NORTHERN OHIO FOOT & ANKLE FOUNDATION

The Northern Ohio Foot and Ankle Journal *Official Publication of the NOFA Foundation*

The Foreign Body Induced Membrane Technique: Review of the Literature

by Chris Tyree, DPM[1]

The Northern Ohio Foot and Ankle Journal 4 (3):

This paper will serve two functions in the foot and ankle literature. First it will serve as a literature review to educate as to what foreign body induced membrane technique is and update its progress in the literature. Second this paper will delve into any literature pertaining to use of the Induced membrane technique within the foot and ankle, in order to educate foot and ankle surgeons as to all of the possible uses of the Induced membrane technique, outside of traditional long bone deficits.

Key Words: Induced membrane, PMMA, bone graft

Accepted: April, 2016 **Published:** May, 2016

The Foreign Body Induced membrane technique or Induced Membrane Technique (IMT) was initially developed to address deficits in diaphyseal bone greater than 4-5 cm and up to 25 cm in length. Nonvascularized bone grafts > 4-5 cm in size are often unsuccessful secondary to resorption of the graft even in patients with a good vascularized muscle envelope[1]. The IMT is often used in patients who have developed deficits in diaphyseal bone and soft tissue as a result of trauma, infection or tumorous growth[2]. Additionally, there have been case reports of its use for patients with charcot foot accompanied with, explant, and more recently congenital pseudarthrosis[5,6].

Address correspondence to: Ctyree@metro.org
[1]Podiatric Resident, Department of Foot and Ankle Surgery, Mercy Regional Medical Center , Lorain, OH

Masquelet proposed the IMT as an alternative to the vascularized bone free transfer and Ilizarov intercalary bone transport techniques. His desire was to: Minimize sequelae at the donor site of free flaps, reduce patient discomfort, and make the bone reconstruction more reliable[3]. The IMT has been shown to have 2 major roles in[1] the promotion of bone healing: First the membrane was shown to have the ability to prevent resorption of non-vascularized autograft. Second the membrane has been shown to produce factors associated with bone healing. The IMT was shown in sheep models to prevent the resorption of cancellous bone while promoting bone healing[4]. The IMT was also shown to produce VEGF, TGF Beta 1, and BMP-2, factors deemed important in bone healing, in a rabbit model[3].

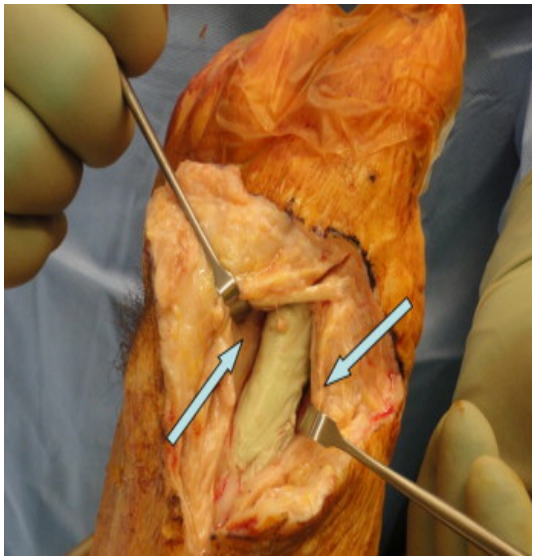

Image 1. Blue arrows point to the induced membrane used in the repair of a 1st metatarsal bone deficit Makridis et al. (15)

PMMA as the Foreign Body

Initially Masquelet and colleagues recommended the use of plain PMMA cement as the foreign body of choice. There were multiple reasons that the cement served as a good candidate. First it prevents collapse of soft tissue into the bony defect, second it served as an excellent witness of successful debridement in the absence of infection in 2 months[1]. In addition PMMA has high compressive strength and can be supportive[9]. Although this is a reasonable approach, peak levels of growth factors occur within one month as pointed out in Masquelet's article printed in 2016. Thus, one would conclude it would be most beneficial to remove the cement spacer at 1 month and implement the new graft at that time[7]. It has also been shown that any remaining bacteria, if present after debridement, may be harder to eradicate because of attachments that the bacteria can create to the PMMA spacer, or to remaining bone. In addition systemic antibiotics, may have difficulty reaching the site of infection because of compromised blood flow in PAD patients as well as in patients with OM where blood flow is decreased[8]. For these reasons, current techniques often incorporate antibiotics into the initial foreign body. The antibiotics have been shown to do the following: bathe the hematoma/seroma in high concentration levels of antibiotic required for bacterial biofilms destruction, it decreases the complications of systemic antibiotics, and costs less than systemic antibiotics[8, 9]. Additionally, elution rates as well as interactions between PMMA and various antibiotics have been studied. The results show that there are several generic factors that determine the elution rate of antibiotics: The brand of bone cement, the volume and surface area of the bone cement, the amount of ABX mixed with the bone cement, and the turnover of fluid surrounding the bead[12, 13].

It was found that as methyl methacrylate is polymerized, there is an exothermic reaction that can potentially denature antibiotics and in turn leaving as little as a 5% release ratio[10]. Understanding this, antibiotics that do not denature under exothermic reactions are most frequently used including: vancomycin, tobramycin, gentamicin, and metronidazole. It has been shown that 100% of gentamycin 70% of tobramycin and 90% of vancomycin can be recovered after polymerization[11]. In 2006 Alonso et al further examined antibiotics that could be useful in orthopaedic applications. They found that elution from PMMA was not only based on the factors listed above but also based on unique properties of the individual antimicrobial agents. They found that

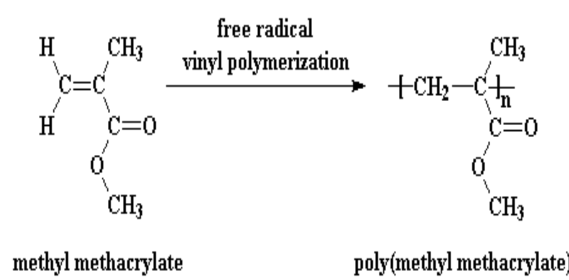

Figure 1 taken from http://pslc.ws/mactest/pmma.htm

ciprofloxacin and levofloxacin, cannot be as easily recovered from PMMA as gatifloxacin. In addition they found that Linezolid had high peak concentrations and AUC as long as concentrations were 7.5 % or higher. Rifampin in this study was found to have two drawbacks: One it had the lowest rate of recovery following polymerization, and two addition of Rifampin to PMMA, prevented PMMA from setting up completely.[14] However all ABX in their study with sufficient percentages were able to reach MIC for S. Aureus[16].

The most inclusive study looking at the use of PMMA to prevent biofilm formation by S. Aureus was performed by Sanchez Jr. et al. The study looked at: cefazolin ciprofloxacin, clindamycin, oxacillin, trimethoprim-sulfamethoxazole, vancomycin, and the rifamycin derivatives rifampin, rifabutin, rifapentine, and rifaximin. Their conclusion was that only rifamycin derivatives were successful at eradicating S. Aureus. Also it was found that rifampin has a sustained release profile being released from PMMA for up to 14 days, and 49% had been released at that time compared to only 39% for vancomycin, other rifamycin derivatives profiles were'nt as promising.

Foreign Body Alternatives

Overall PMMA has a good elution rate, and functions well with a majority of antibiotics. Due to some of its short comings, research has been done to investigate alternatives. Ideally, these materials should work with a larger number of antibiotics, and wouldn't serve as a nidus for infection like PMMA. Additionally, a main focus of looking into foreign body alternatives, is finding an alternative which can be used in a single stage IMT[7, 18].

Inzana et al. did an extensive review of biomaterials used for local infiltration of antibiotics. They broke biomaterials into four categories: Natural polymers, synthetic polymers, ceramics, and Composites[9]. Of the natural polymers chitosan has the most unique and promising properties. Chitosan has both innate antimicrobial properties. Additionally, it has a better extended release profile of antibiotics in vitro[20].

The synthetic polymers have been extensively researched. The two most commonly studied synthetic polymers are polyesters, and polyanhydrides. Of the two polyesters are more popular; however they have a less predictable rate of degradation, and thereby have a less predictable elution rate. Polyanhydrides on the other hand have a rate controlled or zero order release kinetic profile.[21] Lastly both polyesters and polyanhydrides have been deemed biocompatible by the FDA, but both have reported instances of excess inflammatory reaction.

Of the Ceramics, Calcium Sulfate is most commonly used followed by calcium phosphate. Elution of ceramics is found controlled by diffusion and is not affected by degradation[9]. Ceramics are also osteoconductive in nature, a feature not shared by other biomaterials. In general Calcium Sulfate has been the most commonly used biodegradable, biomaterial, used for local infiltration of antibiotics. Similar to PMMA it appears that Calcium Sulfate has elution kinetics that are dependent on the volume and surface area of the calcium sulfate construct (In particular 3.0mm beads have an elution rate that is much higher than that of beads with a 4.8mm size), also individual characteristics of the individual antibiotics play a role[22]. However there have not been any studies looking at other variables, such as correlations between amount of ABX used and elution rates, the turnover of fluid around the calcium sulfate and elution rates, nor have there been any studies looking at the various brands of calcium sulfate and their elution rates. All of which have been examined in PMMA[12, 13].

When comparing elution rates of Calcium sulfate to PMMA, and when looking at various antibiotics, calcium sulfate nearly always has a higher or equal elution rate. It also has a sustained elution rate over a longer period of time. When looking at Tobramycin, Calcium Sulfate eluted 17% at 24 hours whereas PMMA only eluted 7%, in addition calcium sulfate eluted tobramycin for a longer time following initial release, and in higher concentrations. Cefazolin along with voriconazole, and a combo of tobramycin with vancomycin have all also been shown to have higher elution rates in calcium sulfate than PMMA[24]. However all of these studies were in vitro studies of calcium sulfate elution rates. When looking at in vivo studies, PMMA and calcium sulfate have similar results in regards to infection eradication with 86% eradication at 24 months post operatively for both. The most outstanding difference shows in the number of surgical reoperations. PMMA had over 2x as many re-operations compared to calcium phosphate spacers[25]. Other in vitro and in vivo studies support these findings.

A rather unique feature of calcium phosphate is its ability to be printed into 3-D structures, allowing surgeons to fill the dead space in a manner that matches the original bony architecture that was removed[26]. The final group composites are a combination of various biomaterials. In particular often a natural or synthetic polymer is combined with a ceramic. This is done in order to maximize the osteoconductive nature of the ceramic, with the sustained elution rates of the synthetics, or increase biological performance when mixed with a natural polymer[9]. Overall the results of many studies show that there will be a future with many diverse biomaterials.

There is currently miniscule literature comparing newer biomaterials to PMAA. Of the 40 studies which used newer biomaterials reviewed by Inzana et al., only 10 were direct comparison of the alternative biomaterial to PMMA. Of those 10 only 2 of the studies showed a bio-material out-performing PMMA. The only advantage of other biomaterials reliably reproduced is the reduction in reoperation rates when comparing calcium sulfate and PMMA.

A major deficit in biomaterial literature is a lack of validation that biomaterials create the same membranous biofilm that PMMA does via histological comparison. This is important as the one study comparing silicone induced membranes to that of a PMMA induced membrane showed that they had a very different composition. It was found that PMMA in rats produced a thicker 2 layer membrane at 9 weeks whereas the silicone produced a thinner single layer membrane at 9 weeks and then a somewhat thicker 2 layer membrane at 13 weeks.[45]

Source of Autograft for the IMT

There are two main sources for non-vascularized cancellous autograft, reported in the literature, that are used in the IMT: iliac crest and femur. The Iliac crest is the classic location for bone graft harvesting[27].

Traditionally the Iliac crest could only be used to harvest cancellous bone for smaller defects as only 27 cm^3 is harvested on average from the iliac crest. However with the use of acetabular reamers volumes as high as 90 cm^3 have been harvested. Acetabular reamers are a faster method of producing cancellous bone, with a decreased OR time and decrease in cost.[28] Myeroff et al. looked at complications associated with iliac crest harvesting. Minor complications consisted of: persistent or long-term pain at the harvest site, superficial sensory nerve injury, superficial hematoma or seroma, and superficial infection vs major complications consisting of: deep hematoma requiring operative drainage, incisional hernia, permanent neurologic injury, vascular injury, sacroiliac joint injury, ureteral injury, permanent Trendelenburg gait, donor-site fracture, and deep infection. After performing a literature search Myeroff found that complications varied significantly from study to study with the minor complication rate ranging from 7.1% to 39%, and the major complication rate ranging from 1.8% to 10%[32]. Younger et al. and Westrich et al. found that major complications increase with medical comorbidities, whereas both major and minor complications increase with smoking status and increased BMI[30, 31]. Additionally, there have been multiple studies comparing acetabular reaming of the iliac crest to traditional harvesting methods. There has been no reduction in the minor complications, however there is a significant reduction in the major complications with acetabular reaming[33-37]. There have also been case reports of additional complications that are not seen in traditional iliac graft harvesting (spinopelvic dissociation, caused by the reamer going through the harvesting site leading to complete disruption of the posterior pelvic ring)[38].

Harvesting cancellous bone from the femur is a more modern technique with the use of a reamer irrigator aspirator (RIA) to remove the cancellous bone. The RIA was developed for femoral reaming in order to reduce the risk of pulmonary complications that often accompany reaming of the femur. However as an unintended benefit of using the RIA. It was found that large quantities of cancellous bone could be harvested, approaching 90 cm^3 [32].

Several studies have compared the cancellous bone graft from the femur via RIA to that of the iliac crest. The first study looking at this by Shmidmaier et al. in 2006 concluded that they had similar compositions of growth factors noting that RIA had greater concentrations of 5 out of 7 of the growth factors measured[39]. Saqi et al. Performed the first study to directly compare the histological and molecular profiles of the 2 bone grafts. The results of the study showed that the RNA expression profiles of each graft was unique, even when accounting for age, sex, the patient, or any identifiable comorbidity. Additionally they concluded that RIA had greater expression of genes for vascular, skeletal, and hematological repair, and finally RIA also had increased stem cell markers, and additional growth factors[40]. Although RIA appears to produce larger numbers of growth factors and has a greater number of identifiable genes associated with bone healing. There is no evidence to support that genes expressed with RIA are better and lead to better bone healing when used in the IMT, therefore union rates are used as for comparative analysis.

Two notable studies compared RIA to iliac crest graft for union rates. The first looked at tibiotalar fusion, with the use of either RIA or iliac crest graft. The results showed that there were 6 nonunions of 27 patients in the iliac crest graft whereas there was only 1 nonunion of 29 patients when RIA was used[41] . The second study looked at 133 patients with either nonunion or post traumatic segmental bone defect. It was found that 86% of patients receiving the iliac crest achieved union, and 81% of patients with the RIA achieved union[42].

The final factor when comparing iliac crest grafts to RIA femoral grafts is the complication rate. Most of the studies agree that there is no difference in complications requiring reoperation for persistent nonunion or infection at the grafted site. However most articles sight a significant difference in donor site pain scores when the two are compared[41, 42]. Although not a complication, it is important to mention that there was no difference in duration of hospital stay between the RIA and iliac crest groups[41]. Rozalia et al. further examined this topic determining that RIA had a complication rate of RIA was found to only be 6% whereas the complication rate of iliac crest bone harvesting was found to be 19.37%. Most of the complications found to be related to RIA were related to improper reaming technique, such as over aggressive reaming of the neck of the femur, violation of the knee, and penetration of the anterior cortex. There was however one complication that was life threatening when a reamer was lodged in the femur, leading to significant blood loss and bradycardia. Harvesting of the Iliac crest had common complications such as Infection, hematoma formation, fractures, and most commonly donor site pain which was 7.75% of iliac crest bone harvesting complications[43].

Overall it appears that RIA is the superior technique for cancellous bone harvesting based on the literature. The femur produces an adequate supply of bone graft for large defects, and RIA is a faster and cheaper procedure. Histologically and genetically, no conclusions can be drawn. All current studies show RIA has higher or equal rates of union, and all though there may not be a significant difference in complication rates, the literature does support that it has significantly less donor site pain. In addition multiple authors believe that there is a learning curve to RIA and with practice most of the complications can be reduced as they are related to improper technique[41, 43.] These studies are looking at bone union when graft was used in cases of nonunion, fracture, and repair of bone defects. However these studies did not compare RIA and iliac crest harvesting in terms of the IMT. One of the only IMT studies to use RIA cancellous bone graft found that their patients had outcomes comparable to that if Iliac crest bone graft with 90% of patients achieving union[44]. Although this one study is promising Masquelet et al. points out that RIA cancellous bone graft has the appearance of wet thick powder that may result in part of the graft not becoming completely vascularized secondary to a lack of porous structure [7].

Novel applications of the IMT

Initially the IMT was developed for the treatment of long bone defects, in particular the tibia[1]. Since that time it has been used in maxillofacial surgery, hand and wrist surgery, and of focus in this paper in the foot and ankle region[46-51].

One of the first case reports in the literature was the reconstruction of the medial cuneiform via the IMT, for a patient who had bony and soft tissue destruction secondary to a motorcycle accident. In the study PMMA was placed into the defect site, occupying the space that the medial cuboid had previously occupied. The PMMA sufficiently maintained length of the medial column until it was removed and Iliac crest graft was added. After consolidation the talonavicular, cuneonavicular, intercuneal, and 1st metatarsal cuneiform joints were fused. Patient was able to return to activities of daily living at 12 months[48].

Another case involving the medial column was published in 2009 also, but differing in that the MOI was a gunshot to the right lower extremity, injuring the 1st metatarsal, medial cuneiform, and navicular. This injury resulted in medial arch collapse. For this patient a bridge locking plate was used for internal fixation to maintain length, until the PMMA with tobramycin could be added. Upon removal of the PMMA spacer, in this case RIA of the femur was used in place of iliac crest graft. Fixation with a locking plate was made to bridge the gaps between the 1st metatarsal and the calcaneus and talus. Although it was not reported when the patient was able to return to activities of daily living it was noted that at 1 year follow up there was bone healing, and graft incorporation[49.]

Another study showed reconstruction of the 1st metatarsal following open fracture with bone and tissue loss. A mini-external fixator was used to keep the metatarsal out to length, and the non-viable bone and tissue were removed while PMMA was implanted. After removal of the PMMA, an induced membrane had formed. RIA of the femur was placed into the membrane and 2 locking plates were used to hold the 1st metatarsal out to length. At 10 months the 1st MTPJ was fused due to instability, however the 1st metatarsal cuneiform joint was left undisturbed. At 14 months the patient had no pain and was able to resume activities of daily living[50].

A final forefoot IMT was described in a diabetic patient with charcot who developed OM secondary to an ulcer caused by their collapsed arch. After 3 debridements the patient was left with a flail foot which was missing the lateral 1/3rd of the medial cuneiform, the entire intermediate and lateral cuneiforms, and a majority of the cuboid, with some lateral cortex left intact. External ring fixation was used, to hold alignment and length, while a PMMA spacer with gentamicin was placed. Later the medial column was fused via beaming, and a cement spacer was placed. 6 weeks later additional fusion incorporating the first metatarsal, medial cuneiform, navicular, and talus bone of the foot was performed to redistribute forces of the foot and iliac crest Corticocancellous bone graft was placed at that time into the induced membrane. He was eventually fitted with custom molded shoes and a rocker bottom. At 5 months, after iliac crest corticocancellous bone graft placement, he was able to weight bear without crutches. At 25 months there was confirmation of graft integration without signs of infection[51].

There has also been one case report of using the IMT in the rearfoot. In this case a patient sustained multiple fractures after falling from 12 meters. The open fracture of the calcaneus was graded a Gustilo anderson type 2, and subsequently was infected. Following debridement, the void was filled with calcium sulfate with Vancomycin. After 8 weeks a CT was performed verifying membrane formation, and Iliac crest graft was placed in the membrane. Time to ambulation was not noted, however at 1 year fusion was verified on x-ray. It was noted that, Bohler and Gissane angles were still abnormal and decreased calcaneal height was observed. This article was unique in that the authors presented it with the perspective that it may have been done in a one stage IMT. They based this on the fact that the calcium sulfate had created a substantial membrane, and is resorbable. However they noted that it was not performed secondary to the original spacer not including bone graft [52].

Discussion

Plenty of research remains to be done in regards to IMT. The literature has only begun to scratch the surface of what is possible with this technique. In regards to our current state, which material appears to be the best? Literature shows PMMA is a proven means in inducing a membrane that not only does not resorb non-vascularized cancellous bone but also produces factors conducive to bone growth[3, 4]. In addition studies have shown that PMMA will work well enough with Rifampin to prevent biofilm formation[17]. More recently it has been shown that it is effective enough at treating S. Aureus to levels beyond detection[19]. However, PMMA is not without problems. It will not work with all antibiotics, has various elution rates, and is not resorbable necessitating additional surgery after initial implementation.

The leading alternative calcium sulfate, has never had its induced membrane analyzed, has had few case reports, and does have significant seroma formation. Benefits have been show with use of calcium sulfate such as: 1) decreased reoperation rates 2) Better elution rates 3) Potential for a single stage IMT[12, 13, 23, 52]. At this time it would be prudent for additional histological and gene expression testing to be performed before a single stage IMT is used with calcium sulfate. Unless the organism that is cultured in a patient's infection is not covered by antibiotics with which PMMA is compatible, there is no substantiated evidence that calcium sulfate is advantageous in patients with OM in which the IMT is planned.

Regarding discussion of the best method for ascertaining allograft for implementation into the induced membrane; at this time, it appears that RIA from the femur is superior. This is based on increased amounts of growth factors found in RIA femoral grafts, increased union rates with RIA femoral grafts, a decreased complication rate, and finally its successful use in the induced membrane technique. Still additional studies need to be performed, as it would be helpful to see a prospective study directly comparing the two grafts in a given patient population.

Finally it has been shown that the IMT is not reserved for long bone deficits only. There are several articles that illustrate the function of the IMT in both the forefoot and rearfoot[48-51]. Although the materials used to induce the membrane and form new bone may evolve into a single stage procedure. It appears that the induced membrane technique will continue to have utility within the field of bone reconstruction for long as well as other bony structures.

References

1 A. C. Masquelet and T. Begue The concept of induced membrane for reconstruction of long bone deficits. Orthopedic Clinics of North America, The, 2010-01-01, Volume 41, Issue 1, Pages 27-37

2 Giannoudis PV, Faour O, Goff T, Kanakaris N and Dimitriou R: Masquelet technique for the treatment of bone defects: Tips-tricks and future directions. Injury. 42:591–598. 2011.

3 Pelissier Ph., Masquelet A.C., Bareille R., Pelissier M.S., Amedee J., Induced membranes secrete growth factors including vascular and osteoinductive factors and could stimulate bone regeneration.

4 Klaue, K., Anton, C., Knothe, U. et al. Biological implementation of "in situ" induced autologous foreign body membranes in consolidation of massive cancellous bone grafts. J Bone Joint Surg. 1993; 79B: 236

5 Fong M, Stern R, Assal M, Masquelet Technique for Midfoot Reconstruction Following Osteomyelitis in Charcot Diabetic Neuropathy, JBJS Case Connect, 2015 Apr 08; 5 (2): e28 . http://dx.doi.org/10.2106/JBJS.CC.N.00112

6 Pannier S, Pejin Z, Dana C, Masquelet AC and Glorion C: Induced membrane technique for the treatment of congenital pseudarthrosis of the tibia: Preliminary results of five cases. J Child Orthop. 7:477–485. 2013

7 A. C. Masquelet: The Evolution of the Induced Membrane Technique: Current Status and Future Directions,Techniques in Orthopaedics Issue: Volume 31(1), March 2016, p 3–8 DOI: 10.1097/BTO.0000000000000160

8 J.S. Gogia, J.P. Meehan, P.E. Di Cesare, A.A. Jamali: Local Antibiotic Therapy in Osteomyelitis Semin Plast Surg. 2009 May; 23(2): 100–107. doi: 10.1055/s-0029-1214162

9 J. Inzana, E. Shwartz, S. Kates, H. Awad: Biomaterials approaches to treating implant-associated osteomyelitis Biomaterials Volume 81, March 2016, Pages 58–71

10 Ymxhita Y, Uchida A, Yamakawa T, Shinto Y, Araki N, Kato K. Treatment of chronic osteomyelitis using calcium hydroxyapatite ceramic implants impregnated with antibiotic. Int Orthop 1998:22:247-51.

11 Ramos JR. Elution of metronidazole and gentamicin from polymethylmethacrylate beads. Master's Thesis. 2003.

12 Hall EW, Rouse MS, Jacofsky DJ, Osmon DR, Hanssen AD, Steckelberg JM, Patel R. Release of daptomycin from polymethylmethacrylate beads in a continuous flow chamber. Diagn Microbiol Infect Dis. 2004;50:261–265

13 Seeley SK, Seeley JV, Telehowski P, Martin S, Tavakoli M, Colton SL, Larson B, Forrester P, Atkinson PJ. Volume and surface area study of tobramycin-polymethylmethacrylate beads. clin Orthop Relat Res. 2004;420:298–303.

14 Anguita-Alonso, P., M. S. Rouse, K. E. Piper, D. J. Jacofsky, D. R. Osmon, and R. Patel.2006. Comparative study of antimicrobial release kinetics from polymethylmethacrylate. Clin. Orthop. Relat. Res.445:239-244.

15 Makridis KG, Theocharakis S, Fragkakis EM and Giannoudis PV: Reconstruction of an extensive soft tissue and bone defect of the first metatarsal with the use of Masquelet technique: A case report. Foot Ankle Surg. 20:e19–e22. 2014.

16 Clinical and Laboratory Standards Institute. MIC testing:supplemental tables. Supplemental Tables M100-S14 (M7). Wayne, PA: Clinical and Laboratory Standards Institute; 2004.

17 Sanchez, C.J., Jr.; Shiels, S.M.; Tennent, D.J.; Hardy, S.K.; Murray, C.K.; Wenke, J.C. Rifamycin derivatives are effective against staphylococcal biofilms in vitro and elutable from PMMA. Clin. Orthop. Relat. Res. 2015, 473, 2874–2884.

18 R. P. Howlin, M. J. Brayford, J. S. Webb, J. J. Cooper, S. S. Aiken, P. Stoodley:Antibiotic-Loaded Synthetic Calcium Sulfate Beads for Prevention of Bacterial Colonization and Biofilm Formation in Periprosthetic Infections. Antimicrobial Agents and Chemotherapy Mon, 13 Oct 2014 59:111–120. doi:10.1128/AAC.03676-14.

19 Anguita-Alonso P, Giacometti A, Cirioni O, et al. 2007. RNAIII-inhibiting peptide-loaded polymethylmethacrylate prevents in vivo Staphylococcus aureus biofilm formation. Antimicrob. Agents Chemother. 51:2594–96

20 Quaternized chitosan as an antimicrobial agent: antimicrobial activity, mechanism of action and biomedical applications in orthopedics
Int. J. Mol. Sci., 14 (2013), pp. 1854–1869

21 J.P. Jain, S. Modi, A.J. Domb, N. Kumar Role of polyanhydrides as localized drug carriers
J. Control. Release Off. J. Control. Release Soc., 103 (2005), pp. 541–563

22 Roberts R, McConoughey SJ, Calhoun JH. Size and composition of synthetic calciu m sulfate beads influence dissolution and elu-tion rates in vitro. J Biomed Mater Res B Appl Biomater 2014;102:667–673.

23 Bowyer GW, Cumberland N. Antibiotic release from impregnated pellets and beads. J Trauma 1994;36:331–335

24 McConoughey SJ, Howlin RP, Wiseman J, Stoodley P, Calhoun JH. Comparing PMMA and calcium sulfate as carriers for the local delivery of antibiotics to infected surgical sites. J Biomed Mater Res B Appl Biomater. 2014 Aug 20

25 M.D. McKee, E.A. Li-Bland, L.M. Wild, E.H. Schemitsch A prospective, randomized clinical trial comparing an antibiotic-impregnated bioabsorbable bone substitute with standard antibiotic-impregnated cement beads in the treatment of chronic osteomyelitis and infected nonunion J. Orthop. Trauma, 24 (2010), pp. 483–490

26 J.A. Inzana, R.P. Trombetta, E.M. Schwarz, S.L. Kates, H.A. Awad 3D printed bioceramics for dual antibiotic delivery to treat implant-associated bone infection Eur. Cells Mater., 30 (2015), pp. 232–247

27 Kakar S Tsiridis E Einhorn T . Bone grafting and enhancement of fracture repair. In: Bucholz RW Heckman JD Court-Brown C Tornetta P Koval KJ Wirth MA , editors. Rockwood and Green's fractures in adults. 6th ed. Vol 1. Philadelphia: Lippincott Williams and Wilkins; 2006. p 313-31.

28 Brawley SC Simpson RB . Results of an alternative autogenous iliac crest bone graft harvest method. Orthopedics. 2006;29:342-6.

29 Gossman DG Rosenblum W Arosarena O Valentino J . The acetabular reamer: a unique tool for anterior iliac crest bone graft harvesting. Laryngoscope. 2005;115:557-9.

30 Younger EM Chapman MW . Morbidity at bone graft donor sites. J Orthop Trauma. 1989;3:192-5.

31 Westrich GH Geller DS O'Malley MJ Deland JT Helfet DL . Anterior iliac crest bone graft harvesting using the corticocancellous reamer system. J Orthop Trauma. 2001;15:500-6.

32 Myeroff C, Archdeacon M (2011) Autogenous bone graft: donor sites and techniques. J Bone Joint Surg Am 93(23):2227–2236. doi:10.2106/JBJS.J.01513

33 Arrington ED, Smith WJ, Chambers HG et al. Complications of iliac crest bone graft harvesting. Clin Orthop 1996 ; 329 : 300-309.

34 Banwart JC, Asher MA, Hassanein RS. Iliac crest bone graft harvest donor site morbidity, a statistical evaluation. Spine 1995 ; 20 : 1055-1060.

35 Hutchinson AR, Bruce ED. Midline fascial splitting approach to the iliac crest for bone graft. A new approach. Spine 1994 ; 19 : 62-66.

36 Kurz LT, Garfin SR, Booth RE Jr. Harvesting autogenous iliac bone graft. A review of complications and techniques. Spine 1989 ; 14 : 1324-1331.

37 R. Bimmel, K. Govaers Does harvesting of iliac bone grafts with an acetabular reamer reduce complication rate? Acta Orthop Belg, 72 (2006), pp. 598–602

38 T. Higgins, D. Rothberg, M. Daubs, Spinopelvic Dissociation as a Complication of Iliac Crest Bone Graft Harvest Using an Acetabular Reamer; Journal of Spinal Disorders & Techniques: August 2012 - Volume 25 - Issue 6 - p 345–349 doi: 10.1097/BSD.0b013e3182204d73

39 G. Schmidmaier Quantitative assessment of growth factors in reaming aspirate, iliac crest, and platelet preparation Bone Volume 39, Issue 5, Pages 1156–1163, November 2006

40 Sagi CH Young M Gerstenfeld L Shah AR Tornetta P . Quantitative differences between bone graft obtained with a reamer/irrigator/aspirator and from the iliac crest. Presented at the Orthopaedic Trauma Association Annual Meeting; 2009 Oct 7-10; San Diego, CA.

41 S.R. Nodzo, N.B. Kaplan, D.W. Hohman, C.A. Ritter A radiographic and clinical comparison of reamer-irrigator-aspirator versus ilia crest bone graft in ankle arthrodesis Int Orthop, 38 (6) (2014), pp. 1199–1203

42 J. Dawson, D. Kiner, W. Gardner, R. Swafford, P.J. Nowotarski
The Reamer Irrigator Aspirator (RIA) as a device for harvesting bone graft compared with Iliac Crest Bone Graft (ICBG): union rates and complications
J Orthop Trauma, 28 (10) (2014), pp. 584–590

43 R. Dimitriou, G.I. Mataliotakis, A.G. Angoules, N.K. Kanakaris, P.V. Giannoudis Complications following autologous bone graft harvesting from the iliac crest and using the RIA: a systematic review Injury, 42 (2011), pp. S3–S15

44 P.R. Stafford, B.L. Norris Reamer-irrigator-aspirator bone graft and bi Masquelet technique for segmental bone defect nonunions: a review of 25 cases Injury, 41 (Suppl. 2) (2010), pp. S72–S77

45 S. E. de Mones, S. Schlaubitz, H. Oliveira, J.-M. d'Elbée, R. Bareille, C. Bourget, L. Couraud, J.-C. FricainComparative study of membranes induced by PMMA or silicone in rats, and influence of external radiotherapy; Acta BiomaterialiaVolume 19, June 2015, Pages 119–127

46 Zwetyenga N, Fricain JC, De Mones E, Gindraux F (2012) Induced membrane technique in oral and maxillofacial reconstruction. Rev Stomatol Chir Maxillofac 113(4): 231–238

47 A.C. Masquelet, L. Obert Induced membrane technique for bone defects in the hand and wrist Chir Main, 29 (Suppll. 1) (2010), pp. S221–S224

48 Largey A, Faline A, Hebrard W, et al.. Management of massive traumatic compound defects of the foot. Orthop Traumatol Surg Res. 2009;95:301–304

49 Huffman LK, Harris JG, Suk M. Using the bi-masquelet technique and reamer irrigator- aspirator for post-traumatic foot reconstruction. Foot Ankle Int. 2009;30:895-9.

50 Makridis KG, Theocharakis S, Fragkakis EM and Giannoudis PV: Reconstruction of an extensive soft tissue and bone defect of the first metatarsal with the use of Masquelet technique: A case report. Foot Ankle Surg. 20:e19–e22. 2014.

51 M. Mak, R. Stern, M. Assal, Masquelet Technique for Midfoot Reconstruction Following Osteomyelitis in Charcot Diabetic Neuropathy; JBJS Case Connect, 2015 Apr 08; 5 (2): e28 . http://dx.doi.org/10.2106/JBJS.CC.N.00112