Common Concerns and Medical Care of FOP Patients

[Edited Transcript of Question & Answer Telecast from Philadelphia, PA USA with Drs. Frederick Kaplan and Robert Pignolo]

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WHAT IS THE MOST EFFECTVE PAIN MEDICATION RECOMMENDED FOR THE FOP COMMUNITY?

Opiates are not the most beneficial and actually may make it more likely for flare-ups to occur. Paracetamol and/or non-steroidal anti-inflammatory medications are the recommended medications for pain in most situations. Topical anti-inflammatory gels, specifically ketoprofen gel in a concentration of 10-20% applied twice to three times a day over affected areas have been found to be very beneficial to FOP patients in acute pain. Of course, it is important to understand the source of pain - whether it is arthritis or muscle spasm but in general, non-opiate modalities have been found to be the most beneficial. The use of steroids tends to be reserved for the treatment of acute flare-ups, although sometimes a brief course of high dose prednisone may be helpful to break a cycle of chronic pain. Medical marijuana has not been clinically tested but a few anecdotal reports from FOP patients suggest it may be helpful for chronic pain. Presently, no scientific data supports its use.

WHAT ADVICE CAN YOU OFFER FOR THE REMOVAL OF TONSILS AND ADENOIDS IN CHILDREN?

Broadly speaking, the surgical removal of tonsils and adenoids is not a big problem. The biggest risk is with the general anaesthesia which is always very challenging in FOP. There are very few anaesthesiologists who know how to administer general anaesthesia to FOP patients and it is imperative that the Emergency Treatment Guidelines are checked regarding guidelines for general anesthesia for FOP patients. It is critically important for FOP patients that advice is sought from one of the anaesthesiologists listed on the IFOPA medical specialists list. Very few anaesthesiologists have experience with FOP patients and it is essential that any surgery needs to be carefully planned and advice can be sought from Dr. Zvi Grunwald who is more than happy to be contacted for assistance and advice.

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Surgery is a major concern mainly because of the risks associated with anaesthesia, so unless surgery is essential, the preference would be to avoid surgery to minimise the risk of harm. Of course surgery to remove heterotopic bone is strictly prohibited at the present time.

WHAT ARE THE BENEFITS OF PHYSIOTHERAPY AND HYDROTHERAPY FOR FOP PATIENTS?

While physical activity has many benefits for everyone, physical therapy for FOP patients is not advised. Physical therapy often involves modalities that can cause greater range of movement but may stretch vulnerable muscles and joints beyond their capacity and may cause microscopic internal injury which may induce a flare-up. So patients are advised to avoid any activity that may unintentionally cause harm – especially passive range of motion.

On the other hand, warm water hydrotherapy can be very beneficial and fun, and is highly recommended with a comfortable water temperature of 29-32 degrees centigrade. Moving joints comfortably to their capacity is healthy for FOP patients and will benefit circulation and cardiovascular health. Of particular importance to FOP patients is pulmonary health. Movement in water can strengthen the diaphragm which is the muscle separating the chest cavity from the abdominal cavity. In individuals with FOP, the diaphragm is a muscle that does not become affected. The diaphragm is the major muscle for breathing and pulmonary health, so it is important to exercise that muscle. Swimming and singing are the best two exercises for the diaphragm. Join a choir and expand your lung capacity and help prevent pneumonia. Singing is like a treadmill for your diaphragm! By exercising your diaphragm you will help maintain pulmonary health and that is especially important for FOP patients.

DOES THE PROLONGED USE OF OXYGEN WEAKEN THE LUNGS AND CAN YOU BECOME DEPENDANT ON ITS USE?

In individuals without an underlying lung disease, high (CO_2) triggers the response to take a breath and to keep breathing. With an underlying lung disorder, the trigger becomes low oxygen (O_2), and so the concern with the use of oxygen is with this second group. If you take away the stimulus of low oxygen, then the risk of not triggering breathing may occur, and the consequences may be fatal – especially if unmonitored oxygen is used during sleep. The use of oxygen does not weaken the lungs; rather it affects the neurologic drivers of respiration.

Specialised pulmonary function tests need to be performed to determine the need for oxygen. FOP patients commonly experience chest wall restriction. As a result, they are unable to expel CO_2 well and so over time, these levels slowly rise. If a healthy person had the level of CO_2 in their blood that FOP patients had, they would immediately become short of breath. FOP patient bodies have adapted to a higher level of CO2, and don't get short of breath. What causes FOP patients to be short of breath is lower levels of O_2 in the blood. If oxygen is introduced, then the body's trigger to breathe is removed. There have been a number of deaths of FOP patients who have used oxygen unmonitored at night. They have used oxygen during the day and feel better, but continued unmonitored use of O_2 at night is very dangerous. Some FOP patients have gone to sleep and simply have not woken up. There are major warnings in the treatment guidelines about using unmonitored oxygen at night.

A pulmonary evaluation by a doctor who specializes in Pulmonology (breathing problems) is absolutely essential before using oxygen therapy chronically. The pulmonologist may prescribe the use of a simple breathing machine and mask that will allow more oxygen to reach the lungs by increasing the pressure of the air that is

breathed. This is much safer than breathing pure oxygen - but the bottom line is that no FOP patient should receive oxygen therapy without being monitored.

WHAT IS THE ROLE OF PAMIDRONATE AND METHYLPREDNISILONE INFUSIONS?

Some FOP clinicians choose infusions of steroids for flare-ups, but these high doses of intravenously administered steroids need to be monitored in a hospital setting because of the side effects - including high blood pressure. Pamidronate or Zoledronate may be beneficial for patients who have taken high doses of steroids over a long period of time and have concerns about the potential bone loss that my result in the normal skeleton.

DOES FOP AFFECT SPEECH AND THE ABILITY TO FORM WORDS?

FOP generally does not affect speech. Obviously if the jaw is locked, then speech may be altered. Speech problems in children with FOP may indicate hearing impairment, a common occurrence in FOP patients. Audiology evaluations should be performed in every child with FOP.

WHAT ARE THE RECOMMENDATIONS FOR DENTAL WORK AND SPECIFICALLY THE REMOVAL OF WISDOM TEETH?

For FOP patients, the removal of wisdom teeth is a very big deal, and requires assiduous care of an anaesthesiologist as well as a dentist and oral surgeon. Locking of the jaw and anaesthesia are the two major areas of concern. Following the removal of wisdom teeth, some FOP patients have experienced reduced range of movement in the jaw despite the preventative use of prednisone. It is suggested that wisdom teeth not be removed unless there is an exceptional problem and then only with the advice of the medical, dental and anesthesia staff listed on the medical guidelines register.

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WHAT IS THE BEST PRACTICE FOR MANAGING SUBMANDIBULAR FLARE-UPS?

In determining whether swelling is from a submandibular flare-up or an abscess of the jaw, the first response should always be steroids in case it is a flare-up. Antibiotics will treat an infection but waiting two days to see if there is a response will not help the management of a flare-up. Clinicians must be advised not to palpate deeply, which can exacerbate a flare-up – hands off and start steroids early!!! Because submandibular flare-ups involve the muscles that move the tongue and therefore may involve swallowing, a longer course of steroids is needed - often 4 days of high dose steroids followed by a two week taper. Thickened liquids (that are easier to swallow than clear liquids) should be given over this time to diminish the risk of aspiration. Over many months, the swelling will diminish, often leaving behind a tiny piece of bone. Swallowing will improve as the flare-up resolves. Sometimes patients notice swelling under the tongue. That swelling is caused by lymphedema from failure to adequately drain lymphatic fluid from the submandibular flare-up. This causes an uncomfortable feeling of fullness (but no pain) and eventually resolves. A flare-up in the submandibular region should be considered a medical emergency because of the risk to breathing and swallowing and therefore needs to be closely monitored, in line with the treatment guidelines.

WHAT EFFECT DO STEROIDS HAVE ON THE IMMUNE SYSTEM?

While it is true that steroids are immunosuppressants, in general, the short courses of steroids taken during the acute inflammatory phase of flare-ups tend **not** to have an adverse effect on the immune system. This is not the case for patients on prolonged, repeated courses of steroids. FOP patients have an overactive immune system which

was discovered in patients and in animal model studies. Suppressing the immune system with prednisone suppresses flare-ups. If there were no long term side effects of steroids, then we would use them chronically to treat FOP.

WHAT IS THE ADVICE FOR IMMUNIZATIONS AND SPECIFICALLY THE FLU VACCINE?

This is a controversial area covered extensively in the FOP Treatment Guidelines (available on the IFOPA website: www.ifopa.org).

As they can trigger flare-ups, intramuscular immunizations must not be given – period. Diphtheria-Pertussis-Tetanus (DPT) immunizations are the worst offenders. When administered intramuscularly, heterotopic ossification will likely occur, a very high price to pay. Once a diagnosis of FOP is made, no intramuscular immunizations should ever be administered! Despite new formulations that can be administered subcutaneously, experience has shown flare-ups may result from subcutaneously administered DPT immunizations, so we recommend the avoidance of any DPT immunizations. If a tetanus-prone wound occurs, hyperimmune globulin can be administered intravenously.

Vaccinations that can be given subcutaneously include Measles-Mumps-Rubella (MMR), however, under no circumstances should ANY immunisations be given when an FOP patient is experiencing an active flare-up. This would further aggravate an already activated immune system and likely exacerbate any already-existing flare-ups.

Influenza vaccinations are recommended for subcutaneous administration. The intranasal flu vaccine should not be used as it is a live virus and may trigger flare-ups.

Influenza vaccination is a personal decision, but at minimum all household members should be immunized to minimise the risk of infection and Tamiflu should be made available to be used prophylactically at the first sign of flu symptoms.

CAN MUSCLE RELAXANTS BENEFIT DURING FLARE-UPS?

Occasionally muscle relaxants (such as baclofen) are prescribed for limited periods of time (several weeks, maximum) to manage the symptoms of flare-ups where these symptoms are not adequately controlled by steroids or anti-inflammatory medications alone. In our experience, muscle relaxants have had variable effectiveness but because of the muscle destruction during flare-ups, muscle relaxants can be helpful in some situations over a short period of time - but used as an adjunct, not a primary source of care. Patients and clinicians should consult the FOP Treatment Guidelines for more information on this topic.

IS ACNE A COMMON PROBLEM FOR FOP PATIENTS?

Acne is a common problem in the general population, but has **not** been identified as a common feature of FOP. However, the use of prednisone may precipitate and/or exacerbate acne.

WHAT IS THE PROTOCOL FOR THE USE OF BLOOD PRESSURE CUFFS?

This is a pertinent issue for FOP patients and one that is covered in the FOP Treatment Guidelines. Except in the case of life threatening situations, frequent blood pressure readings do not need to be done in FOP patients – and, in fact, should be avoided. If readings need to be taken, then they should be done around a limb that is already locked to reduce the risk of further joint dysfunction. Blood pressure measurements cause transient hypoxia (low oxygen) in the muscles under and distal to the cuff and can potentially induce transient inflammation that may be enough to trigger a flare-up. Certainly in hospitalized patients, vital signs are monitored frequently. Patients and parents should advise clinicians and nursing staff to minimize/avoid the routine use of this procedure as it is not appropriate for FOP patients (unless for monitoring an unstable, intercurrent, life-threatening situation).

HOW ARE FOP VARIANTS DIFFERENT FROM CLASSICAL FOP AND ARE CURRENT INTRVENTIONAL DRUG TRIALs LIKELY TO BE HELPFUL?

Ninety-seven percent of FOP patients throughout the world have an identical mutation in ACVR1, the FOP gene, but 3% have variant mutations in that same gene and have variant features of FOP. Some patients with FOP variants lack the toe malformations and may only experience symptoms later in life, while others have more severe malformations of the great toes. Even among classically-affected patients, there is tremendous variability in the occurrence and rate of disease progression. In order to control variability, it is prudent to test drug-candidates in clinical trials in patients with classical FOP first and then to include patients with FOP variants at a later date.

WHAT IS CURRENT BEST PRACTISE FOR VENIPUNCTURE AND CANNULATION AND DOES IT VARY FOR DIFFERENT AGE GROUPS?

Venipuncture is generally safe any age in FOP patients, but should be done very, very carefully. Few flare-ups result from careful venipuncture. In children, it is recommended that a paediatric phlebotomist be used. It is also recommended that topical numbing treatments be applied to the skin at the venipuncture site prior to blood drawing to minimise emotional stress. If an IV needs to be started, then it should be done by someone familiar with drawing blood from children and with the least amount of stress. Currently, in Philadelphia as part of the clinical trials, nurses tasked with drawing blood are given two chances. If they are not successful after the second attempt, then there has been an arbitrary decision to forgo the blood work. It is far better to err on the side of safety. It should be reinforced that no-one should be probing around. If not successful after two attempts – STOP.

WHAT INFORMATION SHOULD BE CONTAINED ON THE MEDIC ALERT BRACELETS?

The IFOPA has a medical alert bracelet and all patients should check these. The First commandment should be included – thou shalt not have intramuscular injections! Bony prominences should be well-padded and the jaw should not be manipulated. Prednisone should be given prophylactically to prevent flare-ups. Dr. Grunwald

should be consulted, if possible, regarding emergency general anesthesia. Sometimes, there are life-threatening situations that may take precedence over FOP considerations. For example, where an airway is needed, an awake fiberoptic naso-tracheal intubation is indicated. But the Catch-22 is that in true emergencies, clinicians will do what is necessary to sustain life and then, when things are under control, they will have time to refer to FOP specific information. But, please consult with the IFOPA regarding the medical emergency bracelets.

HOW MUCH INFORMATION IS AVAILABLE ON ALTERNATIVE THERAPIES?

The global natural history flare-up study has collected information from patients all over the world about medications and remedies for relief of flare-ups. While there has been a wide variety of different medications and alternative medical therapies used, nothing stood-out as having exceptional value except for corticosteroids. Over the past twenty-eight years, we have seen patients from vastly different geographic regions and cultural backgrounds. There have been many different alternative therapies used with various anecdotal effects. Although it is impossible to recommend one type specifically, any can be tried with alacrity as long as they are well-tolerated, of added benefit to the well-being of the patient and obviously not harmful in any way. Interestingly, there is an example recently where an effective treatment for malaria came from Chinese Herbal Medicine – Artemisia. The founders of this approach were awarded the Nobel Prize for Medicine. It is entirely possible that there are naturally occurring substances that could be beneficial for FOP that have not yet been discovered.

WHAT IS THE MOST FUNCTIONAL AID OR PIECE OF EQUIPMENT USED FOR FOP PATIENTS; PARTICULARLY BEDDING?

Patients should be evaluated from time to time by an occupational therapist who is familiar with gadgets that can make life easier. These gadgets can help with activities of daily living like pulling your socks on, picking up objects from the floor without bending down, combing your hair, brushing your teeth, scratching your back or putting-on your makeup.

A documentary about the astronauts who repaired the Hubble telescope showed them working in space with a range of specially-designed tools that were developed for that unique mission, never to be used again. Humankind has the incredible ability to design tools to allow humans to do jobs without regard to how uncommon the task is. Every FOP patient has unique needs and a locked elbow can be extremely varied from one patient to another - meaning their need for assistive devices may be similar in idea but different in actual design. Occupational therapists are professionals who are very skilled at helping with this need. It is strongly recommended that FOP patients seek advice from occupational therapists in this area.

Social media sites are also a great source of information. By engaging with other FOP patients, you will learn new ideas and hear great suggestions. Reviews and personal recommendations from other individuals with FOP are often extremely helpful. Ingenuity plays a very large role in the development and adaptation of some of this

equipment. Specifically, regarding bedding, many FOP patients around the world report success with Tempurpedic mattresses for comfort and pressure relief.

At the International Symposium on FOP in Philadelphia, USA in 2000, there was a display of assistive devices and gadgets – some store-bought; some personally-made that was one of the most popular parts of the symposium. Information on a variety of assistive products is available on the IFOPA website.

The choice of motorised wheelchairs is extremely important, especially for patients in an upright position. This must be a customised device and needs a comprehensive evaluation. These evaluations are complex and need to be individualised.

Dr. Charles Levy is a world expert on rehabilitation issues in FOP and on motorized wheelchairs for individuals with FOP.

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HOW CAN KIDNEY STONES BE PREVENTED IN FOP PATIENTS?

Kidney stones are two to three times more common in FOP patients than in the general population. While there has not been any unique clinical factor that predisposes individuals with FOP to kidney stones, it is suspected that the lack of mobility, lack of easy access to water and the lack of assistance with toileting had a negative impact on the intake of water and subsequent hydration. Water intake is extremely important for FOP patients and it's the best way for FOP patients to decrease their risk of kidney stones. Cutting back on salt will assist as well.

In the past two years, there was a major publication looking at people who were frequent kidney stone formers and the study found that intake of two liters of water a day prevented significant kidney stones. While this study did not include FOP patients, the subjects were frequent stone formers and the quantity that was deemed adequate as a result of the study was two liters. High water intake, low salt intake!

HOW CAN PRESSURE SORES BE AVOIDED AND TREATED?

By definition, a pressure sore is a breakdown of the skin over a bony prominence, and in FOP there are many bony prominences. Since prevention is better than cure, to prevent pressure sores, the pressure must be reduced over the site of the bony prominence. This can be achieved by increased cushioning between the bony prominence and the pressure point. Patients may require more help with daily activities, avoiding sheering and friction or sliding across mattresses and pulling

limbs in opposite directions from the pressure point. Foams and cushions can be individualised with donut-shaped cut-outs around the bony prominences but thick enough so they don't bottom out. Pressure sores can become a serious issue as they can predispose to infection which requires prompt treatment. If the skin breaks, it needs immediate attention.

Less mobile patients must pay special attention to any changes of position. Tempurpedic mattresses are expensive but patients have reported that their comfort vastly exceeds that of water beds or foam mattresses. Tempurpedic also makes pillows that can help pressure sores from forming on the back of the head.

Adequate nutrition is very important in checking preventing pressure sores. A low albumin level in the serum is a good biomarker for nutritional protein status. Vitamin C is also helpful in promoting the healing of pressure sores. Unlike diabetics who have internal factors that affect the healing of ulcers, FOP patients have a normal microvasculature, and it is simply the skin pressure that is the problem. Cushioning and good nutrition!

CAN TNF BLOCKERS BE USED TO TREAT FLARE-UPS?

There is anecdotal information on the use of TNF blockers and it seems that they are not generally helpful in treating flare-ups in FOP patients. The pathophysiologic basis of flares is more diffuse than just blocking TNF. It has been tried in one of the animal models and wasn't effective. Unpublished reports indicate that blocking mast cells can make a huge difference in FOP, although clinically approved mast cell inhibitors such as cromolyn are not well-absorbed.