

AAE Clinical Considerations for a Regenerative Procedure

Revised 4/1/2018

These considerations should be seen as one possible source of information and, given the rapid evolving nature of this field, clinicians should also actively review new findings elsewhere as they become available.

Case Selection:

- Tooth with necrotic pulp and an immature apex.
- Pulp space not needed for post/core, final restoration.
- Compliant patient/parent.
- Patients not allergic to medicaments and antibiotics necessary to complete procedure (ASA 1 or 2).

Informed Consent

- Two (or more) appointments.
- Use of antimicrobial(s).
- Possible adverse effects: staining of crown/root, lack of response to treatment, pain/infection.
- Alternatives: MTA apexification, no treatment, extraction (when deemed non-salvageable).
- Permission to enter information into AAE database (optional).

First Appointment

- Local anesthesia, dental dam isolation and access.
- Copious, gentle irrigation with 20ml NaOCl using an irrigation system that minimizes the possibility of extrusion of irrigants into the periapical space (e.g., needle with closed end and side-vents, or EndoVac™). Lower concentrations of NaOCl are advised [1.5% NaOCl (20mL/canal, 5 min) and then irrigated with saline or EDTA (20 mL/canal, 5 min), with irrigating needle positioned about 1 mm from root end, to minimize cytotoxicity to stem cells in the apical tissues.
- Dry canals with paper points.
 - Place calcium hydroxide or low concentration of triple antibiotic paste. If the triple antibiotic paste is used: 1) consider sealing pulp chamber with a dentin bonding agent [to minimize risk of staining] and 2) mix 1:1:1 ciprofloxacin: metronidazole: minocycline to a final concentration of **1-5 mg/ml**. Triple antibiotic paste has been associated with tooth discoloration. Double antibiotic paste without minocycline paste or substitution of minocycline for other antibiotic (e.g., clindamycin; amoxicillin; cefaclor) is another possible alternative as root canal disinfectant. Clinicians should be aware that studies have been done using higher concentrations of TAP/DAP, but a recommendation to a higher concentration can't be made at this time due to limited studies.
- Deliver into canal system via syringe
- If triple antibiotic is used, ensure that it remains below CEJ (minimize crown staining).
- Seal with 3-4mm of a temporary restorative material such as Cavit™, IRM™, glass-ionomer or another temporary material. Dismiss patient for 1-4 week

Second Appointment (1-4 weeks after 1st visit)

- Assess response to initial treatment. If there are signs/symptoms of persistent infection, consider additional treatment time with antimicrobial, or alternative antimicrobial.
- Anesthesia with 3% mepivacaine without vasoconstrictor, dental dam isolation.
- Copious, gentle irrigation with 20ml of 17% EDTA.
- Dry with paper points.
- Create bleeding into canal system by over-instrumenting (endo file, endo explorer) (induce by rotating a pre-curved K-file at 2 mm past the apical foramen with the goal of having the entire canal filled with blood to the level of the cemento-enamel junction). An alternative to creating of a blood clot is the use of platelet-rich plasma (PRP), platelet rich fibrin (PRF) or autologous fibrin matrix (AFM).
- Stop bleeding at a level that allows for 3-4 mm of restorative material.
 - Place a resorbable matrix such as CollaPlug™, Collacote™, CollaTape™ over the blood clot if necessary and white MTA as capping material.
 - A 3–4 mm layer of glass ionomer (e.g. Fuji IX™, GC America, Alsip, IL) is flowed gently over the capping material and light-cured for 40 s. MTA has been associated with discoloration. Alternatives to MTA (such as bioceramics or tricalcium silicate cements [e.g., Biodentine®, Septodont, Lancaster, PA, USA, EndoSequence® BC RRM-Fast Set Putty, Brasseler, USA]) should be considered in teeth where there is an esthetic concern.
 - **Anterior and Premolar teeth** - Consider use of Collatape/Collaplug and restoring with 3mm of a nonstaining restorative material followed by bonding a filled composite to the beveled enamel margin.
 - **Molar teeth or teeth with PFM crown** - Consider use of Collatape/Collaplug and restoring with 3mm of MTA, followed by RMGI, composite or alloy.

Follow-up (6-, 12-, 24-months)

- Clinical and Radiographic exam
 - No pain, soft tissue swelling or sinus tract (often observed between first and second appointments).
 - Resolution of apical radiolucency (often observed 6-12 months after treatment)
 - Increased width of root walls (this is generally observed before apparent increase in root length and often occurs 12-24 months after treatment).
 - Increased root length.
 - Positive Pulp vitality test response
 - Recommended yearly follow-up after the first 2 years
 - CBCT is highly recommended for initial evaluation and follow-up visits
- The degree of success of Regenerative Endodontic Procedures is largely measured by the extent to which it is possible to attain primary, secondary, and tertiary goals:
 - Primary goal: The elimination of symptoms and the evidence of bony healing.
 - Secondary goal: Increased root wall thickness and/or increased root length (desirable, but perhaps not essential)
 - Tertiary goal: Positive response to vitality testing (which if achieved, could indicate a more organized vital pulp tissue)

References

Chapters

Hargreaves KM, Law AS. Regenerative Endodontics. Chapter 16. Pathways of the Pulp 10th ed. Eds, Hargreaves KM, Cohen S. Mosby Elsevier, St Louis, MO, 2011: 602-19.

Murray PE, Garcia-Godoy F. Stem cells and regeneration of the pulpodentin complex. Chapter 5. Seltzer and Bender's Dental Pulp – 2nd ed. Eds, Hargreaves KM, Goodis HE, Tay FR. Quintessence Publishing Co Inc, Hanover Park, IL, 2012:91-108.

Articles

Algarni A, H Yassen G, L Gregory R. Inhibitory effect of gels loaded with a low concentration of antibiotics against biofilm formation by Enterococcus faecalis and Porphyromonas gingivalis. J Oral Sci. 2015 Sep;57(3):213-8.doi:10.2334/josnusd.57.213

Alobaid AS, Cortes LM, Lo J, Nguyen TT, Albert J, Abu-Melha AS, Lin LM, Gibbs JL. Radiographic and clinical outcomes of the treatment of immature permanent teeth by revascularization or apexification: a pilot retrospective cohort study. J Endod. 2014 Aug;40(8):1063-70. doi: 10.1016/j.joen.2014.02.016. Epub 2014 Jun 13.

Banchs F, Trope M. Revascularization of immature permanent teeth with apical periodontitis: new treatment protocol? J Endod 2004;30:196-200.

Berkhoff JA, Chen PB, Teixeira FB, Diogenes A. Evaluation of Triple Antibiotic Paste Removal by Different Irrigation Procedures. J Endod 2014;40(8):1172-1177

Bezgin T, Yilmaz AD, Celik BN, Kolsuz ME, Sonmez H. Efficacy of platelet-rich plasma as a scaffold in regenerative endodontic treatment. J Endod. 2015 Jan;41(1):36-44.

Bose R, Nummikoski P, Hargreaves K. A retrospective evaluation of radiographic outcomes in immature teeth with necrotic root canal systems treated with regenerative endodontic procedures. J Endod 2009;35:1343-9.

Chmielewsky F, Jeanneau C1, Dejou J, About I. Sources of dentin-pulp regeneration signals and their modulation by the local microenvironment. J Endod 2014 Apr;40(4 Suppl):S19-25.

de Paz S, Pérez A, Gómez M, Trampal A, Domínguez Lázaro A. Severe hypersensitivity reaction to minocycline. J Investig Allergol Clin Immunol. 1999;9(6):403-4

da Silva LAB, Nelson-Filho P, da Silva RAB, Flores DSH, Heilborn C, Johnson JD, Cohenca N. Revascularization and periapical repair after endodontic treatment using apical negative pressure irrigation versus conventional irrigation plus triantibiotic intracanal dressing in dogs' teeth with apical periodontitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:779-87.

Dabbagh B, Alvaro E, Vu DD, Rizkallah J, Schwartz S. Clinical complications in the revascularization of immature necrotic permanent teeth. *Pediatr Dent*. 2012 Sep-Oct;34(5):414-7.

Diogenes AR, Ruparel NB, Teixeira FB, Hargreaves KM. Translational science in disinfection for regenerative endodontics. *J Endod* 2014 Apr;40(4 Suppl):S52-7.

Flake NM, Gibbs JL, Diogenes A, Hargreaves KM, Khan AA. A standardized novel method to measure radiographic root changes after endodontic therapy in immature teeth. *J Endod* 2014 Jan;40(1):46-50.

Fouad AF, Verma P. Healing after regenerative procedures with and without pulpal infection. *J Endod*. 2014 Apr;40(4 Suppl):S58-64

Galler KM, D'Souza RN, Federlin M, Cavender AC, Hartgerink JD, Hecker S, Schmalz G. Dentin conditioning codetermines cell fate in regenerative endodontics. *J Endod* 2011;37(11):1536-41.

Galler KM, Eidt A, Schmalz G. Cell-free approaches for dental pulp tissue engineering. *J Endod* 2014 Apr;40(4 Suppl):S41-5.

Geisler TM. Clinical considerations for regenerative endodontic procedures. *Dent Clin North Am* 2012;56:603-26.

Guimarães BM, Tartari T, Marciano MA, Vivan RR, Mondeli RF, Camilleri J, Duarte MA. Color Stability, Radiopacity, and Chemical Characteristics of White Mineral Trioxide Aggregate Associated with 2 Different Vehicles in Contact with Blood. *J Endod*. 2015 Mar 19. pii: S0099-2399(15)00135-1. doi:10.1016/j.joen.2015.02.008.

Hargreaves KM, Geisler T, Henry M, Wang Y. Regeneration Potential of the Young Permanent Tooth: What Does the Future Hold? *J Endod* 2008;34:S51-S6.

Hargreaves KM, Diogenes A, Teixeira FB. Treatment options: biological basis of regenerative endodontic procedures. *J Endod* 2013 Mar;39(3 Suppl):S30-43.

Hargreaves KM, Diogenes A, Teixeira FB. Paradigm lost: a perspective on the design and interpretation of regenerative endodontic research. *J Endod* 2014 Apr;40(4 Suppl):S65-9.

Huang GT-J. Apexification: the beginning of its end. *Int Endod J* 2009;42:855-66.

Huang GTJ. A paradigm shift in endodontic management of immature teeth: Conservation of stem cells for regeneration. *J Dent* 2008;36:379-86.

Jadhav GR, Shah N, Logani A. Comparative outcome of revascularization in bilateral, non-vital, immature maxillary anterior teeth supplemented with or without platelet rich plasma: A case series. *J Conserv Dent*. 2013 Nov;16(6):568-72.

Jacobs JC, Troxel A, Ehrlich Y, Spolnik K, Bringas JS, Gregory RL, Yassen GH. Antibacterial Effects of Antimicrobials Used in Regenerative Endodontics against Biofilm Bacteria Obtained from Mature and Immature Teeth with Necrotic Pulps. *J Endod*. 2017 Apr;43(4):575-579

Jenks DB, Ehrlich Y, Spolnik K, Gregory RL, Yassen GH. Residual antibiofilm effects of various concentrations of double antibiotic paste used during regenerative endodontics after different application times. *Arch Oral Biol.* 2016 Oct;70:88-93.

Kahler B, Mistry S, Moule A, Ringsmuth AK, Case P, Thomson A, Holcombe T. Revascularization outcomes: a prospective analysis of 16 consecutive cases. *J Endod.* 2014 Mar;40(3):333-8. doi: 10.1016/j.joen.2013.10.032. Epub 2013 Dec 15. Erratum in: *J Endod.* 2014 Jun;40(6):879

Kahler B, Rossi-Fedele G. A Review of Tooth Discoloration after Regenerative Endodontic Therapy. *J Endod.* 2016 Apr;42(4):563-9. doi:10.1016/j.joen.2015.12.022.

Keskin C, Demiryurek EO, Ozyurek T. Color Stabilities of Calcium Silicate-based Materials in Contact with Different Irrigation Solutions. *J Endod.* 2015 Mar;41(3):409-11

Latham J, Fong H, Jewett A, Johnson JD, Paranjpe A. Disinfection Efficacy of Current Regenerative Endodontic Protocols in Simulated Necrotic Immature Permanent Teeth. *J Endod.* 2016 Aug;42(8):1218-25.

Laurent P, Camps J, De Méo M, Déjou J, About I. Induction of specific cell responses to a Ca(3)SiO(5)-based posterior restorative material. *Dent Mater.* 2008 Nov;24(11):1486-94

Law A. Considerations for regeneration procedures. *J Endod.* 2013 Mar;39(3 Suppl):S44-56.

Lovelace TW, Henry MA, Hargreaves KM, Diogenes A. Evaluation of the delivery of mesenchymal stem cells into the root canal space of necrotic immature teeth after clinical regenerative endodontic procedure. *J Endod.* 2011 Feb;37(2):133-8.

Marciano MA, Costa RM, Camilleri J, Mondelli RF, Guimarães BM, Duarte MA. Assessment of color stability of white mineral trioxide aggregate angelus and bismuth oxide in contact with tooth structure. *J Endod.* 2014 Aug;40(8):1235-40.

Martin DE, Henry MA, Almeida JFA, Teixeira FB, Hargreaves KM, Diogenes AR. Effect of sodium hypochlorite on the odontoblastic phenotype differentiation of SCAP in cultured organotypic human roots. *J Endod.* 2012 Mar(3):e26.

McTigue DJ, Subramanian K, Kumar A. Case series: management of immature permanent teeth with pulpal necrosis: a case series. *Pediatr Dent.* 2013 Jan-Feb;35(1):55-60.

Mori GG, Teixeira LM, de Oliveira DL, Jacomini LM, da Silva SR. Biocompatibility evaluation of biodentine in subcutaneous tissue of rats. *J Endod.* 2014 Sep;40(9):1485-8.

Możyńska J, Metlerski M, Lipski M, Nowicka A. Tooth Discoloration Induced by Different Calcium Silicate-based Cements: A Systematic Review of In Vitro Studies. *J Endod.* 2017 Oct;43(10):1593-1601.

Mullaguri H, Suresh N, Surendran S, Velmurugan N, Chitra S. Role of pH Changes on

Transforming Growth Factor- β 1 Release and on the Fibrin Architecture of Platelet-rich Fibrin When Layered with Biodentine, Glass Ionomer Cement, and Intermediate Restorative Material. J Endod. 2016 May;42(5):766-70.

Nagy MM, Tawfik HE, Hashem AA, Abu-Seida AM. Regenerative potential of immature permanent teeth with necrotic pulps after different regenerative protocols. J Endod. 2014 Feb;40(2):192-8.

Nosrat A, Seifi A, Asgary S. Regenerative endodontic treatment (revascularization) for necrotic immature permanent molars: a review and report of two cases with a new biomaterial. J Endod 2011 Apr;37(4):562-7. Review.

Petrino JA, Boda KK, Shambarger S, Bowles WR, McClanahan SB. Challenges in regenerative endodontics: a case series. J Endod 2010 Mar;36(3):536-41.

Reynolds K, Johnson JD, Cohenca N. Pulp revascularization of necrotic bilateral bicuspids using a modified novel technique to eliminate potential coronal discolouration: a case report. Int Endod J. 2009 Jan;42(1):84- 92.

Rodríguez-Lozano FJ, Bueno C, Insausti CL, Meseguer L, Ramírez MC, Blanquer M, Marín N, Martínez S, Moraleda JM. Mesenchymal stem cells derived from dental tissues. Int Endod J. 2011 Sep;44(9):800-6.

Ruparel NB, Teixeira FB, Ferraz CC, Diogenes A. Direct effect of intracanal medicaments on survival of stem cells of the apical papilla. J Endod 2012 Oct(10);38:1372-5.

Sabrah AH, Yassen GH, Spolnik KJ, Hara AT, Platt JA, Gregory RL. Evaluation of Residual Antibacterial Effect of Human Radicular Dentin Treated with Triple and Double Antibiotic Pastes. J Endod. 2015 Jul;41(7):1081-4.

Schmalz G, Smith AJ. Pulp development, repair, and regeneration: challenges of the transition from traditional dentistry to biologically based therapies. J Endod 2014 Apr;40(4 Suppl):S2-5.

Shah N, Logani A, Bhaskar, U, Aggarwal, V. Efficacy of Revascularization to Induce Apexification/Apexogenesis in Infected, Nonvital, Immature Teeth: A Pilot Clinical Study. J Endod 2008 Aug;34:919–25.

Simon SR, Tomson PL, Berdal A. Regenerative endodontics: regeneration or repair? J Endod 2014 Apr;40(4 Suppl):S70-5.

Simon S, Perard M, Zanini M, Smith AJ, Charpentier E, Djole SX, Lumley PJ. Should pulp chamber pulpotomy be seen as a permanent treatment? Some preliminary thoughts. Int Endod J. 2013 Jan;46(1):79- 87.

Tagelsir A, Yassen GH, Gomez GF, Gregory RL. Effect of Antimicrobials Used in Regenerative Endodontic Procedures on 3-week-old Enterococcus faecalis Biofilm. J Endod. 2016 Feb;42(2):258-62.

Takushige T, Cruz EV, Asgor Moral A, Hoshino E. Endodontic treatment of primary teeth using a combination of antibacterial drugs. Int Endod J. 2004 Feb;37(2):132-8.

Thibodeau B, Teixeira F, Yamauchi M, Caplan DJ, Trope M. Pulp revascularization of immature dog teeth with apical periodontitis. *J Endod* 2007;33:680-9.

Thibodeau B, Trope M. Pulp revascularization of a necrotic infected immature permanent tooth: case report and review of the literature. *Pediatr Dent* 2007;29:47-50.

Torabinejad M, Turman M. Revitalization of tooth with necrotic pulp and open apex by using platelet-rich plasma: a case report. *J Endod* 2011 Feb;37(2):265-8.

Trevino EG, Patwardhan AN, Henry MA, Perry G, Dybdal-Hargreaves N, Hargreaves KM, Diogenes A. Effect of irrigants on the survival of human stem cells of the apical papilla in a platelet-rich plasma scaffold in human root tips. *J Endod* 2011 Aug;37(8):1109-15.

Tziafa C, Koliniotou-Koumpia E, Papadimitriou S, Tziafas D. Dentinogenic responses after direct pulp capping of miniature swine teeth with Biodentine. *J Endod*. 2014 Dec;40(12):1967-71. doi: 10.1016/j.joen.2014.07.021.

Vallés M, Roig M, Duran-Sindreu F, Martínez S, Mercadé M. Color Stability of Teeth Restored with Biodentine: A 6-month In Vitro Study. *J Endod*. 2015 Jul;41(7):1157-60. doi: 10.1016/j.joen.2015.03.014.

Verma P, Nosrat A, Kim JR, Price JB, Wang P, Bair E, Xu HH, Fouad AF. Effect of Residual Bacteria on the Outcome of Pulp Regeneration In Vivo. *J Dent Res*. 2017 Jan;96(1):100-106.

Vishwanat L, Duong R, Takimoto K, Phillips L, Espitia CO, Diogenes A, Ruparel SB, Kolodrubetz D, Ruparel NB. Effect of Bacterial Biofilm on the Osteogenic Differentiation of Stem Cells of Apical Papilla. *J Endod*. 2017 Jun;43(6):916-922.

Wang XJ, Thibodeau B, Trope M, Lin LM, Huang G. Histologic characterization of regenerated tissues in canal space after the revitalization/revascularization procedure of immature dog teeth with apical periodontitis. *J Endod* 2010;34:56-63.

Wigler R, Kaufman AY, Lin S, Steinbock N, Hazan-Molina H, Torneck C. Revascularization: A Treatment for Permanent Teeth with Necrotic Pulp and Incomplete Root Development. *J Endod* 2013 Mar;39(3):319- 26.

Yilmaz S, Dumani A, Yoldas O. The effect of antibiotic pastes on microhardness of dentin. *Dent Traumatol*. 2016 Feb;32(1):27-31.

Yamauchi N, Nagaoka H, Yamauchi S, Teixeira FB, Miguez P, Yamauchi M. Immunohistological characterization of newly formed tissues after regenerative procedure in immature dog teeth. *J Endod* 2011 Dec;37(12):16