Bactericidal levels of antibiotics are difficult to achieve in infected total joint arthroplasty when intravenous antibiotics or antibiotic-loaded cement spacers are used, but intra-articular (IA) delivery of antibiotics has been effective in several studies. This paper describes a protocol for IA delivery of antibiotics in infected knee arthroplasty, and summarises the results of a pharmacokinetic study and two clinical follow-up studies of especially difficult groups: methicillin-resistant Staphylococcus aureus and failed two-stage revision. In the pharmacokinetic study, the mean synovial vancomycin peak level was 9242 (3956 to 32 150; SD 7608 μg/mL) among the 11 patients studied. Serum trough level ranged from 4.2 to 25.2 μg/mL (mean, 12.3 μg/mL; average of 9.6% of the joint trough value), which exceeded minimal inhibitory concentration. The success rate exceeded 95% in the two clinical groups. IA delivery of antibiotics is shown to be safe and effective, and is now the first option for treatment of infected total joint arthroplasty in our institution.

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Revision for infected total knee arthroplasty (TKA) is usually performed in two stages. At the first stage, infected implants are removed and antibiotic therapy is initiated (usually via a combination of systemic antibiotics and an antibiotic-loaded spacer made from polymethyl methacrylate (PMMA) bone cement), and the revision components are implanted between six and 12 weeks later. In order to treat bacterial infections within joints effectively, it is essential that high intra-articular (IA) concentrations of antibiotics are achieved. While antibiotics in cement spacers can produce high IA concentrations of antibiotics initially, the levels decrease rapidly during the first three days as the antibiotics leach from the surface layer of the cement spacer. Intravenous (IV) administration of antibiotics also achieves IA concentrations in excess of the minimal inhibitory concentration (MIC) for susceptible organisms, but the levels achieved are modest and the duration of time above the MIC is short. As a result, even in patients with an infected TKA which has been treated with IV antibiotics, causative organisms can still be isolated from intra-operative tissue biopsies. The effectiveness of glycopeptide antibiotics is proportional to both the concentration and the length of time the concentration is maintained at an effective level. This remains the case whether the antibiotic is used as a prophylactic agent in clean cases, or to eradicate bacteria in infected cases.

Following two-stage revision, re-infection is common, particularly in cases involving resistant bacteria, where re-infection rates between 24% and 82% have been reported. The surgical management of re-infection after two-stage revision for infection is especially challenging with a high rate of complications including repeated re-infection, loosening, and chronic pain.

In an effort to achieve sustained high concentrations of antibiotics in the synovial fluid of an infected joint, we have developed a method to inject antibiotics directly into the knee joint, using Hickman catheters implanted into the joint cavity at the time of surgical treatment for infection, and leaving an external portal for injection. Administration of antibiotics directly into the joint can achieve IA concentrations between two and three orders of magnitude higher than that achieved by IV administration. Similar methods of direct IA antibiotic delivery have been used effectively for treatment of pyarthrosis in veterinary practice for decades and have been used successfully in humans to salvage acutely and chronically infected TKA. Given that knee joint infection may affect structures outside the joint capsule (including adjacent tissues or regional lymph nodes), it is important that IA delivery of antibiotics also generates a therapeutic concentration within the serum. This appears to be the case: previous studies...
have reported mean serum peak (4.1 μg/mL to 6.1 μg/mL) and trough (3.2 μg/mL to 3.3 μg/mL) values within the therapeutic range.22,23

This paper describes a technique developed to treat infected TKA using single-stage exchange arthroplasty using cementless implants and IA infusion of antibiotics. Three cohorts of patients are described: firstly, the technique was evaluated in a study of basic pharmacokinetics in a group of patients to determine antibiotic concentration in the joint and serum. The protocol also was then applied to a group of patients with methicillin-resistant Staphylococcus aureus (MRSA) and a group of patients with re-infection after failed two-stage revision for infected TKA.

Patients and Methods
Pharmacokinetic study.31 Following institutional review board approval, we enrolled 11 patients (11 knees) referred for treatment of infected TKA into a study with the aim of evaluating IA and serum concentrations of vancomycin in response to IA injection. Two Hickman catheters (Bard Access Systems, Inc., Salt Lake City, Utah) (Fig. 1) were inserted into the IA space intra-operatively at the time of revision surgery to allow for direct vancomycin injection. These catheters are silicon tubes with a fibrous cuff that allows fibrous tissue ingrowth to seal the entry point, preventing ingress and egress of fluid around the catheter, and have a Luer-lock module and cap to allow injection with a syringe. Two catheters were inserted to ensure that at least one would remain viable for the six-week term. Both catheters were used for injection only; the only dispersal of antibiotics was through the local venous and lymphatic system.

IA antibiotics were initiated on the evening of the first day after surgery if the incision was dry. Initially, the dose was small (100 mg vancomycin in 3 mL of sterile water); the dose was increased gradually over three to five days to a maintenance level of 500 mg of vancomycin in 5 mL of water every 12 or 24 hours. IV antibiotics were discontinued when the maintenance level of IA delivery was established. The protocol now has been stabilised such that the maintenance dose is 400 mg vancomycin in 5 mL sterile water every 24 hours. Peak and trough serum vancomycin levels were measured following the third dose, and subsequently twice per week, using fluorescent polarisation immunoarray (FPIA).32,33 The dose was decreased if the serum vancomycin levels exceeded 22 μg/mL. In three patients receiving 500 mg of vancomycin every 12 hours, serum trough level was reported in excess of 20 μg/mL. Their doses were decreased to 250 mg, and their trough levels decreased to less than 10 μg/mL. After six weeks, the treatment was concluded and the Hickman catheters were removed in the operating theatre under local anesthesia as a day case procedure. An elliptical incision was made around the catheters, the fibrous cuffs were sharply dissected from the surrounding subcutaneous tissue, and the catheters were extracted gently from the knee. The catheters, made of soft silicon, were handled with care to avoid cutting them and allowing the tip to escape into the knee.

In the theatre, immediately before catheter removal, samples of synovial fluid were taken by arthrocentesis to determine the IA trough concentration. Then the final dose of vancomycin was given through the catheter, the knee was flexed and extended to disperse the antibiotic, and another specimen of joint fluid was taken through arthrocentesis for the peak level. For one patient, additional synovial fluid samples were taken at the one-month follow-up visit.

Resistant organism study.22 In the second study, direct IA injection of vancomycin was prospectively evaluated as a treatment for MRSA in 18 knees (18 patients with a mean age of 69 years (58 to 84), 11 women and seven men) referred to the senior author (LAW) between January 2001 and January 2007. All patients had chronic infections of at least three months’ duration. All patients had important comorbidities: nine patients had Type II diabetes, 12 had chronic dependency oedema and stasis dermatitis, nine were morbidly obese, and 15 had malnutrition and hypo-albuminemia. Of the 18 patients, 17 had two or more comorbidities. Four of these patients had had previous two-stage revisions for infection with antibiotic cement spacers and antibiotic cement and had revision implants in situ. Seven patients had primary total knee components and had had a previous infection treated by debridement with implant retention and between two and six weeks of IV antibiotics. Four patients had undergone re-operations following their primary TKA for patellar tendon avulsion or patellar subluxation.

All patients were treated with a protocol comprising debridement, revision TKA with uncemented components, and IA antibiotics. In 11 patients, the infected components were cemented and had cemented diaphyseal engaging
stems in the femur and tibia. The mean follow-up was 62 months (27 to 96). No patients were lost to follow-up.

In all cases, a thorough debridement was performed including removal of all non-absorbable sutures, a complete synovectomy, and meticulous cement removal with the aid of a high-torque reamer to burr away all bone surfaces exposed to cement. If necessary, a vascularised osteoperiosteal flap osteotomy was used to expose the diaphyseal cement mantle. Hand-pump irrigation with saline solution of vancomycin (1 g/L), polymyxin B (250 000 units/L), and bacitracin (50 000 units/L) was used throughout debridement. After debridement, the surgical area was cleaned and re-draped, surgical gowns and gloves were changed, and new sterile instruments were brought into the sterile field. All revision implants had porous-coated surfaces applied directly to available bone and had diaphyseal-engaging titanium alloy stems. Neither cement nor bone graft was used in any case. Patients received 1 g of vancomycin intravenously at the time of surgery with two further doses given at 12 and 24 hours following surgery. The first IA dose of vancomycin (100 mg of vancomycin in 100 mL of sterile water) was started on the first day after surgery if the incision was dry, which was then increased in 100 μg/ml increments to a maintenance dose of up to 500 mg in 10 mL of sterile water. Again, IV vancomycin was discontinued once the maintenance IA dose was established.

At least one catheter remained in situ and functional in all patients for the duration of treatment, with seven of 18 knees having lost one by the end of the six-week treatment period. Peak and trough serum vancomycin levels were measured using the same method and intervals used in the first study. After six weeks, the Hickman catheters were removed and the joint fluid was cultured. The patients were seen at two weeks for suture removal, and evaluated at three months for tenderness, erythema, and induration, and at yearly intervals. Serum C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR) were evaluated at three months. CRP of less than 25% above the normal range and ESR less than 50% above the normal range were considered as signs of resolved infection.

Revision for re-infection study. The third study was designed to evaluate the success rate of an aggressive protocol to treat infection following failed two-stage revision. A retrospective review was conducted of 18 patients (18 knees; 12 women, six men) who had undergone re-revision between January 1999 and January 2008. A surgical protocol was used that included tibial tubercle osteotomy for exposure when necessary in stiff knees to avoid extensive soft-tissue stripping, bivalve osteotomy of the femur and tibia to extirpate extensive cement mantles, cementless fixation, closure with muscle flaps and subfascial skin flaps in cases with deficient capsule and skin, and IA antibiotics with Hickman catheters.

Mean time to initial revision was seven months (1.5 to 13) and to re-revision was five months (1 to 18). All knees were re-infected with the original organism(s): MRSA in 11 cases, methicillin-resistant Staphylococcus aureus in two, methicillin-sensitive Staphylococcus epidermidis in three, and mixed Proteus mirabilis (P. mirabilis) and Escherichia coli (E. coli) in three. All Staphylococcus aureus organisms were sensitive to vancomycin in concentrations of 2 μg/mL to 5 μg/mL, and the three E. coli and P. mirabilis organisms were sensitive to gentamycin in concentrations of 2 μg/mL. The mean follow-up was 6.1 years (2.3 to 12.0). No patient was lost to follow-up.

Ten knees (56%) underwent single-stage revision and five had two-stage procedures with between three and four months between excision and re-implantation (Fig. 2). Three knees (16%) had extensive soft-tissue reconstructions involving a number of operations including tissue expanders to produce enough skin for closure and external fixators to achieve adequate limb length before definitive revision arthroplasty. Two patients required debridement of the edge of a muscle flap and repeat closure within the first week post-operatively. Three patients had open drainage of haematoma and re-closure during the first two weeks post-operatively. If the bone and soft-tissue had adequate circulation to sustain healing, and adequate soft-tissue was available for closure, revision TKA was performed with the same technique described above. In cases in which bone stock and soft-tissue were not deemed adequate for stable fixation of the implants and secure closure of the joint, implants were not inserted, Hickman catheters were inserted for delivery of antibiotics, and closure completed using available skin and muscle flaps, allowing the extremity to shorten if necessary. These patients were managed post-operatively to achieve bone healing of the osteotomies, restore leg length, and gain skin for closure. Three patients underwent external fixation for gradual lengthening to regain limb length, and three patients had subfascial soft-tissue expanders to provide skin for closure.
Two Hickman catheters were inserted in all knees for IA antibiotic delivery. Post-operatively, the patients received 1 g of vancomycin or 80 mg of gentamicin intravenously every 12 hours for at least 48 hours post-operatively. IA infusion of antibiotics began the evening of the first day after surgery and the IV antibiotics were discontinued after IA administration was established. As a test dose, 100 mg of vancomycin in 30 mL of sterile water or 20 mg of gentamicin in 3 mL of sterile water were given, and the concentration and volume were increased daily if the wound remained quiescent.

Results
Pharmacokinetic study. Patients who received IA vancomycin to treat infected TKA exhibited very high synovial vancomycin levels. Following injection, the mean synovial vancomycin peak level was 9242 (3956 to 32,150; SD 7608 μg/mL). Synovial trough level (mean of 377 μg/mL, 8.4 to 1610) varied with time but exceeded MIC in all samples. Serum trough level ranged from 4.2 μg/mL to 25.2 μg/mL (mean, 12.3 μg/mL; average of 9.6% of the joint trough value), and the MIC was exceeded in all samples. Among individual patients, the elimination half life (t1/2) of IA vancomycin ranged from 1.61 to 4.70 hours (mean 3.22 hours). Among all patients, using β as the slope of the exponential regression curve, t1/2 was 3.06 hours (r² = 0.52, p < 0.001) (Fig. 3). No adverse events were reported; however, three of 11 patients had high serum vancomycin trough levels and their dose was reduced as a result. No patient had elevated urea or creatinine concentrations in the serum.

Resistant organism study. In total 17 of 18 patients were clinically free of infection at last follow-up in January 2007, and had laboratory evidence of resolved infection by the third post-operative month. None of the synovial fluid cultures taken at the time of catheter removal were positive for bacteria. One patient had elevated ESR and CRP concentration at three months post-operatively and redeveloped clinically apparent infection with MRSA five months after initial revision and debridement. The knee was re-explored and a fragment of necrotic bone measuring 2 cm to 3 cm on the anterior surface of the femur was found. Complete debridement was repeated, the polyethylene component was exchanged, and the metal components were retained. Hickman catheters were inserted, and the knee was treated for six weeks with IA vancomycin. At 42 months post-operatively, this knee had no clinical signs of infection. Other than the case with persistent infection, none of the implants has been revised for loosening or other reasons.

Mean serum vancomycin peak concentration was 6.1 (SD 4.1 μg/mL) and mean serum vancomycin trough concentration level was 3.2 (SD 1.0 μg/mL) at two weeks post-operatively. Because of elevated serum vancomycin concentration, five patients required the dose to be decreased to 500 mg once daily, and one required the antibiotics to be held for four days while the levels normalised. Three required discontinuation of the antibiotic infusion for two to three days because of local inflammatory response to precipitated vancomycin. Six patients (six knees) (33%) had elevated urea and creatinine levels during the six weeks of antibiotic infusion and required temporary discontinuation of IA vancomycin for two days. IA infusion then was resumed at a lower dose. None required complete discontinuation of vancomycin infusion for more than four days.

Revision for reinfecion study. Infection was controlled in 17 of 18 knees. One patient had a recurrent infection 13 months after single-stage debridement, revision, and primary closure of the knee. This knee was debrided again, infused with vancomycin for six weeks with no implant in place, and re-implanted with cementless implants six weeks after catheter removal. The CRP and ESR were normal at re-implantation with no sign of infection at 28 months follow-up. In one knee, soft-tissue closure was not achieved intra-operatively; the wound continued to drain and, two months after beginning treatment, the patient underwent an above-knee amputation. CRP and ESR were within normal limits at two-year follow-up in 16 of the 17 patients. One patient, who has chronic gingivitis, stasis dermatitis, and arteriosclerotic coronary artery disease, had elevated markers at one-year, but the knee was asymptomatic and neither examination nor aspiration demonstrated any signs of infection. No patient required chronic suppressive antibiotics.

The mean serum vancomycin peak level at one month post-operatively was 4.1 (SD 1.2 μg/mL), and mean trough level was 3.3 (SD 1 μg/mL). The mean peak gentamicin level was 1.1 (SD 1 μg/mL) and trough level was 0.2 (SD 0.1 μg/mL). Three patients with vancomycin and one with gentamicin infusion required temporary cessation of antibiotic infusion and resumption at a lower dose.
because of excessively high serum antibiotic levels or rising urea and creatinine levels.

**Discussion**

The protocols described above achieved control of infection in the majority of patients in the study. IA delivery of antibiotics produced peak concentrations many orders of magnitude higher than achieved after IV administration, trough levels which remained therapeutic for 24 hours, with therapeutic levels also achieved in the serum. The 11 patients in the pharmacokinetic study had vancomycin concentrations in the synovial space ranging from 39.56 μg/mL to 321.50 μg/mL, which is similar to the amikacin levels achieved with a similar protocol by Perry et al. \(^{28}\) In contrast to the synovial fluid levels achieved from IV dosing, which tend to become subtherapeutic in the knee after six hours, IA administration was shown to maintain the concentration of vancomycin within the knee joint above MIC for at least 24 hours following the dose. IV administration of vancomycin produced joint levels that were 35% of serum levels on average, while IA administration of vancomycin produced a peak joint concentration that on average was 750 times higher than the serum concentration. In addition, serum trough levels following IA administration of vancomycin remained therapeutic, with the mean value greater than the 10 μg/mL recommended to avoid resistance. \(^{11}\)

Extremely high antibiotic concentrations in the synovial fluid have a distinct advantage in treating IA infections involving a metal implant. The therapeutic effectiveness of antibiotics such as vancomycin that inhibit cell wall and RNA synthesis is proportional to both the concentration achieved and the time during which the concentration remains high. \(^{11-14}\) This factor is especially important when bacteria have formed a glycocalyx on implant surfaces. \(^{34}\) Since the formation of small colony variants with long reproductive intervals contributes to antibiotic resistance in treatment, \(^{35,36}\) it seems likely that the sustained high concentrations of antibiotics that are achieved with daily IA injection will be important in the effective management of IA infections involving metallic implants.

Direct IA antibiotic infusion with single-stage revision using cementless implants safely and effectively eradicated MRSA and provided a well-fixed implant in spite of the lack of antibiotic-loaded cement. Single-stage revision avoided the morbidity and inconvenience associated with the use of an antibiotic spacer and the need for a second surgical procedure. Infection was controlled in 17 of 18 patients with the first procedure, and in the failed procedure after debridement and repeat single-stage revision.

Two-stage revision, using IV antibiotics and antibiotic-loaded PMMA spacers to deliver antibiotics into the joint is considered the conservative surgical approach to this condition, \(^{3,4,19,37}\) but its clinical results are disappointing. Re-infection rates varying from 11% to 24% have been reported in centres experienced in care of these difficult cases using two-stage debridement and re-implantation. \(^{15,16,18,38}\)

Cemented fixation of implants is less successful in revision than in primary cases, \(^{19,39-43}\) and would appear to have a higher failure rate in cases with persistent infection from indolent bacteria. The use of cementless fixation with porous devices in revision arthroplasty leads to a high rate of successful fixation in the hip and has become the dominant mode of fixation in revision THA. \(^{44-46}\) Our centre has reported excellent results using cementless fixation for revision of infected TKA, with a success rate similar to that reported using cementless revision THA. \(^{37}\)

The re-infection cohort, where the revised cases had previously undergone failed two-stage revision for infected TKA, illustrates the severity of the bone loss in such cases and the effort required to achieve successful, infection-free reconstruction. The use of proven surgical procedures combined with IA antibiotic infusion led to control of infection in 17 of 18 knees. The types of cases in this cohort involve problems that cannot be solved only with high levels of antibiotics, but also require aggressive exposure and limb salvage techniques and often multiple procedures to prepare the extremity for reimplantation of the arthroplasty components.

These studies have demonstrated that daily IA injection of antibiotics achieves and maintains high synovial antibiotic concentrations, well above concentrations achievable using IV infusion. At our institution the single-stage procedure - including debridement and use of Hickman catheters for six weeks of IA antibiotic administration - is our protocol, even with highly resistant organisms.

**Supplementary material**

Further information regarding the samples used in this study is available alongside the online version of this article at www.bij.boneandjoint.org.uk.

**Author contributions:**

L. A. Whiteside: Performed all surgical cases, Designed study; Analysed data, Wrote paper.

M.E. Roy: Assisted with study design, Data collection, Data analysis, Paper construction.

T. A. Nayfeh: Assisted with study design, Data collection, Data analysis, Paper review.

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References