Negative Pressure Wound Therapy and Intra-Articular Antibiotics Instillation (NPWTiai) for the Treatment of Chronic Arthroplasty-associated Infections and Implant Retention: An Alternative Approach

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SUMMARY: Despite current low rates, the incidence of arthroplasty-associated infections (AAI) is likely to increase over the next few years as the number of joint replacement operations continues to rise worldwide. Debridement and implant retention is not a widely considered option for chronic AAI probably due to low success rates. Negative Pressure Wound Therapy and intra-articular antibiotics instillation using VAC ULTA/VeraFlo system is an alternative strategy in the management of chronic AAI where implant retention is sought. Further evaluations and studies are needed to assess the efficacy of this strategy and its cost effectiveness.

Key Words: NPWT—NPWTiai—infection—arthroplasty.
(Tech Orthop 2013;28: 201–206)

The most serious complication to arise after arthroplasty is infection, with rates of 1% to 3% for primary surgery and at least 4 to 8 times higher for revision procedures.3–6 Infection may carry a high morbidity rate, it may increase mortality, and it is an extensive burden on the health economy.4 Over the past years there has been a significant increase in the number of joint prosthesis replacements. In 2006, about 800,000 hip and knee arthroplasties were performed in the United States and 130,000 in England.7 The number of total joint arthroplasties and revision joint arthroplasties performed worldwide is increasing every year and it has been estimated that by 2036, 4 million total knee or hip arthroplasties will be performed annually in the United States.8,9 Therefore, even though the infection rates are low, the future true incidence of AAI is likely to increase dramatically as the number of operations continues to rise and the follow-up periods get longer.8

Generally, there are several treatment courses available for the management of AAI.9–13 The choice depends on many factors including the onset of infection, the causative bacterial agent, if known, the extent of tissue damage, the quality of the implant, and presence of comorbidities and patients' and surgeons' preferences. Debridement and implant retention is not a widely considered option for chronic AAI. The reason for this is multifactorial including low success rates of around 30% for this type of procedure.10–18 This has led to the need for more innovative technology in the management of this type of infection. The main aim of this type of orthopedic surgery is not only to meet the urgent needs of patients with chronic AAI, but also to reduce cost from complex and frequently ineffective revisions and re-revisions. In this manuscript we would like to report: (1) A successful management of a chronic AAI after surgical debridement and using VAC ULTA/VeraFlo system to deliver Negative Pressure Wound Therapy and intra-articular antibiotics instillation (NPWTiai) with implant retention, (2) work plan, antibiotic choice, and concentration that was selected in this case and briefly comment on other potential antibiotics that can be used via NWPTiai, and (3) in addition, what impact this technique could have on cost savings to the health economy.

To our knowledge this is the first that there has been a detailed description of antibiotic choice, concentration, and dose frequency used with this novel technology.

BRIEF CASE INFORMATION

In January 2012 at the Royal Hampshire County Hospital, Winchester, UK, VAC ULTA/VeraFlo system was applied to deliver NPWTiai to a 75-year-old lady with a chronically infected right total hip replacement. The patient had had multiple revision operations, initially for mechanical reasons, then multiple re-revisions due to repeated AAI. Her last re-revision was in 2008 due to an infective process without positive microbiological culture; this is not unusual after receiving many weeks of broad spectrum systemic antibiotic therapy. Despite aseptic procedures and perioperative antibiotics, this was complicated by another clinical infection and it was decided to use prolonged antibiotic therapy in the community to suppress the infection. However, as in most cases with time, the patient suffered further breakthrough infection with localized and occasionally systemic symptoms. A clinical management plan was agreed by the patient, the orthopedic surgeon, and infection team to undergo further surgical debridement followed by NPWTiai aiming to eradicate the infection and implant retention (Figs. 1–5).

VAC ULTA/VeraFlo SYSTEM

The VAC ULTA/VeraFlo system [KCI Medical Products (UK) Ltd., Wimboume, Dorset, UK] is an integrated wound

Techniques In Orthopaedics® • Volume 28, Number 2, 2013

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management system that provides cyclic multiphase negative pressure wound therapy (NPWT) with an instillation of a topical solution which may include a chosen antibiotic as outlined in the work plan below. The advantage of traditional NPWT has been published before.\(^9\)\(^-\)\(^2\) The VAC ULTRA/VeraFlo system has additional advantages over traditional NPWT, this is probably due to its special VeraFlo dressings, automatic volumetric fluid delivery pump that allows for volume and pressure accuracy with a homogenous and uniform distribution of solutions throughout the entire wound bed, during its instillation and hold phases, and also equal vacuum distribution, during its vacuum phase, which are central for promoting adequate microcirculation and granulation (Fig. 3).\(^2\)

**WORK PLAN AND METHODOLOGY**

**Debridement Phase**

Before the procedure, antibiotics were withdrawn from the patient for at least 4 weeks. The patient then underwent surgical debridement, wound clearance with the implant left in situ (Fig. 2). About 400 mL of pus was evacuated from around the implant; this plus other intraoperative tissue samples were sent to the microbiology department at the Royal Hampshire County Hospital. All samples were cultured and grew *Pseudomonas aeruginosa*, sensitive to piperacillin/tazobactam, ciprofloxacin, cefazidime, gentamicin, and meropenem. The wound was left open by the surgeon and covered by VAC ULTRA/VeraFlo system while still in theatre (Fig. 3). Treatment was then commenced using intra-articular gentamicin by VAC ULTRA/VeraFlo system and systemic intravenous piperacillin/tazobactam as a targeted therapy.

**VAC ULTRA/VeraFlo Cycles**

This system was used to deliver NPWT, continuously for 24 hours a day over 3 weeks using regular cycles, which can be altered by the operator. After applying VeraFlo dressings and connecting the system to instillation fluid and the drainage bags, the system performs an automatic seal check and calculates the exact volume required to be instilled to the wound cavity. Each cycle is composed of 3 phases, with approximately 12 cycles being used each day, that is, around 2 hours (120 min)/cycle as below:

- **Instillation Phase:** This usually takes <1 minute and the fluid volume used usually depends on wound size and capacity, which can be automatically calculated by the system itself.
FIGURE 5. Wound 4 months after the procedure.

In this case – 125 mm Hg pressure, with medium intensity was used and the (instillation) solution was composed of 5 mg/kg gentamicin/500 mL sodium chloride 0.9%.

- **Hold phase**: This allows the solution to have adequate contact with the wound bed; in this case it was kept for 20 minutes.
- **Vacuum phase**: Finally the extraction of the instilled solution through a separate vacuum tube, this phase was sustained for about 100 minutes to complete a full NPWTai cycle, before automatically starting the next instillation phase.

**Dressing Change and Review Instillation Fluid Volume With Time**

The entire dressing, including the sponge and tubing, was changed every third or fourth day with the dressing foam from the deep portion of the wound sent for microbiological culture. At the time of dressing change to check for bacterial growth. As the wound size got smaller the fluid volume in the instillation phase was reviewed. In this case negative culture was achieved with the first dressing change that is, only 48 hours after surgery and commencement of gentamicin by NPWTai.

**Review Need For NPWT and NPWTai**

On the basis of the wound progress (Fig. 4), it was decided to stop the NPWTai after 3 weeks, but to continue for an additional 3 weeks with ordinary NPWT.

**PATIENTS OUTCOME FOLLOW-UP**

After a single surgical debridement and implant retention, the patient received 3 weeks intravenous piperacillin/tazobactam and 3 weeks of gentamicin by NPWTai while in hospital. This was followed by a further 3 weeks of ordinary NPWT and oral ciprofloxacin in the community. The patient was followed up and monitored regularly, by district nurses and appeared fortnightly in the orthopedic/infection clinic, for wound healing, localized and systemic signs and symptoms of infection, and up to the time of writing this report (July 2012) she remained well and no symptoms and signs of infection has been reported to suggest deep seated or implant re-infection (Fig. 5).

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**TABLE 1. Other Potential Antibiotics That May Be Used Via NPWTai**

<table>
<thead>
<tr>
<th>Antibiotics†</th>
<th>Dosage and Suspension§</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>2 g/L of sodium chloride 0.9%</td>
<td>Active against Gram-positive organisms only including Methicillin-resistant Staphylococcus aureus strains. Change bag at least every 24 h. Serum levels can be measured if concerns about renal functions</td>
</tr>
<tr>
<td>Fluoxacinil</td>
<td>4-6 g/L sodium chloride 0.9%</td>
<td>Please note penicillin allergy. Change bag at least every 24 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>4-6 g/L sodium chloride 0.9%</td>
<td>Change bag at least every 48 h due to poor stability in room temperature. It should be used for confirmed resistant Gram-negative infections, particularly extended spectrum β-lactamase producers</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>2-4 g/L sodium chloride 0.9%</td>
<td>Change bag at least every 24 h. Can be used for treating infections with Gram-negative bacilli including sensitive Pseudomonas</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.5-1 g/0.5 L sodium chloride 0.9%</td>
<td>Active against Gram-positive organisms only including Methicillin-resistant Staphylococcus aureus strains. Change bag at least every 12 h. Please monitor Creatinin kinase</td>
</tr>
<tr>
<td>Ciladacmycin</td>
<td>0.9-1.2 g/L sodium chloride 0.9%</td>
<td>Active against some Gram-positive organisms (Sensitive staphylococci and streptococci) and some anaerobes. Change bag at least every 24 h</td>
</tr>
<tr>
<td>Colistim</td>
<td>2-4 megunit/L sodium chloride 0.9%</td>
<td>Change bag at least every 24 h. Can be used for confirmed resistant Gram-negative infections, particularly extended spectrum β-lactamase producers and some metallo-beta-lactamase producers. Serum levels can be measured if concerns about renal functions</td>
</tr>
</tbody>
</table>

*These choices are based on agreements among multidisciplinary teams and expertise. VAC ULTRA/VeraFlo is traditionally used for chronic osteomyelitis cases and is licensed for use with antiseptics. Antibiotics are not licensed to be used via NPWTai, please seek legal advice and consent form patients or guardians before application.
### TABLE 2. Itemized Costs of VAC ULTA/VeraFlo System

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost*</th>
<th>Cost for 3 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rental price of the VAC ULTA/VeraFlo unit</td>
<td>£20.27/d</td>
<td>£62.57</td>
</tr>
<tr>
<td>Medium VeraFlo dressings</td>
<td>£316/box of 5 (£63.20 each)</td>
<td>£568.80</td>
</tr>
<tr>
<td>Veraline cassettes</td>
<td>£149/box of 5 (£29.80 each)</td>
<td>£285.20</td>
</tr>
<tr>
<td>1000 ml. canisters</td>
<td>£250/box of 5 (£50 each)</td>
<td>£250</td>
</tr>
<tr>
<td>Total cost</td>
<td>£1,512.67 or £334.5</td>
<td></td>
</tr>
</tbody>
</table>

*These prices are agreed between KCI Ltd and Hampshire Hospitals NHS Foundation Trust, please note prices may vary according to local contracts.

As with any novel technique, there are no recommended standards, agreed choices, or dosage in the literature regarding using antibiotics through NPWTiA. Planning an appropriate antibiotic choice, deciding the concentrations and frequency of dosing via NPWTiA were based on communication within a multidisciplinary team that included orthopedic surgeons, clinical pharmacists, and clinical microbiologists and infection specialists. Culture-directed antibiotics may increase the success, as in this case, a detailed history of possible drug allergies and ongoing clinical monitoring are needed to avoid serious allergic or toxic reactions to the solution in use. In general the chosen antibiotic should be soluble in saline or the reconstituted solution, preferably with a long stability at room temperature, so it should be nonirritant to local tissue, and solutions used should be compatible with the dressings. In addition to gentamicin, the antibiotic detailed in Table 1 may potentially be used via NPWTiA under VAC ULTA/VeraFlo system either empirically or as targeted therapy in presence of positive microbiological culture, allowing MICs up to around 1000 seconds times higher than the recommended in vitro susceptibility testing advocated by various microbiology and infection diseases societies worldwide.

### COST IMPLICATIONS AND POTENTIAL SAVINGS FROM IMPLANT RETENTIONS

In our institution, the basic cost of using the VAC ULTA/VeraFlo system is around £512.67 for 3 weeks, with current exchange rate (of £1 to $ 1.55) this is almost equal to $ 2345 for 3 weeks (Table 2). The economic cost of infection-related revision arthroplasty varies and has been reported as being as much as $50,000 per procedure.10,11,12 This means the basic cost of 100 revisions of AAI would be around $5,000,000 in the United States, a figure which will not be greatly different in the UK. A greater number of studies are needed to determine implant retention rates with this technique. A report in Germany suggested success rates of about 80% using debridement and NPWTiA.16 However, even with potential 50% to 80% implant retention rates with this novel technique, a crude evaluation would point to potential savings of about 45% to 75% from limiting operative expenditure in any institute (Table 3).

### DISCUSSION, CONCLUSIONS, AND FUTURE DIRECTIONS

AAI are challenging problems for patients, surgeons, and the healthcare system. The commonly used treatment strategies for this type of infection are (1) debridement, antibiotics, and implant retention, (2) 1-stage revision surgery with systemic antibiotic therapy, (3) 2-stage revision surgery with systemic antibiotic therapy, (4) removal of infected implant without replacement with systemic antibiotic therapy, and (5) prolonged suppressive systemic antibiotic therapy in some cases.17-19 Revisions are associated with loss of bone stock, protracted immobilization or rehabilitation and perioperative complications, especially in patients with significant comorbidities. Re-revision is associated with 3 times the risk of implant failure, a more complicated surgical course, repeated episodes of general anesthesia, more frequent unplanned debridement before reimplantation, more frequent perioperative fractures, and more often required prolonged antibiotics after reimplantation and a protracted period of rehabilitation.16-18 The economic cost of infection-related revision varies and has been reported to have reaching up to $50,000 per patient.16,24-26 Therefore, on the basis of 1% to 3% infection rates and the predicted 4 million operations by year 2030, the conservative cost of primary revisions due to infection in the United States would be between $200,000,000 to $600,000,000 per year, a substantive impact on the health budgets.7

### TABLE 3. Cost of Revisions in Chronic Infected Arthroplasty and Potential Savings From 50% to 80% Implant Retention Rates Using VAC ULTA/VeraFlo System to Deliver NPWTiA

<table>
<thead>
<tr>
<th>VAC ULTA/VeraFlo for 3 wk at $2345 With 50% Implant Retention Rate in, Only 59 Revisions Would be Done out of 100 Chronic Infections</th>
<th>VAC ULTA/VeraFlo for 3 wk at $2345 With 89% Implant Retention Rate in, Only 28 Revisions Would be Done out of 100 Chronic Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cost of 100 Revision TKR Without Using VAC ULTA/VeraFlo</td>
<td>Total Cost of 100 Revision TKR Without Using VAC ULTA/VeraFlo</td>
</tr>
<tr>
<td>5,000,000</td>
<td>2,500,000</td>
</tr>
<tr>
<td>2,500,000</td>
<td>1,000,000</td>
</tr>
<tr>
<td>0</td>
<td>234,500</td>
</tr>
<tr>
<td>234,500</td>
<td>234,500</td>
</tr>
<tr>
<td>0</td>
<td>2,265,500</td>
</tr>
<tr>
<td>2,265,500</td>
<td>1,765,500</td>
</tr>
<tr>
<td>0</td>
<td>45.3</td>
</tr>
<tr>
<td>45.3</td>
<td>75.3</td>
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A minimally invasive surgical approach which can result in implant retention is thus an attractive form of treatment. Although debridement, antibiotics, and implant retention tends to be tried in acute AAI, implant retention is not a widely considered option for chronic AAI as success rates are much lower. This may be due to the fact that conventional ways of delivering antibiotics may fail to achieve adequate concentration at the site of infection, which in itself is a complex issue as bacteria in biofilms have significant tolerance to antimicrobial agents compared with planktonic forms of bacteria. However, in our case the NWPTtai proved successful in managing a complex P. aeruginosa biofilm infection without removal of the implant. Before this approach, our patient had undergone almost all other treatment modalities used for management of AAI, but without success. The system allowed for delivering high concentration of antibiotics locally and directly to the implant, avoiding the "collateral" damage of systemic antibiotics such as antibiotics toxicity, antibiotic-associated C. difficile colitis, and selective pressure on normal flora. The underlying mechanism of the success this time is not fully understood; one could postulate that the NWPTtai may have disturbed the biofilms, creating a more aerobic environment in the wound and allowing for more membrane permeability which in turn means that the locally delivered high concentration of gentamicin is able to work better against the P. aeruginosa. There is evidence in animals that intra-articular injections of antibiotics create concentrations that far exceed those achieved by intravenous administration. Intravenous antibiotics, generally used for 6 weeks after revision arthroplasties, can produce synovial fluid concentrations as high as 20% to 50% serum levels when gentamicin and cefalosporins are used, respectively. These levels are too low to be effective particularly in cases of resistant organisms. Antibiotic concentration many times higher than MICs can be achieved and maintained for weeks with this novel technique even in cases with highly resistant organisms.

Implant retention is not only ideal for patients, but may also prove advantageous for institutes' economics. Our evaluation provides a basic comparison between costs of NWPTtai via VAC ULTRA/VeraFlo system versus cost of revisions in AAI, suggesting a potential saving of about 45% to 75% from limiting operative expenditures (Table 3), these evaluations do not account for additional savings from prevention of repeated procedures, bed days, prolonged intravenous and oral antibiotics, staff time, and other hidden costs that tend to be more difficult to calculate, for example, negative psychological effects that are associated with revisions and re-revisions.

This report highlights that NWPTtai could be added to the armamentarium of orthopedic surgeons as an alternative approach in managing acute and chronic AAI especially where implant retention is intended or unavoidable because of patient comorbidities. However, there are still many unanswered questions in regards to standardization and duration of the antimicrobial therapy and NWPTtai therapy and formal cost benefit analysis. Further evaluations and larger studies with simultaneous controls and comparative groups and/or wounds are needed to address many of these questions.

ACKNOWLEDGMENTS

The authors thank Medical Microbiology, Medical, and Nursing staff on St Cross ward at the Royal Hampshire County Hospital for their enthusiasm and support with NWPTtai. The authors greatly thank Mick Denison: Orthopedics Consultant and Rob Townsend; Consultant Microbiologist at Sheffield Teaching Hospitals NHS Foundation Trust, UK for their support and advice regarding choices and dosages of antibiotics. Finally, the authors thank KCI for training their staff to use VAC ULTRA/VeraFlo system.

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