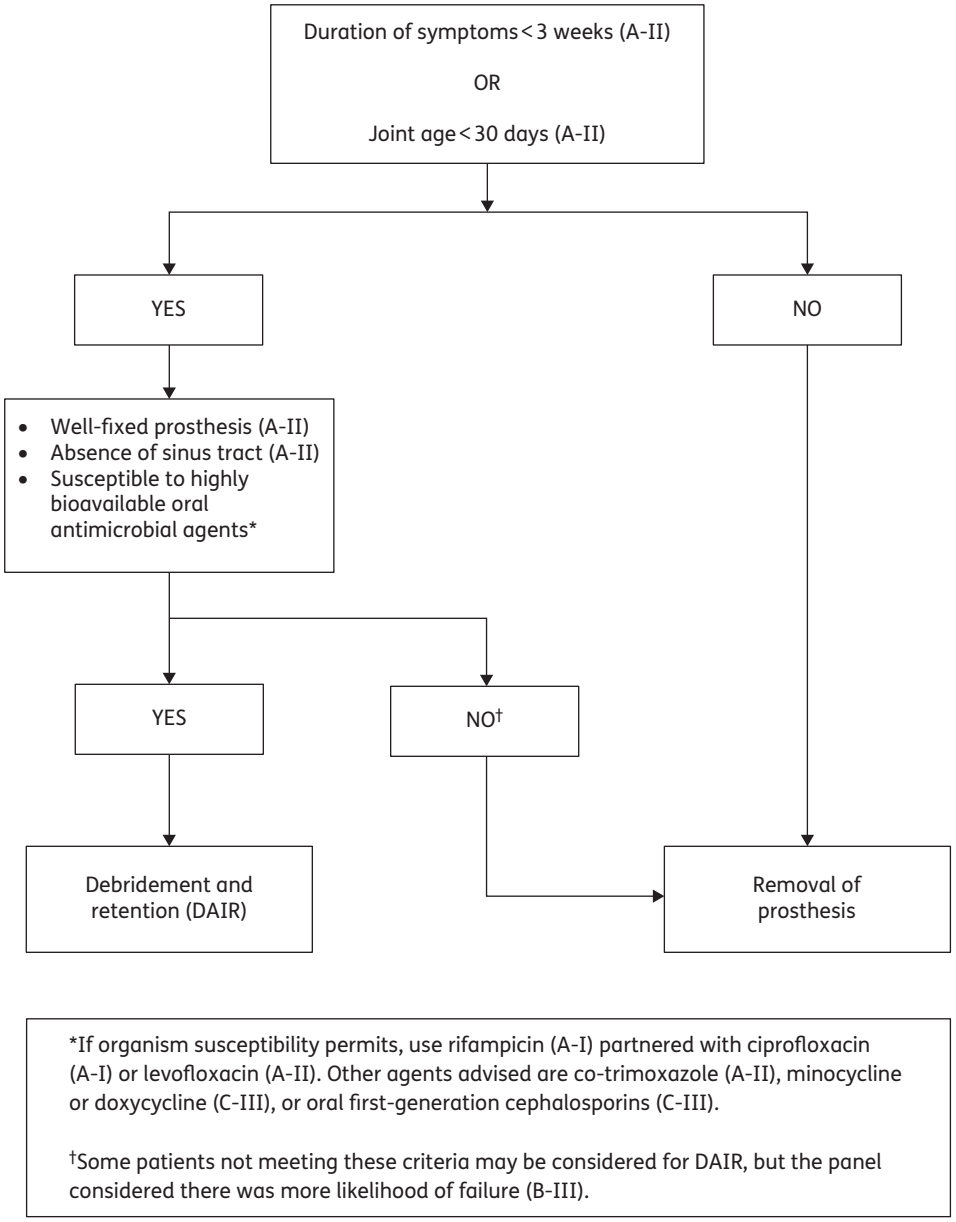

Figure 2. Criteria for DAIR. Adapted with permission from Osmon *et al.*[2]

nonetheless be suitable for DAIR (B-III), the overall advice is that all other patients proceed to one- or two-stage revision surgery. Criteria for considering one-stage revision (B-III) are set out in the summary Figure 3; otherwise, and for the majority of cases, two-stage revision is recommended (B-III). When not suitable due to massive bone or soft tissue loss, highly resistant microorganisms, unacceptable medical or surgical risks from another reconstructive attempt or patient preference, resection arthroplasty is advised (B-III; see summary Figure 4). Both the IDSA and International Consensus guidelines recommend that when amputation is considered as a last resort, a specialist centre be consulted for a second opinion (B-III), in view of the high associated mortality rates.

The IDSA guidelines give much specific information on the antibiotic treatment to accompany each of the surgical strategies of DAIR, one-stage revision, two-stage revision, excision arthroplasty and amputation (see summary Figure 5). The guideline panel considered the issue of suppressive therapy following DAIR and reports being split over whether it should be offered, and whether a long-term suppressive regimen should contain or avoid rifampicin as an agent. The identification of these differences of view and practice, even within a small expert panel, reflects the weakness of the evidence base available to help make informed decisions that factor in not only the true chance of successful implant retention but the morbidity of treatment, the functional outcome and the resulting quality of life for the patient. The International Consensus also makes no recommendation on duration of therapy following DAIR due to the absence of any controlled trial data. It directly quotes and concurs with the IDSA guidelines on the

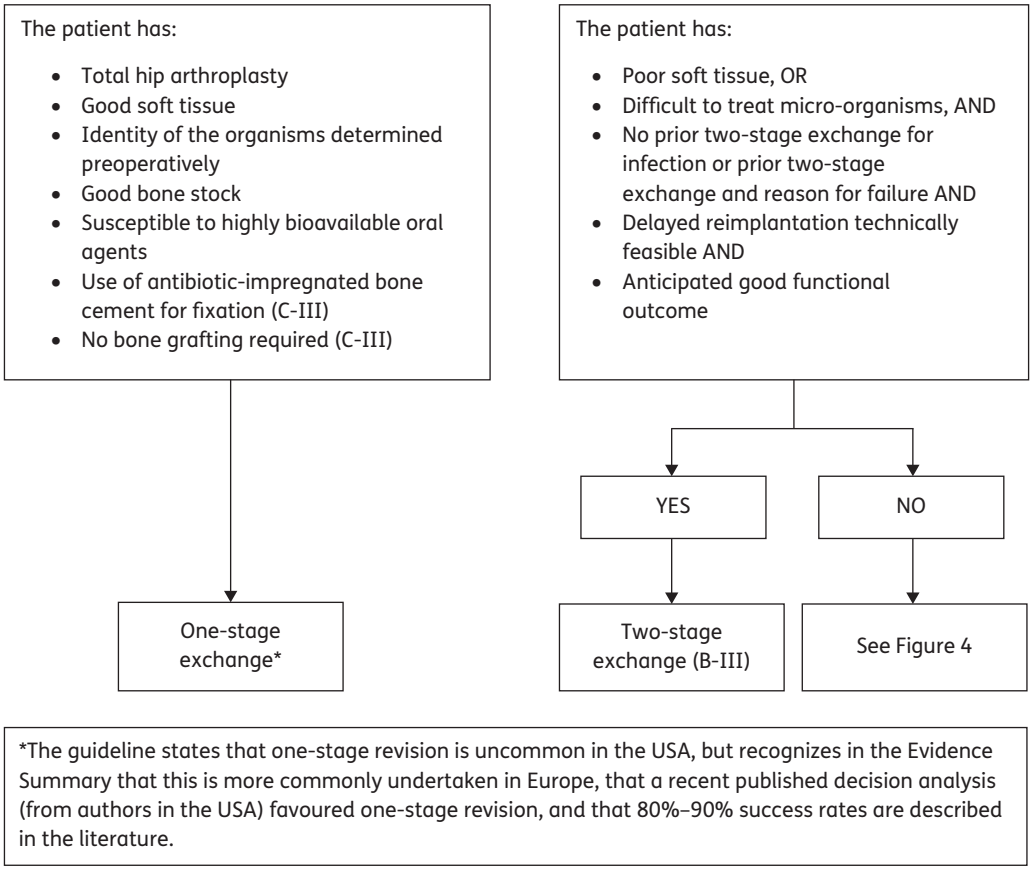

Figure 3. Criteria to guide choice of one- or two-stage revision (evidence graded at B-III or lower). Adapted with permission from Osmon *et al.*[2]

duration of antibiotic therapy accompanying the various alternative surgical strategies.

Gaps in evidence highlighted by the guidelines

Part of the IDSA guidelines structure includes a requirement to draw specific attention to research gaps that merit future study. Continuing uncertainties in the incidence of different types of infection, different types of arthroplasty and the risk factors for developing infection are highlighted, with the implication that further national registries may be useful. Limitations of the guidelines in providing evidence are highlighted by the heterogeneity of definitions, classification and surgical approaches, even in the few randomized controlled trials performed on the management of PJIs.[6,7] The International Consensus discusses both significant and potential risk factors for PJI (although the quality of data is acknowledged to be limited), with identified risk factors for surgical site infection often extrapolated to PJI.

Diagnostically, the roles of PCR and implant sonication to increase test sensitivity are deemed to merit more study, as do the use of beadmill processing of samples, duration of incubation of samples, the role of serum and synovial fluid biomarkers, and optimized imaging, culture and molecular methods. Recommendations for duration of incubation are changing—the International Consensus recommends that routine cultures should be maintained between 5 and 14 days, depending on organism virulence and pre-operative yields.

The most cost-effective algorithms for treatment, including the efficacy of oral versus intravenous antibiotic therapy, the efficacy of adjunctive rifampicin therapy, options in methicillin-resistant *Staphylococcus aureus* (MRSA) infection and the role and optimal regimen for long-term suppression, are all identified as requiring more research. So too are comparisons of one- and two-stage revision, timing of re-implantation and risk factors for success and failure. Finally, while there are no specific discussions of prevention in the IDSA guideline (considered out of scope when it was produced), the role of prophylaxis for patients with prostheses undergoing dental or invasive procedures, the value of *S. aureus* decolonization before joint replacement surgery and the PJI-specific impact of peri-operative warming and oxygenation are all identified as unknowns. The International Consensus has many detailed recommendations on prevention.

Next steps: implement or ignore?

Practitioners now have a choice to make regarding the IDSA guidelines (which are the first universally accessible, PJI-specific, clinical practice guidelines available) and/or the International Consensus. The main strength of the IDSA guidance lies in the explicit nature of the evidence base and the easy-to-follow clinical algorithms. The levels of evidence supporting the International

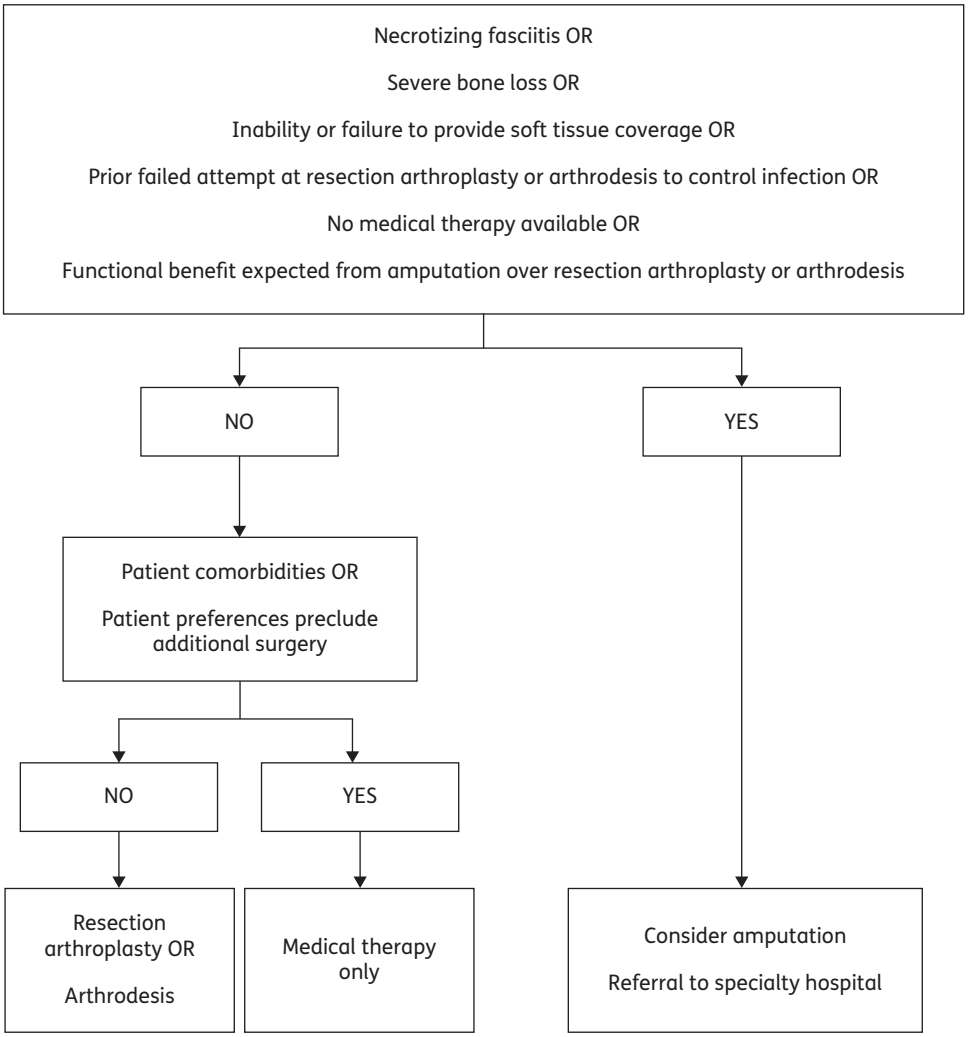

Figure 4. Management of PJI when patients are not a candidate for a new prosthesis (for all of this part of the guideline, evidence graded at B-III). Adapted with permission from Osmon *et al*.[2]

Consensus are less explicit and the guidelines less algorithmic by comparison, although they cover certain areas in more detail. On the one hand, some will wish to discount these recommendations and algorithms on the grounds that the levels of evidence are rarely strong and that a consensus statement does not remove clinical disagreements based on differing individual or centre-specific protocols. On the other hand, the guidelines can be adopted, or adapted for local relevance, using the algorithms and structures to standardize many elements of care, including pre-operative investigation, peri-operative sampling techniques, definition of infection and the duration and route of administration of antibiotics.

Inevitably, there are some elements upon which both guidelines are relatively silent. These include issues such as the role of articulating spacers during two-stage revision,[8] which remains controversial, and the role of sonication in isolation of causative bacteria, which has not yet been widely studied or adopted, but for which there is now increasing supporting evidence.[9] Some important questions are being addressed in high-quality randomized studies. For example, the OVIVA (oral versus intravenous antibiotics) trial, funded by the UK National Institute for Health Research (NIHR), is a multicentre study that aims to recruit nearly 1000 cases of bone and joint infection, including PJI, to investigate whether the first 6 weeks of therapy can be given principally by the oral route or should be given intravenously.[10]

Meanwhile, depending on the rate at which new, higher-quality evidence emerges, we can also expect updating of the IDSA guidance, taking account of new evidence grading methods (the GRADE system[11]) and the outputs of other groups.

Conclusions

After a long history of surgeon-specific practice, gradually evolving increasingly into protocol-driven, multi-disciplinary care delivered in specialized units or hospitals, PJI is today recognized as a complex and challenging entity requiring the coordinated and collaborative inputs of a range of disciplines to deliver the best results

- In situations where foreign material remains present (DAIR and one-stage revision), treatment with a combination of a fluoroquinolone and rifampicin (A-I) for 3–6 months is recommended, following on from 2–6 weeks of intravenous or oral (with highly bioavailable drugs) antibiotics (A-I for DAIR; C-III for one-stage revision). Where rifampicin combinations are not possible due to intolerance or bacterial resistance patterns, 4-6 weeks of pathogen-specific intravenous antibiotic therapy is recommended (B-III).
- When the prosthesis has been removed, for the purposes of a long-term excision arthroplasty or a two-stage revision, 4–6 weeks of pathogen-specific antimicrobials are recommended either as intravenous or oral (highly bioavailable) therapy (A-II).
- The required duration for amputation may be very brief when the residual bone and soft tissue is uninvolved (C-III), or prolonged if there is residual infected and/or dead bone, and/or bone cement (C-III).

Figure 5. Antibiotic treatment to accompany each of the surgical strategies of DAIR, one-stage revision, two-stage revision, excision arthroplasty and amputation. Adapted with permission from Osmon *et al.*[2]

for the patient. The development of clinical guidelines and clinical consensus processes represent major steps forward and will pave the way for more effectively auditable practices. Ultimately, large multicentre studies become possible when there are more widely agreed ways of working and when there is more transparency about what we do and do not know. The future, which we should anticipate eagerly, will be of the more consistent application of best practice in infection control to prevent infections, and the development of clinical networks to ensure the patient with PJI gets the most appropriate care at the right time. We should also increasingly expect empowered patients wishing to choose care from practitioners who are implementing guidelines, collating and publishing their results, and participating in large trials to resolve the longstanding uncertainties and deliver the best possible clinical outcomes.

Transparency declarations

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