Regional Prophylactic Vancomycin with Restricted Tourniquet Time in Primary Total Knee replacement

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Project Summary

Resistance to cefalosporins in Staphylococcus Aureus (SA) and Coagulase negative Staphylococci (CoNS) isolates is increasing, and vancomycin has been suggested as an alternative prophylactic agent in TKA[1]. Recently, we have investigated prophylactic vancomycin via intraosseous regional administration (IORA) in primary TKA[2], which allowed the use of a lower dose (500mg) while still achieving tissue concentrations 4-10 times higher than systemic administration.

The use of IORA vancomycin requires the use of a tourniquet for the duration of the procedure. Many surgeons prefer to perform the surgery with tourniquet use minimised or without a tourniquet at all. The aim of this study is to evaluate whether IORA vancomycin can achieve effective tissue concentrations with tourniquet use minimised.

Based on a power calculation using previous IORA data, 26 patients undergoing primary TKA for osteoarthritis will be enrolled in a prospective, randomized, controlled trial. Patients will be randomized into two groups. Group A would receive a weight based dose of 15mg/kg systemic IV vancomycin via a forearm vein, given over a 1-2 hour infusion timed to finish immediately prior to surgery. Group A would have a tourniquet used for cementation only. Group B would receive 500mg vancomycin via IORA into a proximal tibial cannula, after tourniquet inflation and immediately prior to skin incision. In group B, the tourniquet would be inflated for a total of 10 minutes after completion of IORA injection, then deflated, then reinflated for cementation only. In addition, patients in both groups would receive standard IV systemic prophylaxis with a cephalosporin.

:

	Vanc dose	Route	Tourniquet
Group A	1g	IV	Inflate for cement only
Group B	500 mg	IORA	Up 10 min, down, up for cement

Primary TKA would then be carried out as normal, and during the procedure ten tissue samples (6 subcutaneous fat, 4 bone) will be taken at set time intervals. These samples would then be processed using a previously validated technique involving high performance liquid chromatography (HPLC) to determine the tissue concentration of vancomycin. Samples would be stored in a -80C freezer in the laboratory at Mayo Arizona, before being sent as one shipment to a laboratory in Christchurch, New Zealand for processing. Tissue concentrations would then be compared between the two groups.

Introduction

Total knee Arthroplasty (TKA) remains one of the most successful interventions in medicine. Patients who are facing lifelong, crippling pain due to knee arthritis now have the opportunity to return to near normal function.

The cost of treating an established infection is estimated at $US107,000 per case[3-5], and even after successful treatment results in a significantly compromised functional outcome for the patient.

Prophylactic antibiotics are currently the most effective measure available to prevent deep infection following knee replacement, but increasing antibiotic resistance is reducing their effectiveness[6-10]. In particular, resistance to the most commonly used cephalosporin agents among Staphylococcus Aureus (SA) and Coagulase negative Staphylococci (CoNS) isolates continues to rise[1,11]. Vancomycin, which retains broad efficacy against such organisms, has been suggested as an alternative prophylactic agent in TKA[1,12].

However, systemic vancomycin requires a prolonged administration time, risks promoting further antibiotic resistance, and can cause systemic toxicity. Regional administration of medication using a tourniquet achieves higher tissue concentrations than systemic administration, by limiting distribution of the drug to the targeted limb. Recently, we have investigated prophylactic vancomycin via intraosseous regional administration (IORA) in primary TKA[2,12], which allowed the use of a lower dose (250mg or 500mg) while still achieving tissue concentrations 4-10 times higher than systemic administration. This low-dose IORA method optimizes timing of vancomycin administration, and minimizes potential side effects. In addition, greater efficacy of the IORA technique has been demonstrated in an animal model of TKA infection.[13]

Regional administration however requires the use of a tourniquet during the procedure, which may have negative effects including increasing post-operative pain[14], upregulating inflammatory enzymes[15], and reducing quadriceps strength[16]. For this

reason, many surgeons prefer to minimise the use of the tourniquet during the procedure[17].

It may be possible to perform IORA with the tourniquet inflated for a short period of time following intraosseous injection, as the depot effect may mean tissue concentrations remain high for the remainder of the procedure. The aim of this study is to evaluate whether IORA vancomycin can achieve effective tissue concentrations for the duration of the procedure with tourniquet use minimised in primary TKA.

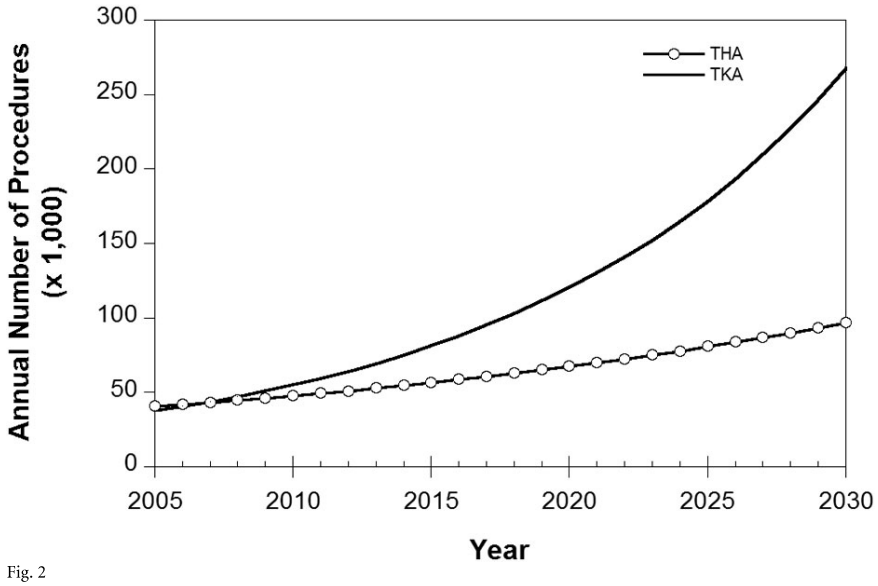

Fig. 2
The projected number of revision total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures in the United States from 2005 to 2030.

From Kurtz et al, JBJS 2007

Potential Benefits of Regional Vancomycin Administration

Regional administration of vancomycin has the following potential advantages:

1) Lower risk of toxicity

Vancomycin carries the risk of toxicity to other organs. In particular, higher systemic concentrations on vancomycin have been associated with a greater risk of nephrotoxicity.[2,12,18,19] Because regional administration restricts all of the medication to its site of action, lower doses may still provide effective tissue concentrations while minimising the risk of systemic toxicity.

2) More effective prophylaxis

As well as the advantage of more effective coverage of resistant organisms with vancomycin, by using regional administration the antibiotic stays in the area where it is needed. Therefore a higher tissue concentration of the antibiotic can be achieved, even with a lower dose. This is relevant as higher concentrations of vancomycin have been associated with greater efficacy in a clinical setting.[18-20] In addition, greater efficacy of the IORA technique has been demonstrated in an animal model of TKA infection.[13]

3) Ease of administration

Vancomycin is normally given systemically over one hour, as high systemic concentrations can cause histamine release and a subsequent 'red man syndrome', caused by dilation of blood vessels secondary to the histamine release. The timing of prophylactic antibiotics is extremely important, and the dose should be given within the 60 minutes preceding the surgical incision.[2,12,21,22] Due to the long infusion time vancomycin is normally given, achieving optimum timing as a prophylactic antibiotic is difficult to achieve in a busy operating room. In a review of 18,342 arthroplasty procedures, vancomycin was given with appropriate timing in only 22% of cases, compared to 77% of cases given a cephalosporin[3-5].

The lower doses of vancomycin used with regional administration and the fact that its distribution is limited to the limb reduces the risk of 'red man syndrome'. This allows for more convenient administration of the antibiotic thus ensuring correct timing of administration.

4) Less resistance pressure

Development of resistance to antibiotics relates to both duration and dosage of the antibiotic, which applies a 'selection pressure' to bacteria promoting the emergence of resistant organisms. The advantage of regional administration over systemic is that a lower overall dose can be used, while still maximizing the effectiveness of the antibiotic at its site of action.

Aim

The aim of this study is to evaluate whether IORA vancomycin can achieve effective tissue concentrations with tourniquet use minimised in primary TKA.

Patients and Methods

Patients under undergoing revision total knee replacement would be eligible for enrolment in a prospective, randomized trial.

Inclusion Criteria

Primary TKA for osteoarthritis
Informed consent given

Exclusion Criteria

Current or treatment with IV Vancomycin within preceding 7 days
Previous hypersenstivity to vancomycin
Significant cardiac or respiratory abnormality
Patient has contraindications to IO vascular access using the EZ-IO

Both groups would receive weight-based dose of systemic cefazolin (or alternative antibiotic if allergic to cefazolin) 15 minutes prior to tourniquet

inflation – either 2g for patients between 80-120kg or 3g for patients over 120kg. This ensures all patients in the study receive effective antibiotic prophylaxis regardless of randomisation. Both groups of patients would then undergo routine prep and draping Group B will have the limb exsanguinated and an above knee tourniquet inflated to 300mmHg.

Group A would receive 15mg/kg based on actual body weight (maximum of 2g) of vancomycin via the systemic route at a rate of 15mg/kg as per hospital guidelines (acceptable to give 2g over 2 hours). Systemic IV vancomycin is given via a forearm vein, given over an infusion timed to finish immediately prior to surgery.

Immediately following tourniquet inflation, Group B will receive 500mg of vancomycin, via an EZ-IO (Teleflex Medical, San Antonio, Texas) intraosseous cannula. This system has been well validated in multiple studies[6-10], showing high user satisfaction and low complication rates. The vancomycin would be administered in 150ml of saline solution following the recommendations of Waisman et al.[1,11]. The intraosseous cannula would be placed into the epiphysis of the proximal tibia as previously described [1,12].

In group B, the tourniquet will be left inflated for 10 minutes following *completion* of the IORA injection then deflated.

Total knee replacement would then be carried out as normal and the tourniquet will be inflated for cementation of the implants in both groups. A fat sample will be taken immediately after skin incision, and then bone and fat samples with be taken at set intervals during the surgery, including immediately prior to closure. Each patient will have a total of 10 tissue samples taken intraoperatively. In addition, drain samples will be taken from the intra-articular drain site to measure vancomycin concentration the morning following surgery. Three blood samples will be taken in both groups, intraoperatively, in recovery, and the following morning.

A timeline for each group is presented below. Samples will be taken at specific steps during the procedure, and actual times will be recorded with each sample as the

duration of the surgical procedure may vary. Times given below in italics represent approximations only.

	Group B (Intraosseous)	**Group A** (Systemic)
-90 minutes		1g systemic Vancomycin infusion
-10 minutes	**1g systemic Cefazolin (or alternative antibiotic) injected**	**1g systemic Cefazolin (or alternative antibiotic) injected**
-1 minute	Routine prep and draping	Routine prep and draping
0 minutes	Exsanguination & Tourniquet inflation for 10 minutes	---------- (No Tourniquet inflation)
1 minute	**500mg intraosseous Vancomycin injected into tibial cannula**	----------
Surgery Commences *2 minutes*	Skin incision	Skin incision
Post incision *2 minutes*	**1st sample – subcutaneous fat** **Blood Sample 1**	**1st sample – subcutaneous fat** **Blood Sample 1**
Distal Femoral Cut *(10-15 minutes)*	**2nd and 3rd samples – fat and bone** Tourniquet deflated at 10 minutes	**2nd and 3rd samples – fat and bone**
Tibial Cut *15-25 minutes*	**4th and 5th samples – fat and bone**	**4th and 5th samples – fat and bone**
Implant Trialling *(25-45 minutes)*	**6th and 7th samples – fat and bone**	**6th and 7th samples – fat and bone**
Implant Cementing *(45-60 minutes)*	Tourniquet inflation pre-cementing **8th and 9th samples – fat and bone** Tourniquet deflation post cementing	Tourniquet inflation pre-cementing **8th and 9th samples – fat and bone** Tourniquet deflation post cementing
Prior to Closure *60+ minutes*	**10th Sample - fat**	**10th sample - fat**
Surgery Complete		
Recovery	**Blood Sample 2**	**Blood Sample 2**
Next Morning	**Drain Sample** **Blood Sample 3**	**Drain Sample** **Blood Sample 3**

Samples

Ten tissue samples will be taken from each patient, 6 'fat' samples and 4 'bone' samples. Each sample will be approximately the size of a pinhead. Bone samples will be taken from the femur only to ensure no direct contamination from the site of injection (tibia). Where possible, both bone and fat samples will be taken from tissue which is normally discarded during the course of a total knee replacement procedure, otherwise samples will be taken from tissue that is already exposed with no further incisions or invasive procedures required. Due to the small size of the samples it is anticipated that there will be no detrimental effect on the patient. Samples will be stored the Mayo Clinic Hospital lab at -90°C, before being transported to Christchurch, New Zealand for analysis using a previously validated technique[2,12]. Bone samples will be crushed with pliers, finely cut further with a scalpel, then weighed and immersed in phosphate buffered saline pH 7.3 for 15 h at 4C. The fat samples will finely cut with a scalpel, and then treated in a same way as the bone samples. The immersed bone or fat tissue suspension will be vortexed for 30 seconds and centrifuged at 15,000 g for 10 min. The supernatant will be transferred to a clean tube and perchloric acid added to precipitate the proteins. After centrifugation at 15,000 g for 5 min, 50 uL of clear supernatant will be analysed. Drain fluid samples will be processed by the Mayo Clinic laboratory by being centrifuged at 2500rpm for 10 minutes. The supernatant will be placed in a 1.8ml cryovial. The remaining supernatant and cell pellet will be discarded. The drain fluid samples will be stored at -90°C until they are shipped with the other samples to Christchurch, New Zealand.

Power Calculation

Data from a previous randomized trial comparing (IORA) of 500 mg vs. systemic administration of 1g vancomycin provide AUC of concentrations during the procedures. The following table provides the information of AUC and standardized AUC (AUC/length of procedure).

	AUC (AUC/procedure mins) (mean)	AUC (AUC/procedure mins) (median)	AUC (AUC/procedure mins) (STD)	AUC (AUC/procedure mins (Min)	AUC (AUC/procedure mins) (Max)
Bone					
IO	1236 (15.3)	1190 (13.2)	561 (7.1)	542 (7.6)	2151 (29.1)
Systematic	259 (3.2)	221 (3.0)	185 (1.9)	87(1.0)	697(7.4)
Fat					
IO	2398	1652	1913	617	6846
Systematic	194	190	56	126	315
Blood					
IO	1236	1158	280	863	1638
Systematic	2547	2684	782	1454	3554

Using AUC

The standardized area under the curve is 30.5 (STD: 26.6) in the IO arm, and 2.4 (STD: 0.6) in the systematic arm. To achieve 90% statistics power with type I error rate of 0.05, 12 patients will be required for each group after accounting for 10% missing data.

While data on pharmacodynamics of vancomycin for prophylaxis are lacking, in treatment models of infection, the area under the concentration-time curve divided by the Minimum Inhibitory Concentration (MIC, a parameter that reflects the sensitively of a bacterial strain to a given antibiotic) is the pharmacokinetic-pharmacodynamic

parameter most predictive of efficacy. Therefore, further increases in tissue vancomycin concentrations are likely to enhance the effectiveness of prophylaxis, particularly in organisms with MICs of 1g/L or more such as MRSA and CoNS[20]; this suggests the differences used in our power analysis are clinically relevant.

Statistical analysis

Means, standard deviations, and the 95% confidence limits will be calculated for the concentrations in the different samples. Different tissue samples were pooled according to surgical steps. Coefficient of variations (CV) of concentration level will be summarized at each surgical step for the comparison between two arms. Repeat measure analysis of variance will be used to compare the average level of concentration across time between groups adjusted by BMI, age, and length of surgical procedure; Shapiro-Wilk test will be used to assess the normality of the residuals. Adverse event will be recorded by contingency table.

Safety of the intraosseous route

The technique of intraosseous regional administration of antibiotics has been evaluated in humans in two randomised controlled trials [2,12]. No complications related to the use of the technique were found.

The use of the intraosseous route for administration of both fluids and medications is well established. In 1947, Heinld[4] reported on the use of the intraosseous route in over 1000 paediatric patients, reporting a 95% success rate in administering fluids, blood products, and a variety of medications. The technique has been more popular in paediatric patients because intravenous access is more difficult; however intraosseous administration is equally as effective in adult patients. A summary of more current literature is included below, and a copy of a comprehensive review article recently published by Tobias[7] is attached.

Of particular relevance to the current study, 3 papers have investigated the regional (with tourniquet on) intraosseous delivery of antibiotics in horses. Scheuch[27] compared intraosseous versus intravenous infusion of amikacin (an antibiotic) and found similar tissue levels of antibiotic in 21 horses. Mattson[28] found effective tissue concentrations of gentamicin after intraosseous regional delivery in 12 horses, and recommended this as a form of treatment for infection. Similarly Rubio[29] compared regional intravenous versus intraosseous administration of vancomycin in 12 horses and found equivalent tissue perfusion for both routes. None of the above studies reported any complications with the intraosseous route.

The use of regional (with tourniquet inflated) intraosseous infusions of medications has also been investigated in humans. Waisman[11] on 109 patients who were given local anaesthetic agents through the regional intraosseous route, in both the upper and lower limbs, to allow surgical procedures to be performed on the limb with the patient awake. The procedure was successful in 106 of 109 patients, with 3 failures. In one patient the needle was incorrectly positioned, and two patients had inadequate anaesthesia which the authors attributed to an insufficient amount of medication infused. No other complications were reported. This paper is a useful reference as it has a very similar concept to our study (substituting the intraosseous route for

intravenous in the regional delivery of medications) and provides evidence of the safety of the technique in a large number of patients.

There are 4 main complications of intraosseous infusion that have been reported in adults. All relate to technical errors or prolonged infusions in an emergent setting, and are therefore extremely unlikely to occur in the single, controlled injection proposed in this study.

1) Extravasation of fluid (due to incorrect needle placement)

This complication occurs when a needle is not place correctly (outside the bone), and infusion of fluid or medication is commenced. With modern intraosseous needles this complication is reduced by closely monitoring the patient, particularly at the IO needle insertion site, and using appropriate length IO needles to prevent over penetration through the bone. The reported success rates for the EZ-IO needle used in the current study range from 94-100%, and it is anticipated that as the needle will be placed by a trained orthopaedic surgeon in a controlled theatre environment the chance of incorrect needle placement will be very low.

2) Compartment Syndrome

Compartment syndrome again relates firstly to incorrect needle placement, and has been described rarely in a isolated case report following intraosseous infusions[30]. It occurs if the tip of the needle is placed into soft tissues rather than bone, then prolonged infusion of fluids commenced and the situation is not recognised. Large published series of intraosseous infusions have not reported this complication suggesting it is very rare.[7] It is extremely unlikely to occur in the context of this study as the needle is left in situ for a very short time, and fluid is injected as a single bolus so needle malposition or fluid leakage into the tissue will be immediately recognised.

3) Fracture

There have been isolated reports of fracture following intraosseous needle placement in the literature. This is thought to relate to the use of excessive force with manual needle placement, and to our knowledge has not been reported with the powered needle driver used in the current study.

4) Infection / osteomyelitis

A meta-analysis of 4359 intraosseous insertion attempts reported an incidence of infection of 0.6%[7]. It is anticipated that as the insertions in our study will take place in a full sterile environment and antibiotic will be injected through the needle the incidence of infection is likely to be even lower.

The above complications will be outlined in the patient information sheet.

Vancomycin and 'Red Man Syndrome'

Vancomycin has been administered successfully via the intraosseous route in both human[12] and animal studies[29,31]. One advantage of using the regional technique outlined in this study is the potential to use lower doses to achieve high local concentrations, and thus minimize systemic side effects such as 'Red Man Syndrome'.

Red man syndrome is an anaphylactoid reaction caused by the degranulation of mast cells resulting in histamine release. It is not an allergic reaction and is independent of preformed immunoglobulin E. It occurs in 30% to 90% of healthy volunteers given vancomycin[32], and symptoms are usually mild and alleviated by use of an antihistamine. Incidence is related to both dosage and rate of infusion; Polk et al.[33] observed the reaction during systemic infusion of 1 g vancomycin in 82% of volunteers, but no reaction occurred when a 500-mg dose was used. Healy et al.[34] noted symptoms in eight of 10 volunteers (80%) given 1 g vancomycin over 1 hour but in only three of 10 volunteers (30%) given the same dose over 2 hours. In a recent trial of TKA patients 500mg vancomycin was given using the same IORA protocol as this in study, and no cases of red mean syndrome were seen[12]. This is likely due to both the lower vancomycin dose and the depot effect of the high tissue concentration, that causes antibiotic to be released gradually into the systemic circulation after tourniquet deflation[29].

As a precaution, the patients receiving IORA vancomycin in this study will be monitored closely after tourniquet deflation and an antihistamine will be available if clinical signs of red man syndrome are seen.

References

1. Smith EB, Wynne R, Joshi A, Liu H, Good RP. Is it time to include vancomycin for routine perioperative antibiotic prophylaxis in total joint arthroplasty patients? *J Arthroplasty*. 2012;27(8 Suppl):55–60. doi:10.1016/j.arth.2012.03.040.

2. Young SW, Zhang M, Freeman JT, Vince KG, Coleman B. Higher cefazolin concentrations with intraosseous regional prophylaxis in TKA. *Clin Orthop Relat Res*. 2013;471(1):244–249. doi:10.1007/s11999-012-2469-2.

3. Bull AL, Worth LJ, Richards MJ. Impact of vancomycin surgical antibiotic prophylaxis on the development of methicillin-sensitive staphylococcus aureus surgical site infections: report from Australian Surveillance Data (VICNISS). *Ann Surg*. 2012;256(6):1089–1092. doi:10.1097/SLA.0b013e31825fa398.

4. Heinild S, Sondergaard T, Tudvad F. Bone marrow infusion in childhood. *J Pediatr*. 1947;30:400–412.

5. Kapadia BH, Pivec R, Johnson AJ, et al. Infection prevention methodologies for lower extremity total joint arthroplasty. *Expert Rev Med Devices*. 2013;10(2):215–224. doi:10.1586/erd.12.76.

6. Cooper BR, Mahoney PF, Hodgetts TJ, Mellor A. Intra-osseous access (EZ-IO) for resuscitation: UK military combat experience. *J R Army Med Corps*. 2007;153(4):314–316.

7. Tobias JD, Ross AK. Intraosseous infusions: a review for the anesthesiologist with a focus on pediatric use. *Anesth Analg*. 2010;110(2):391–401. doi:10.1213/ANE.0b013e3181c03c7f.

8. Shavit I, Hoffmann Y, Galbraith R, Waisman Y. Comparison of two mechanical intraosseous infusion devices: A pilot, randomized crossover trial. *Resuscitation*. 2009;80(9):1029–1033. doi:10.1016/j.resuscitation.2009.05.026.

9. Yamada K, Matsumoto K, Tokimura F, Okazaki H, Tanaka S. Are Bone and Serum Cefazolin Concentrations Adequate for Antimicrobial Prophylaxis? *Clin Orthop Relat Res*. 2011;469(12):3486–3494. doi:10.1007/s11999-011-2111-8.

10. Levitan R, Bortle C, Snyder T, Nitsch D, Pisaturo J, Butler K. Use of a Battery-Operated Needle Driver for Intraosseous Access by Novice Users: Skill Acquisition With Cadavers. *Annals of emergency medicine*. July 2009. doi:10.1016/j.annemergmed.2009.06.012.

11. Waisman M, Roffman M, Bursztein S, Heifetz M. Intraosseous regional anesthesia as an alternative to intravenous regional anesthesia. *The Journal of trauma*. 1995;39(6):1153–1156.

12. The Mark Coventry Award: Higher tissue concentrations of vancomycin with

low-dose intraosseous regional versus systemic prophylaxis in TKA: a randomized trial.

13. Young SW, Roberts T, Johnson S, Dalton JP, Coleman B, Wiles S. Regional Intraosseous Administration of Prophylactic Antibiotics is More Effective Than Systemic Administration in a Mouse Model of TKA. *Clin Orthop Relat Res*. 2015;473(11):3573–3584. doi:10.1007/s11999-015-4464-x.

14. Kumar N, Yadav C, Singh S, Kumar A, Vaithlingam A, Yadav S. Evaluation of pain in bilateral total knee replacement with and without tourniquet; a prospective randomized control trial. *J Clin Orthop Trauma*. 2015;6(2):85–88. doi:10.1016/j.jcot.2015.01.095.

15. Jawhar A, Hermanns S, Ponelies N, Obertacke U, Roehl H. Tourniquet-induced ischaemia during total knee arthroplasty results in higher proteolytic activities within vastus medialis cells: a randomized clinical trial. *Knee Surg Sports Traumatol Arthr*. 2016;24(10):3313–3321. doi:10.1007/s00167-015-3859-2.

16. Dennis DA, Kittelson AJ, Yang CC, Miner TM, Kim RH, Stevens-Lapsley JE. Does Tourniquet Use in TKA Affect Recovery of Lower Extremity Strength and Function? A Randomized Trial. *Clin Orthop Relat Res*. 2016;474(1):69–77. doi:10.1007/s11999-015-4393-8.

17. Zhang P, Liang Y, He J, Fang Y, Chen P, Wang J. Timing of tourniquet release in total knee arthroplasty: A meta-analysis. *Medicine (Baltimore)*. 2017;96(17):e6786. doi:10.1097/MD.0000000000006786.

18. Zimmermann AE, Katona BG, Plaisance KI. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. *Pharmacotherapy*. 1995;15(1):85–91.

19. Blom AW, Brown J, Taylor AH, Pattison G, Whitehouse S, Bannister GC. Infection after total knee arthroplasty. *J Bone Joint Surg Br*. 2004;86(5):688–691.

20. Crawford T, Rodvold KA, Solomkin JS. Vancomycin for Surgical Prophylaxis? *Clinical Infectious Diseases*. 2012;54(10):1474–1479. doi:10.1093/cid/cis027.

21. Phillips JE, Crane TP, Noy M, Elliott TSJ, Grimer RJ. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: A 15-YEAR PROSPECTIVE SURVEY. *J Bone Joint Surg Br*. 2006;88-B(7):943–948. doi:10.1302/0301-620X.88B7.17150.

22. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of Primary and Revision Hip and Knee Arthroplasty in the United States from 2005 to 2030. *The Journal of Bone and Joint Surgery*. 2007;89(4):780–785. doi:10.2106/JBJS.F.00222.

23. Lazzarini L, Novelli A, Marzano N, et al. Regional and systemic prophylaxis with teicoplanin in total knee arthroplasty: a tissue penetration study. *J*

Arthroplasty. 2003;18(3):342–346. doi:10.1054/arth.2003.50053.

24. de Lalla F, Viola R, Pellizzer G, Lazzarini L, Tramarin A, Fabris P. Regional prophylaxis with teicoplanin in monolateral or bilateral total knee replacement: An open study. *Antimicrob Agents Chemother*. 2000;44(2):316–319.

25. de Lalla F, Novelli A, Pellizzer G, et al. Regional and systemic prophylaxis with teicoplanin in monolateral and bilateral total knee replacement procedures: study of pharmacokinetics and tissue penetration. *Antimicrob Agents Chemother*. 1993;37(12):2693–2698.

26. Hoddinott C, (null), Lovering AM, Fernando HC, Dixon JH, Reeves DS. Determination of bone and fat concentrations following systemic cefamandole and regional cefuroxime administration in patients undergoing knee arthroplasty. *J Antimicrob Chemother*. 1990;26(6):823–829.

27. Scheuch BC, Van Hoogmoed LM, Wilson WD, et al. Comparison of intraosseous or intravenous infusion for delivery of amikacin sulfate to the tibiotarsal joint of horses. *Am J Vet Res*. 2002;63(3):374–380.

28. Mattson S, Bouré L, Pearce S, Hurtig M, Burger J, Black W. Intraosseous gentamicin perfusion of the distal metacarpus in standing horses. *Veterinary surgery : VS : the official journal of the American College of Veterinary Surgeons*. 2004;33(2):180–186. doi:10.1111/j.1532-950x.2004.04026.x.

29. Rubio-Martínez LM, López-Sanromán J, Cruz AM, Santos M, Andrés MS, Román FS. Evaluation of safety and pharmacokinetics of vancomycin after intravenous regional limb perfusion in horses. *Am J Vet Res*. 2005;66(12):2107–2113. doi:10.2460/ajvr.2005.66.2107.

30. Atanda A, Statter MB. Compartment syndrome of the leg after intraosseous infusion: guidelines for prevention, early detection, and treatment. *Am J Orthop*. 2008;37(12):E198–E200.

31. Chastagner P, Lozniewski A, Lascombes P, Barberi-Heyob M, Merthes PM, Merlin JL. Pharmacokinetic longitudinal studies of antibiotics administered via a permanent intraosseous device in micropigs. *Med Pediatr Oncol*. 2001;36(6):635–640. doi:10.1002/mpo.1141.

32. Sivagnanam S, Deleu D. Red man syndrome. *Critical Care*. 2003;7:119–120.

33. Polk RE, Healy DP, Schwartz LB, Rock DT, Garson ML, Roller K. Vancomycin and the red-man syndrome: pharmacodynamics of histamine release. *J Infect Dis*. 1988;157(3):502–507.

34. Healy DP, Sahai JV, Fuller SH, Polk RE. Vancomycin-induced histamine release and “red man syndrome”: comparison of 1- and 2-hour infusions. *Antimicrob Agents Chemother*. 1990;34(4):550–554.