September 2017 Update on ENS from the US Institute for Advanced Sinus Care and Research

Dear ENS Community,

Attached is our update for our ongoing efforts on the treatment of Empty Nose Syndrome

1. <u>What services do you now offer?</u>

We offer a variety of services for patients with ENS and other nasal/sinus related disorders.

Telephone consultations for Empty Nose Syndrome and Other Nasal/Sinus Disorders
We provide telephone consultations to provide general information about ENS and our therapies to patients. We charge $150 for a 20 minute phone consultation and these can be scheduled at flexible times. We also can communicate via a variety of internet apps such as Facebook, Whatsapp, Skype, and others. Please provide written summaries of your symptoms and medical histories and also images of any ct scans prior to the consult to improve the efficiency of your consultation. We accept major credit cards and Paypal. These maybe scheduled by contacting Melanie Clark via email at info@usasinus.org

Platelet-rich plasma mixed with MatriStem by Acell, Inc.

For patients with suspected nerve dysfunction, poor moisture production, poor immune function, or poorly functioning turbinates we often recommend a treatment with platelet-rich plasma and MatriStem by Acell. This therapy is intended to stimulate constructive tissue remodeling of the turbinate structures to induce new nerve growth, new blood vessel growth, new goblet cell growth for moisture production, new cilia formation of the epithelium, improved epithelial cell functioning, and improved vascular dilation/constriction to regulate the nasal airflow mechanics. MatriStem is an approved therapy by the US FDA for the treatment of poor wound healing. The use of MatriStem has been scientifically proven to induce new tissue and nerve growth. http://stm.sciencemag.org/content/6/234/234ra58 Platelet rich plasma transfer is an autologous transfer of body tissue from one site to another and therefore is not regulated by the FDA, however several machines that harvest PRP are approved by the FDA for human use. PRP combined with MatriStem is thought to enhance the functioning of MatriStem in its ability to induce constructive tissue remodeling and the delivery site. Prior to this treatment at the first visit, we perform a full nasal endoscopy and consultation. The treatment cost for the first treatment is $1985 and any subsequent injections are $1635. Unfortunately, these treatments are not covered by insurance but do quality for Health Savings Account expenditures. Patients interested in these therapies may contact Melanie Clark via email at info@usasinus.org to schedule an appointment. These therapies typically take 1 hour to perform and patients may fly both immediately before and immediately after the procedure. Patients do not need a separate driver to receive this procedure.

PRP/Acell/Adipose-derived autologous fat transfer (stromal vascular fraction)

For patients with 33%-66% of their turbinates resected or patients who have not benefited from PRP/Acell therapy, we are offering stromatolites vascular fraction transfers into the inferior turbinate. This is performed by performing a mini-liposuction to harvest abdominal fat. This fat is then centrifuged to isolate the stromal vascular fraction, which is then mixed with PRP and Acell and injected into the inferior turbinates. This procedure adds more bulk to the inferior turbinates compared to PRP/Acell alone and the stromal vascular fraction is enriched with adipose-derived mesenchymal stem cells, which may enhance wound healing. This procedure costs $2850 for the

first injection and $2500 for any repeat injections. Unfortunately, these treatments are not covered by insurance but do quality for Health Savings Account expenditures. Patients interested in these therapies may contact Melanie Clark via email at info@usasinus.org to schedule an appointment. These therapies typically take 1-1.5 hours to perform and patients may fly both immediately before and immediately after the procedure. Patients do not need a separate driver to receive this procedure.

Alloderm Implants coated in PRP/Acell/Adipose-derived stromal vascular fraction

For patients with greater than 66% of their turbinates resected or with a positive cotton test and areas of noticeable airflow disruption that could be best improved with implants, we have started offering Alloderm implants coated with PRP/Acell/Adipose-derived stromal vascular fraction that can now be delivered via an in-office surgery with local anesthesia and does not require anesthesia fees or fees associated with the surgery center. This procedure remains quite expensive at $8350 however, this is a significant cost savings of the nearly $15,000 it costs to perform this procedure at our hospital or surgery center. We have made significant advances in the shape and placement of our implants in part due to the work of Dr. Kai Zhou at the Ohio State University and his work with computational fluid dynamics of the nasal airway. In many cases, the harm caused by turbinate surgery and/or septoplasty is the redirection of a majority of airflow through the medial portion of the middle meatus and therefore bypassing the inferior meatus where greater than 50% of nasal airflow travels through. Dr. Zhao's work has significantly improved our ability to properly place implants in the correct location of the nose. We also offer temporary placement of hyaluronic acid, which mimics an implant but fully absorbs within a year for $1100 for injections into both inferior turbinates.

Nasal valve reconstruction

For patients with lateral nasal valve collapse, we offer placement of Latera Absorbable Nasal Implants, which are used to support the cartilage in the nose and reduce nasal obstruction. These implants are placed in the office under local anesthesia. This procedure costs $3150.

2. <u>What have your results been with each of the procedures you have provided?</u>

Platelet-rich plasma mixed with MatriStem by Acell, Inc.

As of September 17th, 2017, we have treated 392 patients with ENS with PRP/Acell Injections. Of this, there have been 92 patients (23.4%) for whom we would deem have had a very significant and lasting improvement to their symptoms. 168 patients (42.9%) have had a minor to moderate improvement, 28 patients (7.1%) have had either no improvement or a very minor improvement that has completely faded or regressed, 45 patients (11.5%) of patients who have had no improvement, 2 (0.5%) of patients who felt they got worse after an injection, and 57 patients (14.5%) who have not provided feedback. In the two patients who got worse, one said she suffered an allergic reaction to the injection and said she felt much better after treatment with a medrol dose pak. One patient said he felt some mouth burning after the injection which resolved after one month. We have had a few patients who said they felt worse many months after their injection but we felt their symptoms were unrelated to the injections.
In percentages, this represents a 77.6% benefit rate (92+168/392-57). On average, patients have had 2.8 injections, with 3 patients having greater than 10 injections, and 203 patients having had one injection.

While there have been several patients who report dramatic and life-changing positive benefits with these injections, many people report that treatment benefits with the PRP/MatriStem are temporary

and then fade. We are also discouraged when this occurs, and we have been trying to analyze why this occurs. These are our theories: During the initial injection, the distribution of PRP and MatriStem and the trauma/bleeding from the injection site likely induces some tissue inflammation that leads to increased bloodflow, swelling, and nerve sensitivity, which, in the case of ENS, are all positive side effects, which enhance the benefit of the treatment. These initial inflammatory effects are likely to be temporary and would be expected to last between 72 hours to 1 week or so, and then subside. The true regenerative effects and constructive tissue remodeling that the PRP/Acell combo are attempting to achieve are likely to occur gradually and be poorly noticeable from a day-to-day observation standpoint, but would likely be noticeable when analyzing results from a month-to-month observation standpoint. It is possible that in some cases, patients are getting an initial inflammatory benefit and then the PRP/Acell are failing to initiate any regenerative activity, or in some cases that the PRP/Acell causes some benefit, but the degenerative processes that are the root cause of ENS persist unabated and eventually wash out the benefit that the PRP/Acell induced. We are continuing to investigate methods to make the regenerative process more robust and long-lasting in patients. Doubling our Acell concentration unfortunately has not seemed to cause a noticeable improvement in treatment efficacy. Currently, due to its ease of delivery and safety profile, we still recommend PRP/Acell as a first-line therapy for most patients with minimal turbinate tissue loss, suspected nerve damage, and in cases where the pathology that the patient is suffering from is not clearly volume loss.

PRP/Acell/Adipose-derived autologous fat transfer (stromal vascular fraction)

We have performed 52 adipose-derived autologous fat transfers in the last two years. Of these patients, 15 (28.8%) patients have noted significant improvement, 31 (59.6%) patients have noted mild to moderate improvements, and 6 (11.5%) patients have reported no improvement. 1 (1.9%) of 52 patients developed a skin infection from the liposuction site that resolved with antibiotics. The benefit rate for this procedure was 88.4%. The benefits from the adipose-tissue transfer have also seemed to be longer lasting than that from the PRP/Acell injection. The fat transfer does add bulk to the turbinates so it is often recommended for patients who have had a portion of their turbinates resected. However, in the last several months, we have improved in our ability to adjust the level of fat to the needs of each individual patient.

Alloderm Implants coated in PRP/Acell/Adipose-derived stromal vascular fraction

We have begun reoffering Alloderm implants and have been soaking our Alloderm implants with PRP/Acell/Adipose-derived stromal vascular fraction. We have also become better at sculpting the implants for each’s patients turbinate anatomy, and have been using our implants to obstruct airflow in the medial portion of the middle meatus. Alloderm implants are appropriate for patients with significant turbinate resections and positive cotton tests. We also offer hyaluronic acid injections as a test implant prior to placement of the Alloderm implant. This injection lasts between 6-12 months until it is fully absorbed. We are able to place the Alloderm implants in an in-office procedure under local anesthesia only which reduces the need for general surgery, for staying overnight in Columbus, and significantly reduces the cost to our patients. We have performed Alloderm implants soaked with PRP/Acell/Adipose-derived stromal vascular fraction on 12 patients, all with positive cotton tests. Of these 4 patients have had a significant benefit; 6 have had a mild-moderate benefit, and 2 patients have not had any benefit.

3. Can you compare your therapies to other surgeons?

In the U.S., there are 2 other surgeons that are performing Alloderm implants for ENS at significant volumes that we are aware of. Dr. Steven Houser at Case Western Reserve University and Dr. Jayakar Nayak at Stanford University. Both of these surgeons are my colleagues who I have tremendous respect for, and would recommend patients seek second opinions with these doctors and consider pursuing their recommendations. There are several new centers in Europe offering therapies for ENS. We have received several requests to compare our therapies to the Acqua Clinic in Germany. To our knowledge, the Acqua Clinic reports using a REF therapy for a turbinate injection. We do not know what is contained in these injections, nor have met the surgeons or know of their work. As a result, we can not comment or offer any recommendations for this therapy.

4. What about offering erythropoetin to your Acell/PRP injections?

We have heard that REF therapy may contain a variety of hormones such as erythropoetin in their concoction, and have been asked to include these hormones in our therapy. Initially, I studied many hormones and assessed their risk/benefit profile for addition to our PRP/Acell injections. For erythropoetin, also known as EPO, there was a large, randomized controlled trial known as the Normal Hematocrit Cardiac Trial (NHCT), in which treatment with EPO was associated with an increased risk for death, and a significantly increased risk for blood clots in the legs. Two more randomized controlled trials, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin B (CREATE), and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) showed a 45% increased risk of death in patients treated with EPO, increased blood clots, increased strokes, and increased heart attacks associated with EPO use. These studies were performed in the 1990's and 2000's. Since these studies were published, the FDA has released a black box warning admonishing doctors to not prescribe the drug unless a patient has severe kidney disease and anemia with a hemoglobin level less than 13, due to increased risks of blood clots, strokes, heart attacks and death. As a result, we have deemed EPO as too dangerous of a drug to add to our therapies and we will not consider using EPO for any of our therapies.

5. What new therapies are you considering for ENS?

We are excited about several advances in stem cell and regenerative therapy for the nose. There have been recent advances of using nanotechnology to reprogram skin cells to grow new types of tissue types. Unfortunately, these therapies are several years from becoming clinically available, however we are in talks with many researchers and startup companies and will consider participating in clinical trials when these new therapies are being tested for FDA approval in the U.S. However, we are very hopeful for continuous improvements in ENS therapies in the future.

Best wishes,
Subinoy Das, MD, FACS