TREATMENT

3.1. TREATMENT: ANTIMICROBIALS

Authors: Timothy L. Tan, Matthias Wimmer, Camelia Marculescu

QUESTION 1: What is the optimal choice and duration of antibiotic therapy in polymicrobial surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The optimal choice and duration of antimicrobial therapy in polymicrobial PJIs remain unknown. Antimicrobial therapy for polymicrobial PJI should be targeted at the organisms that are present. There is limited literature on the antibiotic treatment as polymicrobial PJIs are very heterogenous. We recommend four to six weeks of intravenous or highly-available oral antimicrobial therapy, that is based on the in vitro susceptibilities of the individual microorganisms, patient allergies and intolerances.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Polymicrobial PJI, as identified by isolation of multiple organisms by culture, constitutes between 6% and 37% of reported PJI [1–4]. Patients with polymicrobial PJI have worse outcomes when compared to monomicrobial PJI and culture-negative PJI, regardless of the surgical treatment [5,6]. Studies have shown a lower success rates of polymicrobial PJIs (37 to 67%) compared to that of monomicrobial PJIs (69% to 87%) [5–9]. The treatment often requires broad-spectrum antibiotics or multiple antibiotics given that multiple organisms need to be targeted. Unfortunately, there is minimal literature regarding the optimal choice and duration of antibiotic therapy in patients with polymicrobial PJI. This is largely due to the fact that polymicrobial PJIs are very heterogenous and may represent many combinations of infecting organisms including fungi. However, there are many studies that have demonstrated that polymicrobial PJIs are associated with certain bacteria. Marculescu et al. found that methicillin-resistant *Staphylococcus aureus* (26.4% versus 7.1%) and anaerobes (11.7% versus 2.8%) were more common in polymicrobial PJIs. In addition, Tan et al. reported that the isolation of gram-negative organisms ($p < 0.01$), enterococci ($p < 0.01$), *Escherichia coli* ($p < 0.01$), and atypical organisms ($p < 0.01$) was associated with polymicrobial periprosthetic joint infection. Furthermore, many of these organisms are associated with high failure rates and the optimal antimicrobial for these organisms are still being defined [10,11].

While there are no randomized studies to compare the duration of treatment for polymicrobial PJIs compared to monomicrobial PJIs, patients treated for polymicrobial PJIs received four to six weeks of antimicrobial therapy [6–8], with the choice of an initial two weeks of parenteral antimicrobial therapy followed by four weeks of oral and highly-bioavailable antibiotic therapy [7,8]. Current Infectious Disease Society of America (IDSA) guidelines, while not specifically addressing polymicrobial PJIs, suggest four to six weeks of pathogen specific intravenous or highly-bioavailable oral antimicrobial therapy, which does not differ from the treatment of monomicrobial PJIs [12].

A study done by Moran et al. on 112 patients showed that polymicrobial organisms were present in 46.7% in the early postoperative period (within 3 months after prosthesis implantation) [3]. While in this study gram-negative organisms were seen only in 8% of the polymicrobial isolates, among these isolates were organisms classically associated with chromosomal Amp C-inducible beta-lactamases (*E cloacae, Serratia spp, Morganella morganii),* and resistant *Acinetobacter spp.* These findings, along with a high rate of beta-lactam resistance among coagulase-negative staphylococci (CoNS) have led the authors to recommend a broad-spectrum empirical antimicrobial coverage with a glycopeptide and a carbapenem [3]. In contrast, a study by Sousa et al. found no increased prevalence of polymicrobial infection in the early postoperative period, but they too recommend a carbapenem and vancomycin as empirical antimicrobial therapy for chronic and hematogenous infections when polymicrobial infection was present [13].

When selecting empirical antimicrobial therapy for polymicrobial PJIs, it is therefore important to be aware of the local and institutional gram-negative and gram-positive resistance pattern. Broad-spectrum antimicrobials should be stopped as soon as susceptibility results are available and effective antimicrobials with the narrowest spectrum of activity should be selected for completing the therapy.

Given that outcomes are poor with polymicrobial PJIs, chronic suppression may be warranted as multiple studies have demonstrated increased survivorship with the addition of oral antibiotics [14,15]. Frank et al. demonstrated that patients treated with oral antibiotics failed secondary to infection less frequently than those not treated with antibiotics (5% versus 19%, $p = 0.016$) in a prospective randomized controlled trial [14].

Search Methodology: A PubMed Search for the MeSH Terms ((“Infection”[MeSH]) AND (“Prostheses and Implants”[MeSH] OR “Prosthesis Implantation”[MeSH] OR “Prosthesis-Related Infections”[MeSH] OR “Prosthesis Failure”[MeSH])) AND “Coinfection”[MeSH] as well as for the terms polymicrobial[All Fields] AND (“joints”[MeSH Terms] OR “joints”[All Fields] OR “joint”[All Fields]) AND (“infection”[MeSH Terms] OR “infection”[All Fields]) on February 12, 2018 revealed a total of n = 161 results. All publications were screened and evaluated for relevance regarding the research question and duplicates.

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Authors: Juan Pablo Horcajada, John Stammers

QUESTION 2: What systemic antibiotic therapies should be used in patients with surgical site infection/periprosthetic joint infection (SSI/PJI) caused by resistant organisms?

RECOMMENDATION: The choice of antibiotic therapy in patients with SSI/PJI caused by resistant organisms is not fully answered by literature. There are a number of antibiotic choices available for patients with SSI/PJI caused by resistant organisms. The antibiotic selection process should consider patient comorbidities, mode of administration, risk of Clostridium difficile, need for monitoring, allergy profile of the patient, intolerance, regional resistance patterns, cost and availability. Ideally, apart from having activity against the resistant organisms, antibiotic choice should have good bone and soft tissue penetration and activity against biofilm. Consultation with infectious diseases specialists and clinical microbiologists is warranted in these cases.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Success rates in the treatment of PJI produced by resistant bacteria are lower than those from sensitive organisms, resulting in an increase in morbidity and cost. Successful treatment requires a multidisciplinary approach, including orthopaedic surgeons, infectious diseases specialists and microbiologists with an interest and experience in treating these complex infections.

Relative resistance is conferred by biofilms even when treated with susceptible antimicrobials, particularly in debridement and implant retention (DAIR). Antimicrobial decision-making needs to consider not only the minimum inhibitory concentration (MIC) but also the minimum biofilm-inhibitory concentration (MBIC) and minimum biofilm bactericidal concentration (MBBC), if performed.

Staphylococcus, streptococci, enterococci, enterobacteriae such as *Escherichia coli* or *Klebsiella pneumoniae*, *Pseudomonas*, and Candida are common microorganisms that form biofilms and are implicated in PJI [1]. The biofilm results in physiological, physical and adaptive resistance mechanisms to commonly-used antibiotics in PJI including aminoglycosides, β-lactams, quinolones and glycopeptides [2].

The transcriptional inhibitor rifampin has demonstrated consistent antibiofilm activity in gram-positives and is recommended by the Infectious Diseases Society of America (IDSA). Fluoroquinolones are the first choice as antibiofilm agent in gram-negative infections. Colistin and fosfomycin could be alternatives [1].

Gram-positive PJI/SSI

The main gram-positive PJI are *Staphylococcus aureus* and *Staphylococcus epidermidis*. Methicillin resistance is more common in *Staphylococcus epidermidis* (MRSE) compared to *Staphylococcus aureus* (MRSA). The majority of clinical studies include both MRSA and MRSE sharing treatment options. *Enterococcus spp*. is a rare cause of gram-positive PJI including vancomycin resistant *enterococcus* (VRE).

The initial therapy for MRSA or MRSE PJI infections after debridement should be directed against planktonic cells and is currently based in glycopeptides [3]. However, at high inocula vancomycin's efficacy is often suboptimal and in monotherapy poor clinical data have been published [4]. Interestingly the combination of daptomycin plus oxacillin has shown synergy in in vitro MRSA models, also against biofilm-embedded bacteria [5–7]. Although clinical experience is lacking, this combination could be used in the first days of MRSA PJI infection.

After the initial acute period (one to two weeks), targeted anti-biofilm therapy is warranted. As stated previously, rifampin has excellent activity against staphylococci in biofilm [8]. There is some indication that rifampin in combination with other anti-staphylococcal agents may improve the outcome of treatment. This was highlighted by one of the few clinical randomized controlled trials on antibiotic use in PJI. In patients with staphylococcal infection surgically managed by DAIR, the addition of rifampin to flucloxacillin or vancomycin for two weeks and three to six months of ciprofloxacin improved cure rate from 58% to 100% compared to antibiotics with a rifampin placebo [9]. The latter study has been criticized for consisting of a very small number of patients and its findings have not been embraced by the entire orthopaedic community. It is important to note that rifampin monotherapy is associated with a high likelihood of resistance and is not recommended by IDSA guidelines. Many methicillin-resistant staphylococcal PJI are also resistant to fluoroquinolones. However, if susceptible, it combines well with rifampin with good outcomes [9–12]. This combination has a good bioavailability, activity and safety, as has been shown in several clinical studies and it is considered the first choice if the *Staphylococcus* is susceptible to both agents [9,11–14]

There are numerous combinations with rifampin suggested in the literature for resistant staphylococci and alternatives if rifampin cannot be used. The majority of clinical studies are non-comparative retrospective reviews. The animal studies and in vitro studies provide comparative results, but there is little consensus and different methodologies used limit meta-analysis to make conclusions. A number of studies compare the following agents in combination with rifampin: vancomycin, daptomycin, linezolid, cephalosporins, carbapenems, fosfomycin, tigecycline, minocycline, fusidic acid, co-trimoxazole. Vancomycin is often the first line in MRSA/MRSE PJI [15]. A number of studies have concluded that year-on-year MRSA strains have a higher vancomycin MIC [16,17]. Some studies have demonstrated improved efficacy with vancomycin and rifampin in vitro [18], but this combination also results in rifampin resistance [19]. In comparison to levofloxacin, daptomycin has favorable results when combined with rifampin in vitro. Monotherapy use produced rifampin and daptomycin resistance and should be avoided [20,21]. Compared with linezolid and vancomycin, animal studies similarly favored daptomycin and rifampin [21–23]. A similar animal study comparing linezolid, vancomycin and daptomycin as a monotherapy and in combination concluded superiority of the daptomycin rifampin combination [24]. Clinically, non-comparative series using daptomycin achieved good outcomes if the implant is removed with 91% (10/11) [25] and 100% (22/22) [26] success with two-stage revision, respectively. Poorer results occurred after debridement and implant retention using daptomycin and rifampin, with success rates ranging from 50 to 80% (4/5, [25], (6/12, [27]) (9/18, [28]).

The fifth-generation cephalosporin, ceftaroline, is an option with similar activity to vancomycin and improved side effect profile. It is more effective in combination with rifampin in MRSA animal models [29]. An in vitro biofilm study, in contrast, concluded that the addition of rifampin to ceftaroline was not beneficial and antagonistic with some MRSA strains. They found that ceftaroline and daptomycin combination was the most effective but accepted that in vivo studies were required before its clinical applicability is known [30].

Tigecycline has been investigated as an alternative in MRSA PJI. Animal models comparing it to vancomycin as monotherapy or combined with rifampin concluded it was as effective as vancomycin with rifampin, but tigecycline alone was least effective [31]. Tigecycline combined with other antimicrobials produces an indifferent response, but has been shown to be effective against multi-resistant gram-positive and gram-negative organisms and could be considered as part of a combination regimen when first- and second-line options are contraindicated [32,33].

Thompson et al. compared 10 antibiotic groups in a MRSA animal model. The study did not confirm superiority, but that linezolid, vancomycin, daptomycin, ceftaroline in combination with rifampin were successful at eradicating bacteria. No antibiotic monotherapy cleared the bacteria [34].

In comparison to the oral antimicrobials fusidic acid, linezolid, rifampin and minocycline, linezolid was the only monotherapy effective against biofilm-embedded MRSA [35]. In an animal methicillin-susceptible *S. aureus* (MSSA) model, linezolid with rifampin prevented rifampin resistance and demonstrated superior activity compared to linezolid alone or cloxacillin with or without rifampin [36].

The retrospective clinical results of linezolid with rifampin following DAIR achieved successful remission in 69% (34/49). Linezolid was used as second line where previous treatment failed or therapy intolerance [37].

Another retrospective review of 39 gram-positive cocci PJI, remission of infection was achieved in 72% using linezolid following DAIR. Some patients also received rifampin which in this series was associated with a higher failure rate of 36% vs.18% which the authors commented that the rifampin group had a higher proportion of MRSA, diabetes and longer symptom duration before DAIR [38].

Combinations of rifampin plus linezolid have shown an increase in the antibacterial effect of linezolid in biofilm and a synergic activity against MRSA isolates [19,35,36]. Clinical series have demonstrated acceptable clinical outcome, although the studies are heterogeneous [37–39]. It is not well established the possible effect of rifampin in metabolism of linezolid. In vivo studies such as that by Gandelman et al. [40] showed that the combination is safe and well-tolerated, with only a small effect on the clearance of linezolid.

Results of co-trimoxazole and fusidic acid highlight that they still have a role in resistant staphylococcal PJI. Lower cost and oral administration are advantageous if the microorganisms are susceptible. A study of 56 bone and joint infections, including 36 with infected implants, received either linezolid or co-trimoxazole in combination with rifampin. There was no significant difference in cure rates with 89.3% success with linezolid and 78.6% with co-trimoxazole [41]. Co-trimoxazole has historically been an oral agent active against resistant staphylococcal infections, achieving success in 67% in a prospective study of 39 PJI. Treatment was between six and nine months. Device removal improved outcomes, but 60% were successful with implant retention [42].

A large retrospective review of 345 *Staphylococcus aureus* PJI managed with DAIR concluded that there was no difference in success between β-lactams or quinolones for MSSA or glycopeptides, co-trimoxazole, linezolid or clindamycin for MRSA in a series where 88% were used in combination with rifampin. Overall success was 55%, of which 80% had received rifampin for over 4 weeks [11].

Options in Rifampin Resistance

Rifampin resistance in association with resistant organisms is associated with inadequate surgical debridement or inadequate combination antibiotic treatment [43]. The IDSA recommends a four-to-six-week intravenous course of antibiofilm-guided therapy in rifampin resistance [44].

Fosfomycin has been investigated as an alternative to rifampin in gram-positive resistant PJI. Vancomycin with fosfomycin or rifampin were superior to tigecycline for planktonic bacteria and vancomycin combinations with fosfomycin or minocycline was superior for antibiofilm activity [18]. Fosfomycin with daptomycin was as effective as daptomycin-rifampin. Fosfomycin-imipenem was ineffective and resulted in resistance [23]. An in vitro biofilm comparison model found higher rifampin resistance with vancomycin, teicoplanin, daptomycin and tigecycline [19] A similar model used the same antibiotics, except daptomycin, but combined them with fosfomycin. They concluded that fosfomycin enhanced activities of linezolid, minocycline, vancomycin and teicoplanin and was superior to rifampin combinations [45].

Interestingly an animal model study suggested that rifampin resistance can be transient and that rifampin-based combination therapy can be effective even if rifampin-resistant bacteria was previously selected by rifampin exposure [46].

Some studies have even demonstrated that using resistant antibiotics in combination with a non-resistant antibiotic may be effective. Combining cloxacillin with daptomycin was active in an MRSA animal model [5] and was as effective as cloxacillin with rifampin in an MSSA model in rifampin resistance [6]. In vitro and in vivo lab studies have demonstrated synergy between daptomycin and β-lactams or carbapenems including nafcillin, cefotaxime, amoxicillin-clavulanic and imipenem. Combination therapy prevented daptomycin resistance [7]. An in vitro MRSA biofilm study concluded that neither daptomycin nor linezolid were active against biofilm embedded bacteria however in combination they were successful [47]. In other studies, linezolid monotherapy exhibited excellent inhibitory effects against biofilm-embedded MRSA [19,45]. There is considerable literature on the use of linezolid in monotherapy, showing high success rates [38,48–50]. Its excellent bone and tissue penetration is one of the main reasons for this. So, it could be an alternative in rifampin resistant staphylococcal infections.

Drug Interaction and Concentration Levels

Although the majority of studies demonstrate a benefit from combination therapy, drug interactions and pharmacokinetics must be considered. A randomized control trial comparing fusidic acid with rifampin versus vancomycin was stopped. The authors identified that the fusidic acid concentrations were lower than expected and at low levels rifampin resistance occurred [51]. In contrast, a study of 62 patients taking rifampin and fusidic acid demonstrated pharmacokinetics resulting in high drug exposure [52]. Decreased trough clindamycin concentrations were associated with concomitant rifampin use in an observational study of 61 patients infected with gram-positive organisms [53]. A crossover study into the pharmacokinetics of linezolid in combination with rifampin in 16 healthy adults demonstrated an interaction resulting in increased linezolid metabolism resulting in a lower concentration for the dosing interval [40].

Enterococcus

Enterococcal PJI is rare (3 to 10%) and associated with high failure rates [54]. Unlike rifampin in staphylococcal PJI there is no antibiofilm agents active against *Enterococcus.* Strains can be penicillin-susceptible, penicillin-resistant or vancomycin-resistant. IDSA guidelines recommend combination therapy with aminoglycosides. Typical combinations of gentamicin with ampicillin for penicillin susceptible, vancomycin for penicillin resistant and linezolid or daptomycin for vancomycin resistant are recommended. In vitro and animal studies of *E. faecalis* had cure rates of 17% with vancomycin, 25% with daptomycin, 33% with vancomycin and gentamycin and 55% with daptomycin and gentamycin [55]. Fosfomycin with gentamicin was shown to be superior to vancomycin and daptomycin with eradication of *E. faecalis* in 42%. Combinations of cephalosporins, ampicillin, aminoglycosides, daptomycin and linezolid are options for VRE PJI but there is no consensus across the literature and clinical series are too small and heterogenous to make firm conclusions on antibiotic therapy. Due to the low success treating these resistant organisms that lack antibiofilm therapy DAIR is unlikely to work and aggressive surgical management is required.

Gram-negative PJI/SSI

Ten to 30% of PJIs are caused by gram-negative bacteria. These include *Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella* species, *Proteus* species, *Pasteurella* species and *Serratia spp*. [56,57]. Appropriate antibiotics include cephalosporins, carbapenems and fluoroquinolones often in combination, directed by antibiofilm including fluoroquinolones in the combination when susceptible. Colistin and fosfomycin have good biofilm activity and can be used in combination, particularly against fluoroquinolone resistant organisms. Extended spectrum β-lactamase (ESBL) producing enterobacteriaceae, *Klebsiella pneumoniae* carbapenemase producing (KPC) enterobacteriaceae and Pseudomonas strains are resistant to a variety of antibiotics and are difficult to eradicate.

Like the biofilm in gram-positive organisms, many gram-negative organisms demonstrate resistance to phagocytosis when adherent to the surface of implants even when treated with susceptible antibiotics. Clinical outcomes of gram-negative PJI in the literature vary between high rates of success, even following DAIR or small series of very difficult to treat infections where despite combination antibiotics and aggressive surgical management with staged revision they have low rates of success. Fluoroquinolone sensitivity or resistance explains the dichotomy. Fluoroquinolones have good activity against *E. coli* due to efficacy against non-growing and adherent bacteria [58]. A retrospective series of 17 gram-negative infections managed with debridement and implant retention achieved successful remission in 15. Antibiotic use included intravenous cephalosporins or carbapenams initially followed by medium term oral ciprofloxacin. The authors concluded that the ciprofloxacin provided good antibiofilm activity [59]. A retrospective review of 24 gram-negative bone infections successfully eradicated infection in 79% using a combination of cefepime and fluorquinolone. Approximately half were treated with device retention and half with removal but there was no difference in success [60]. Ceftazidime and ciprofloxacin combination therapy was effective with implant retention in 24 pseudomonas infected implants [61]. A large retrospective series of 242 gram-negative PJI infections also demonstrated that including fluorquinolones in the combination therapy had higher successful rates [62].

Carbapenam-resistant *Klebsiella pneumoniae* has advanced mechanisms to rapidly generate resistance on therapy, including colistin and aminoglycosides. A failure to respond to treatment warrants not only a change of antibiotics but repeated debridement and new samples for sensitivity testing [63]. An animal model of KPC-producing *Enterobacteriaceae* demonstrated that synergistic combinations of tigecycline with rifampin or gentamicin were effective whereas there was antagonism using a combination of tigecycline with meropenem or colistin [64].

An in vitro and animal study of fluoroquinolone resistant *Escherichia coli* comparing fosfomycin, colistin, tigecycline, gentamycin, alone and in combination concluded the highest cure rate was with fosfomycin and colistin. Fosfomycin was the only monotherapy able to eradicate ESBL-producing *E. coli* biofilms [65].

IDSA guidelines recommend combination therapy for *Pseudomonas* PJI due to the limited antibiotic options [44]. In vitro studies combining fluoroquinolones with β-lactams or aminoglycosides reduces the risk of resistance to *Pseudomonas* and *Acinetobacter spp.* [66,67]. Multidrug resistant *Pseudomonas* was more effectively treated by combination therapy of colistin with β-lactams (cure rate 11/15) compared to monotherapy (cure rate 6/19) [68].

Interestingly, combining drugs even if one of them is resistant can be associated with antimicrobial activity. An in vitro study of biofilm and planktonic multidrug resistant *Pseudomonas aeruginosa* concluded that colistin in combination with doripenem was effective against both carbapenem susceptible and resistant strains and reduced colistin resistance. The role of the carbapenem is to prevent colistin resistance, not treat the resistant organism [69].

Some newly-approved antibiotics for resistant gram-negative infections utilize the synergy of antibiotic combinations. Ceftazidime/avibactam and ceftolozane/tazobactam combine second generation β-lactamase inhibitors with cephalosporins. In vitro activity is demonstrated against multiple drug-resistant gram-negative organisms including *Pseudomonas* and KPC producing Enterobacteriaceae. Clinically they are licensed for ventilator associated pneumonia, compliated intra-abdominal infections and complicated urinary tract infections [70] Currently, there are no studies specifically using these novel drugs in PJI.

Fungal PJI

Less than 1% of PJI are due to fungal infections. They are often associated with multiple revisions for infection, immunosuppression and prolonged antibiotic therapy [71,72]. Candida is the most common species and is known to produce a complex biofilm conferring rapid resistance. IDSA guidelines recommend fluconazole initially but ultimately based on antifungal susceptibility testing. Antibiofilm activity can require high antifungal doses associated with systemic toxicity, therefore staged arthroplasty and use of antifungal bone cement is routinely advocated. Amphotericin B [73] or voriconazole [74] is heat-stable and achieve high local concentrations.

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Authors: Scott R. Nodzo, Randi Silibovsky, K. Keely Boyle

QUESTION 3: Should periprothetic joint infection (PJI) caused by *C. acnes* be treated the same as other bacterial causes of PJI?

RECOMMENDATION: Yes. PJIs caused by *C. acnes* should be treated in the same fashion as other causes of PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

C. acnes is a non-spore-forming, gram-positive, facultative bacillus classified as an anaerobe with aerotolerant properties [1–3]. *C. acnes* has previously been categorized as a laboratory handling contaminant and is considered nonpathogenic, largely due to the presumed commensal nature of the bacterium, as well as identification on normal skin flora and maintenance of the microbiome [2,4]. Despite previous thinking, *C. acnes* is becoming increasingly recognized as an opportunistic and pathogenic organism in orthopaedic surgery. *C. acnes* often presents in a subacute or delayed manner due to an indolent clinical presentation and unreliable utility of classically used markers of infection, however this organism may represent 6 to 10% of orthopaedic infections [2,5–9]. It is speculated that *C. acnes* colonizes the surgical site at time of prosthesis implantation and grows unrecognized by the body through biofilm formation [10–12]. In the shoulder, the clinical and traditional inflammatory laboratory indicators of infection with *C. acnes* are often within normal limits, however its presentation during hip and knee arthroplasty infection may be more overt with classical signs and symptoms of infection [8,13]. Accurate identification of *C. acnes* requires long hold cultures up to 14 days, which is likely why this organism has previously been under-appreciated as the cause of orthopaedic infections [2,3].

In the orthopaedic literature, *C. acnes* has been identified as both a possible commensal organism observed at the time of surgery and as a definite pathological bacterium implicated in orthopaedic implant related infections. One prospective study evaluating intraoperative cultures showed *C. acnes* to be present in 8.5% of skin cultures, 7.6% of superficial cultures and 13.6% of deep cultures at the time of primary shoulder surgery [14]. The prevalence of *C. acnes* in patients undergoing revision shoulder arthroplasty has been shown to exceed that of other common offending organisms, with a recent study showing 38% of patients having a positive *C. acnes* culture [15]. A recent study utilizing next-generation sequencing in patients presumed to be undergoing aseptic revision hip and knee arthroplasty isolated microbial DNA in 27% of patients with *C. acnes* being the most prevalent organism [16].

Previous work has attempted to distinguish between these commensal and pathogenic strains through phylotype associations and phenotypic markers of the bacteria such as hemolysis [17,18]. A distinct pathogenic phenotype has yet to be clearly associated with true clinical infections, however phylotypes IB and II have most commonly been implicated in orthopaedic infection [17]. These phylotypes have varying adaptive virulence properties that may influence pathogenic potential, including the ability to degrade and invade host cells, produce an enhanced host inflammatory response, form biofilms and demonstrate antibiotic resistance [19–21]. Beta-hemolytic activity has been noted in certain strains of *C. acnes* and may be directly correlated with the bacteria's pathogenicity [18]. The hemolytic Christie-Atkins-Munch-Peterson (CAMP) factor is found in the *C. acnes* genome and functions as a toxin to host cells, which may be responsible for this observed beta-hemolytic activity [20,22]. A *C. acnes* hemolytic phenotype observed on brucella blood agar media has been shown to be a marker of definite infection with 100% specificity and 80% sensitivity along with an increased pattern of antibiotic resistance [18,23]. Suggestions of enhanced virulence of *C. acnes* have been implicated when it serves as a co-infectant with other bacterial species, which may be why at times it is found in polymicrobial cultures and erroneously characterized as a contaminant in some clinical situations [24,25].

Pathogenic *C. acnes* strains are well-known to form a robust biofilm on implant surfaces resistant to antibiotic penetration, similar to more commonly recognized bacterial pathogens [20,26,27]. Implant biofilm is difficult to treat without implant removal and reported treatment success of a *C. acnes* PJI has been variable with treatments involving implant or polyethylene retention having the poorest results [13,28,29].

Currently, there are no prospective studies evaluating varying treatment strategies of *C. acnes* orthopaedic infection, with most studies being retrospective in nature. Retrospective studies evaluating various treatments for shoulder, hip, knee and spine *C. acnes* infection have reported variable success [13,28–30]. Studies evaluating total shoulder arthroplasty (TSA) and upper extremity infection have shown good outcomes with treatments involving one or two-stage revision procedures with success rates ranging from 74 to 95% [5,13,31,32]. One retrospective analysis found nonsurgical treatment with four to six weeks of intravenous antibiotics led to 67% of patients not requiring subsequent surgical management as compared to 71% of patients not requiring further surgery after initial surgical management [33]. Two studies evaluating all orthopaedic infections caused by *C. acnes* reported a 100% failure rate when partial or no implant removal was performed with success rates ranging from 62 to 75% when one and two-stage exchanges were performed [28,29]. A similar retrospective study evaluating hip, knee and shoulder arthroplasty PJI with *C. acnes* showed a 95% success rate in TSA

PJI treated with a two-stage procedure while those treated with an irrigation and debridement (I&D) with component retention had a 37% success rate [13]. Hip and knee success rates in the same study were lower when a two-stage procedure was utilized at 67% and 64% respectively. However, other studies have reported success rates as high as 94% to 100% with a two-stage exchange for hip and knee PJI with *C. acnes* [13,30]. One retrospective study specifically evaluated *C. acnes* total knee arthroplasty (TKA) PJI treated primarily with two-stage exchange and I&D with liner exchange as compared to methicillin-sensitive staphylococcal TKA PJI. This study showed similar success rates between treatment groups and suggested a PJI treatment strategy similar to methicillin-susceptible *S. aureus* (MSSA) TKA PJI be performed for *C. acnes* TKA PJI [8].

C. acnes has also been noted as a common pathogen in spine surgery with one large study showing *C. acnes* representing 9.7% of positive cultures [9]. Similar treatment strategies with partial and complete hardware exchange have been evaluated in the literature with patients having partial implant removal resulting in inferior infection eradication rates as compared to those patients who had complete exchange of spinal components [9,34].

C. acnes is usually susceptible to beta lactams, quinolones, clindamycin and rifampin, but resistance is emerging and antibiotic susceptibility testing should be considered for PJI [23]. There is no general consensus on how to treat these infections. Many recommend three to six months of antibiotic treatment, including two to six weeks of intravenous (IV) treatment with a beta lactam, but no randomized controlled trials have been performed and some studies favor shorter treatment durations [20]. Given the lack of randomized controlled trials, following the Infectious Disease Society of America (IDSA) guidelines of four to six weeks' duration is recommended [35].

The role of rifampin is also unclear. An in vitro study showed activity against *C. acnes* biofilms [36]. One low-quality retrospective cohort study in patients with a primary or revision joint arthroplasty of the shoulder, hip or knee evaluated the role of rifampin in combination therapy and showed no difference in treatment success [37]. There are currently no randomized controlled human studies on the efficacy of rifampin in combination anti-microbial treatment for *C. acnes* PJI. Given the limited data, the addition of rifampin to the treatment regimen is not recommended at this time.

Although no prospective studies are currently available regarding the optimal treatment strategy for *C. acnes*, careful review and synthesis of the available literature suggest *C. acnes* be considered a true pathogen when the appropriate constellation of findings are present. When *C. acnes* PJI is identified, treatment algorithms should model after those of other invasive offending organisms. Caution should be taken when treating *C. acnes* PJI without explantation of exchangeable components or efforts to eliminate biofilm on retained implants due to the low success rates of simple irrigation and debridement with component retention.

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Author: Harriet Hughes

QUESTION 4: What is the most effective antibiotic in the treatment of *C. acnes* periprosthetic joint infection (PJI)?

RECOMMENDATION: Unknown. High rates of susceptibility to narrow spectrum beta-lactams make these a good initial intravenous (IV) option, though the optimum oral switch is not known. The role of rifampin is controversial. Prospective clinical studies are required to determine the optimal antimicrobial therapy for *C. acnes* PJI.

LEVEL OF EVIDENCE: No evidence

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

C. acnes is an anaerobic gram-positive bacillus and a common skin commensal found deep in sebaceous glands and hair follicles. As well as being commonly implicated in acne vulgaris, it is a well-recognized pathogen of device related infection including prosthetic joints [1–4].

The ability of *C. acnes* to form biofilm is a major virulence factor in the development of these infections, including PJI, and is an important consideration for optimizing treatment strategies. Management should follow well recognized guidelines of a combination of surgery and targeted antibiotic therapy [5–7], though this has been challenged by at least one retrospective analysis [8]. Pragmatically, however, without doing prospective studies and controlling for the surgery performed, the duration of therapy and individual host factors, comparisons of different antibiotic regimens in the real world are very difficult.

This problem is compounded by the difficult issue of determining the significance of cultured *C. acnes* from orthopaedic specimens, as it is a common and well-recognized contaminant. It has been shown to be present in fluid washed across the skin incision [9], has been found on surgeons' gloves after handling the subdermal layer [10] and is not reliably removed from the skin by surgical skin antisepsis [11]. The multiple sampling method of Atkins et al. [12] is commonly used to aid interpretation of the significance of *C. acnes* isolates, with one specimen positive out of three to five usually being deemed a contaminant [12]. The recommended duration of incubation of enrichment broths has been extended in recent years to 10 to 14 days to improve the pick-up rate of relatively slow-growing *C. acnes* in these samples. By increasing the isolation of significant isolates, however, the rate of contaminants also increases and requires careful interpretation [13]. It has been suggested that those isolated from true infections flag earlier than those that represent contamination. Sonication is recommended by some to improve pick-up rates of *C. acnes* associated with biofilm [14]. Some authors have gone further, by creating scoring systems to aid identification of true *C. acnes* infections [3,4].

For these reasons, accurate identification of *C. acnes* PJIs retrospectively is fraught with difficulties and thus interpretation of the outcome data comparing treatment strategies is very limited. The clinical details are imperative to aid interpretation. As well as varying in the clinical information available, retrospective studies also often span many years or decades, and straddle changes to sampling methods, culture methods and recommended duration of enrichment cultures. These differences further limit the ability to draw detailed comparisons between different interventions.

In vitro susceptibilities of *C. acnes* are reported widely. Surveillance studies show it remains susceptible to many antibiotics commonly used in treatment of bone and joint infection, but with increased and variable resistance to macrolides, clindamycin, tetracyclines and trimethoprim-sulfamethoxazole. A European surveillance study showed wide variations in rates of resistance across Europe, confirming the need to undertake susceptibility testing for individual isolates [15] and this has been replicated in other smaller series [15,16]. Looking at isolates from clinical specimens taken at shoulder surgery, Crane et al. showed that rates of resistance to beta-lactams (e.g., penicillin, amoxicillin, cefalozin and ceftriaxone) remained very low [17,18]. However, they found slightly higher minimum inhibitory concentrations (MICs) to vancomycin and taking that information with the minimum biofilm eradication concentration (MBEC) from other studies [19,20], vancomycin may be less favorable than alternatives in the context of biofilm. This study also looked at quinolones (ciprofloxacin and moxifloxacin) but not levofloxacin and showed high rates of susceptibility.

It is well-recognized that the susceptibility of microorganisms is dramatically reduced in biofilms. For infections with staphylococci, there is good evidence for the use of rifampin in combination therapy for its biofilm effect. The use of dual therapy with rifampin for *C. acnes* infections is theoretically attractive, though there is controversy in the literature. Bayston et al. found that linezolid plus rifampin led to relapse-free eradication after 14 days compared to linezolid alone [5]. Interestingly, in this study, penicillin alone was as effective as linezolid and rifamcin, but the effect of rifampin and penicillin was not examined. Tafin et al. in 2012 used an experimental foreign-body infection model to determine MIC and MBEC with and without rifampin for *C. acnes* from cage fluid and from explanted cages [19]. There was good activity of all antimicrobials tested for the planktonic forms, but rifampin was needed for activity in the biofilm. They used an in vivo animal model to evaluate susceptibility to levofloxacin, vancomycin, daptomycin and rifampin. The highest cure rate was found with daptomycin and rifampin (63%) followed by 46% for vancomycin and rifampin combination. Emergence of rifampin resistance associated with the presence of the rpoB gene has, however, been shown to occur in vitro [21].

Combination therapy for *C. acnes* has been further examined in vitro by Khassebaf et al. [15] who took *C. acnes* isolated from orthopaedic implant infections and carried out susceptibility testing in addition to looking for synergistic, additive and antagonistic effects of combinations. None of the antimicrobials examined were synergistic with each other and antagonistic effects were rare. Interestingly, the combination of rifampin and benzyl penicillin showed an additive effect on almost 50% of isolates tested. However, a retrospective cohort study by Jacobs et al. [22] showed no significant difference in success after two years between groups treated with combination antimicrobial treatment including rifampin (88%) or not including rifampin (82%). The most used antimicrobial in combination with rifampin was clindamycin.

The performance of these antimicrobials in clinical studies is not easy to assess and there are very few published good quality studies with no prospective studies identified and limited utility of retrospective studies. Over a decade ago, Zeller et al. conducted a retrospective cohort study of 50 patients with *C. acnes* PJI [23]. Treatment involved surgery with antibiotics for the majority of patients. Intravenous therapy with cefazolin and rifampin was administered to 24/50 patients and clindamycin with rifampin to 11 cases for a duration of 5 +/- 2 weeks followed by oral step down for a further 16 +/- 8 weeks. Oral regimens were similar to the IV regimes: cephalexin and rifampin or clindamycin and rifampin [23,24].

Reinmuller's retrospective review of a tertiary infection center database included 24 cases of *C. acnes* PJI over 14 years [25]. A strength in this study, despite it being retrospective, was the use of contemporaneous clinical diagnosis of infection alongside the microbiological diagnosis. All patients underwent surgery and were treated with antibiotics but the specifics of antimicrobial treatment are not given, other than stating that they followed recommendations by Zimmerli [7] and were guided by the specific antibiogram. Lutz reports 52 cases over 7 years but differences in outcome between antimicrobial regimes were not given [3].

In summary, there are no randomized control trials (RCTs) or formally conducted comparative studies of specific antibiotic combinations for the treatment of *C. acnes* PJI. Publications are confounded by difficulties and variations in definitions of infection, likely mixing true infections with contaminated cases. Surveillance studies suggest *C. acnes* remains highly susceptible to beta-lactams which are attractive from an antimicrobial stewardship point of view and are commonly used and recommended in Infectious Disease Society of America (IDSA) guidelines [4–7,22,26,27]. Increasing rates of resistance for clindamycin and doxycycline are seen and antimicrobial therapy must therefore be based on the susceptibility testing of infecting pathogens determined using accredited methods. Additive or synergistic testing might be helpful, but the utility of this needs corroboration in clinical studies. Determining an appropriate targeted regimen at this stage can only be based on in vitro susceptibilities, on knowledge of oral bioavailability and bone penetration and on an individual risk/benefit assessment for the use of rifampin and other agents. Both the best oral antimicrobial and the role of rifampin as part of combination therapy remain unclear and well conducted prospective RCT studies are needed to help answer these questions.

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Authors: Giovanni Riccio, Luca Cavagnaro, Parham Sendi

QUESTION 5: What antibiotic therapy and duration should be used in surgical site infection/periprosthetic joint infection (SSI/PJI) caused by *Mycobacterium tuberculosis* (TB)?

RECOMMENDATION: TB PJI must be treated in collaboration with an infectious diseases specialist noting that the duration of treatment (minimum six months and up to two years) and the type of antimicrobials (usually a combination of four drugs) is determined based on the resistance profile of the pathogen.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

The review of the available literature on PJI caused by TB is mainly based on retrospective cohort studies and case reports. Our exhaustive search of the literature revealed a total of 44 publications reporting on 62 patients with PJI caused by TB, over a period of 40 years [1–44].

Eight of the studies did not report on the type of antibiotic treatment utilized [1–8]. In other studies, reporting on the antimicrobial treatment, 3 patients were treated by a two-drug combination regimen [9] and 23 patients received a three- or four-drug therapy [10–32]. Four patients were treated with more than four drugs [33–36]. Regarding the length of treatment [37], it was 6 to 9 months in 10 patients [38], 9 to 18 months in 21 patients and more than 18 months in 19 patients [39]. Based on the literature, only three patients had less than six months of antimicrobial therapy [40], but this may relate to the fact that two patients died during treatment.

The date related to surgical treatment was also evaluated. Eleven patients underwent debridement and retention of the prosthesis (DAIR) [41], 38 had resection arthroplasty and reimplantation [42], while 13 patients had no surgical treatment [43].

Due to the scarcity of the data related to PJI caused by TB, we are unable to draw definitive recommendation for the antimicrobial treatment of surgical treatment for that matter. However, based on the recommendations of the World Health Organization (WHO) [44] for the treatment of osteomyelitis caused by drug-susceptible TB, we feel that the four drugs regimen (isoniazid (H) with pyridoxine, rifampin (R), pirazinamide (P) and ethambutol (E)) for two months followed by a two-drug regimen (rifampin (R) and isoniazid (H) with pyridoxine) for a total treatment duration of six to nine months (i.e., four to seven months two drugs) may be the most optimal management of PJI caused by drug-susceptible TB.

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Authors: Feng-Chih Kuo, Alex McLaren

QUESTION 6: Which antifungal agents are heat-stable and what dose of these agents should be used in cement spacers for fungal periprosthetic joint infection (PJI)?

RECOMMENDATION: Amphotericin B, preferably the liposomal formulation, and voriconazole are heat-stable antifungal agents that are available in powder form and can be added to polymethyl methacrylate (PMMA) cement for spacers during treatment of patients with fungal PJI. The optimal dose of the antifungals that need to be added to a spacer is not known. However, in the literature, the dose of amphotericin B ranges from 150 to 1,500 mg per 40 gm cement and the dose of voriconazole ranges from 200 to 1,000 mg per 40 gm cement. Antibiotics combined with antifungals should be considered for treatment/prevention of coexisting fungal and bacterial infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 2%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Fungi are known to form biofilms on implant and tissue surfaces with associated tolerance to antifungal agents. Data on the antifungal concentrations needed to achieve the minimum biofilm eradication concentration (MBEC) is limited. Parenteral/systemic administration of antifungals can achieve minimum inhibitory concentration (MIC) but not MBEC, which is tens to hundreds of times higher than the MIC for most antifungal-pathogen pairs. Local delivery is therefore required for most cases, because it is expected that at a minimum, some biofilm fragments remain in the wound following debridement. The local delivery vehicle that is most commonly used is PMMA formed into a spacer. To incorporate sufficient antimicrobials for the required local release, the antimicrobial must be in powder form because sufficiently high concentrations are not currently available in solution form. Echinocandin antifungals (e.g., caspofungin and micafungin) are available in powder form and are water-soluble [1], but their heat stability is not established and there is limited data on release from PMMA [2]. 5-flucytosine is also available in powder form, but 5-flucytosine does not retain its bioactivity when incorporated into PMMA [3]. Amphotericin B and voriconazole are available in powder form [4–6]. Amphotericin B is heat-stable and voriconazole has limited heat degradation over the polymerization time for PMMA [7–9]. Both have release data available and are active when eluted from antifungal loaded bone cement [6,10,11]. However, neither amphotericin B nor voriconazole are water-soluble [12,13].

TABLE 1. Summary of literature pertaining to the use of antifungal-loaded bone cement spacers

Year	Author	Antifungal	Dose (mg/40 gm cement)	Study Design	Follow-up (months)	# Infection Free (%)	Organism
2018	Burgo [17]	Voriconazole and vancomycin	Not reported	Case report	24	1 (100%)	*Trichosporon inkin*
2017	Daniele [18]	Voriconazole	V – 200	Case report	0	0 (0%)	*Scedosporium inflatum*
2016	Geng [15]	Amphotericin B +/- vancomycin +/- meropenem	A – 200	8 patients retrospective review	35-78	7 (87.5%)	6 Candida species, 1 *Aspergillus* 1 mold
2015	Wang [19]	Amphotericin B	A – 100	5 patients retrospective review	46	5 (100%)	Candida species in 4 cases and *Pichia anomala* in 1 case
2015	Ong [20]	Amphotericin B	A – 150	Case report	24	1 (100%)	*Arthrographis kalrae*
2015	MacLean [21]	Amphotericin B	A – 1500	Case report	24	1 (100%)	Blastomycoses
2014	Skedros [22]	Amphotericin B	A – 500	Case report	12	0 (0%)	*Candida glabrata* and S marcescens
2013	Reddy [23]	Amphotericin B	Not reported	Case report	24	1 (100%)	*Candida tropicalis*
2013	Deelstra [24]	Amphotericin B voriconazole	A – 250	Case report	72	1 (100%)	*Candida albicans*

			V – 1,000				
2013	Ueng [25]	Amphotericin B +/- vancomycin	Not reported	16 patients retrospective review	41	8 (50%)	9 C. albicans, 6 C. parapsilosis, 1 C. tropicalis
2012	Hwang [16]	**None** Spacers had 2 gm vancomycin/batch No antifungal	Systemic	30 patients retrospective review	52	28 (93%)	24 were Candida species
2012	Hall [26]	Amphotericin B	A – 150	Case report	24	1 (100%)	*Aspergillus*
2012	Denes [27]	Voriconazole	V – 300	Case report	Not reported	Not reported	*Candida glabrata*
2011	Wu [28]	Amphotericin B	A – 1,200	Case report	12	1 (100%)	*Candida albicans*
2011	Gottesman-Yekutieli [29]	Itraconazole	I – 250	Case report	24	1 (100%)	*P. boydii*
2009	Wilkins [30]	Amphotericin B	Not reported	Case report	36	1 (100%)	Rhizopus
2009	Azzam [14]	Amphotericin B in 5 of 29 spacers	Not reported	29 patients retrospective review	45	9/19 (47%) reimplants	20 C. albicans, 4 C. parapsilosis, 3 C. albicans + *C. parapsilosis,* 3 non-Candida speies
2004	Gaston [31]	Amphotericin B + vancomycin	Not reported	Case report	9	0 (0%)	*Candida glabrata* amputation
2002	Phelan [32]	Fluconazole	F – 200	4 patients retrospective review	60.5	1 (25%)	Candida
2001	Marra [33]	Amphotericin B	A – 187.5	Case report	not reported	0 (0%)	*Candida albicans*

Amphotericin B is formulated with deoxycholate as a solubilizing agent. Liposomal formulations are also available in powder form and act to increase the release of amphotericin B from PMMA by an order of magnitude greater than amphotericin B deoxycholate. Eight hundred milligrams of liposomal amphotericin B (Ambisome®) per 40 gm of cement has been found to maximize amphotericin B release and not cause excessive mechanical weakness [10]. Toxicity studies are reported with cell injury in vitro, but no tissue injury in vivo at concentrations as high as 1,000 µg/mL [14]. Voriconazole is formulated with cyclodextrin as a solubilizing agent [15]. The cyclodextrin powder is 16 times the mass of voriconazole, resulting in a large enough powder volume to cause weakening of the cement [11]. Three hundred milligrams of voriconazole per 40 gm of cement leads to high levels of release, but also weakens compressive strength below the 70MPa ISO 5833 standard for normal implant fixation. When the dose is increased to 600 mg per 40 gm of cement, there is further weakening of compressive strength to about 20MPa after elution [11]. For spacer fabrication, some level of attention needs to be paid to structural integrity, and the use of metal reinforcement within the cement may help to minimize the risk of spacer fracture.

Currently, there is limited data on the local tissue levels needed, the duration of MBEC exposure required and the elution characteristics necessary to eradicate fungi from biofilm fragments. Clinical judgment must be used when choosing and dosing antifungal agents. The culture sensitivity in addition to the potential for antifungal toxicity must be weighed with the patient's medical history. Case reports and retrospective case series are valuable to consider in conjunction with the elution and mechanical data and the clinical factors specific to individual cases when dosing decisions are being made. Thorough debridement remains the foundation of PJI management, including fungal PJI. High-quality prospective clinical trials will be needed to determine clinical outcomes when local tissue level targets and thorough debridement are achieved.

Studies and case reports on the use of antifungal-loaded bone cement spacers are provided in Table 1. In these reports, amphotericin B and voriconazole were the dominant antifungals used in spacers with the dose of amphotericin B ranging from 150 to 1,500 mg per 40 gm cement and the dose of voriconazole ranging from 200 to 1,000 mg per 40 gm cement. Most report clinical success when used in conjunction with thorough debridement and systemic antifungals, however there are reports of acceptable outcomes even when antifungals were not used in any or all of the spacers [16–18].

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