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The standards of medical care are in a constant state of change, and medical information is increasing exponentially. New treatment procedures, technologies and medications are driving rapid changes in healthcare standards. Treatments once considered experimental or investigational become medically necessary quicker than ever before. Each year it gets harder for claims and medical management professionals to stay abreast of these changes in order to make the right care management decisions.

In the face of this increasing complexity, this publication is dedicated to helping claims and UR professionals get their jobs done more easily. This publication will be produced regularly with updates on cutting edge treatments and changing standards of care. All articles are written by top specialists from AllMed’s panel of board-certified peer review specialists.

To make this publication more useful to our readers, we encourage you to provide us with feedback on new or emerging treatment areas that you are interested in learning more about. We want you to help direct the content of this guide. Please e-mail us your requests or suggestions at guide@allmedmd.com.

Treatment of Multiple Myeloma: Two Steps Forward – One Step Back?

by A. Robert Thiessen MD, MBA

Multiple myeloma (MM) is a malignancy of plasma cells, the antibody-producing cells of the bone marrow. Approximately 17,000 individuals are diagnosed with MM in the United States each year, most over 65 years of age. Less than 10 percent are under 50. Symptoms include bone pain and fractures caused by weakening of bones, anemia, weakness, fatigue and weight loss. Individuals under 65 have generally better outcomes, but the typical survival is between 20 and 40 months.

Allogeneic Stem Cell Transplant (ASCT)

Allogeneic SCT has been used in MM. While it is an effective tool, it is limited by the severe toxicity and significant treatment-related mortality (30-50 percent) because most MM patients are over 55. Hoping to reduce mortality, investigators are pursuing non-myeloablative allogeneic SCT following an ASCT. The primary benefit of this technique is the graft versus myeloma effect in which the immune cells of the transplanted marrow attack the “foreign” myeloma cells of the host. Researchers hope this additional anti-myeloma effect may result in longer disease-free intervals and survival rates.

High-risk Patients

While results are promising, more data is needed before recommending this approach. One exception is those patients with high-risk myeloma – those with deletion of chromosome 13 or hypoploidy, a plasma cell labeling index of 3 percent or higher, or certain translocations on genetic studies. These patients have an extremely poor prognosis despite good response to initial chemotherapy and ASCT. Doctors may consider allogeneic non-myeloablative SCT following autologous SCT in those cases (national guidelines and expert opinion suggest “novel approaches” as standard therapy for those patients).

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Medical Update for UR & Claims Managers

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Assessing Treatment

In assessing requests for treatment in MM, case managers should pay particular attention to several issues:

- Standard therapy for initial chemotherapy is dexamethasone and thalidomide – any variation from that needs to be supported by information such as resistance to standard treatment, high-risk status, intolerance of thalidomide, etc.
- Requests for the second of two autologous SCTs should be supported by evidence of less than a complete remission (CR) or a very good partial remission (VGPR) to first transplant.
- Requests for maintenance therapy after autologous SCT should be supported by evidence of less than a CR or VGPR to transplant.
- Request for non-myeloablative allogeneic SCT should be supported by documentation of high-risk status. It may also be considered in those patients progressing after autologous SCT whose disease remains chemosensitive to salvage chemotherapy.

While myeloma is now a very treatable disease, it is not yet curable. Despite the two steps forward and one back progress, exciting new approaches are under study and show promise.

Early Penile Rehabilitation Following Radical Prostatectomy

by Michael J. Kaempf, MD, FACS, DABU

Quality of life issues have become increasingly important in the overall treatment of all diseases, including impotence, erectile dysfunction (ED), especially after postoperative radical prostatectomy (RP). Penson and Litwin reported that at 24 months after the time of primary prostate cancer treatment sexual dysfunction had the biggest effect on quality of life. All the following single and combined treatments lead to earlier erections, improved spontaneous natural erections and earlier sexual functioning both with and without continued long-term treatment compared to no treatment.

Single Therapies**Oral therapies**

Oral therapies are commonly prescribed. Studies of 5PDEI (sildenafil sold under the trade name Viagra) have evaluated early treatment with 50-100 mg daily or every other day, with

the highest doses producing the best results. Early use of 5PDEI preserves the smooth muscle content and at higher doses (100 mg) it actually increases the smooth muscle content of the cavernosa (Schwartz, 2004). In addition, patients will accept a lower degree of sexual satisfaction if the oral therapy is effective (Raina, 2004).

Vacuum devices

A vacuum erectile device or a vacuum constriction device (VCD) used early after radical prostatectomy facilitates early sexual intercourse, early patient spousal sexual satisfaction and potentially earlier recurrence of natural erections sufficient for vaginal penetration and preservation of penile length and girth (Raina, 2002).

Injections and suppositories

Injected vaso-active substances, such as alprostadil (Prostaglandin E1, [PGE1]), expand blood vessels and increase blood flow. Initial treatments with intracavernous injection of PGE1, showed that it can prevent longer term damage by increasing periodic oxygenation of the penis (Montorsi, 1997). Intraurethral PGE1, (Medicated Urethral Suppository for Erections or MUSE) also showed that it facilitated early sexual activity and return of spontaneous erections (Raina, 2005).

Statin

Early post-operative statin use improves ED over 5PDEI alone, especially 10 mgs atorvastatin daily (Hong, 2007). Intracavernous PGE1 or VCDs are best suited for the first few post-operative months because they allow sexual activity starting earlier as well as facilitate longer-term healing. During the period of initial neuropraxia, 5PDEI medications are rarely successful in producing erections concurrently but their efficacy increases with time.

Combination Therapies**Tri-mix**

Tri-mix or Triple P is a combination of PGE1, phentolamine, and papaverine in varying concentrations. It allows patients to use even lower doses of each and with less pain. Early low-dose Triple P can produce more effective erections than earlier low-dose PGE1.

Oral and injection therapy

Using oral 5PDEI and intracavernous PGE1 have been shown to increase early sexual activity and improve long-term natural erections. The addition of sildenafil to the injections allows a lower dose of PGE1 with subsequent decreased pain.

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Genetic Therapies Show Promise

In addition to the vasoactive substances used for treatment of ED, there are other novel therapeutic strategies under investigation. These include neurotrophic and neuroprotective factors, such as growth hormone neurturin immunophilins ligands (FK506, GPI-1046), vasoendothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), brain derived neurotrophic factor (BDNF), non-immunosuppressant immunophilins ligands, and insulin-like growth factor 1, sonic hedgehog protein potassium channel therapy (h Slo) and calcium system (rho A/rho kinase pathway).

Gene therapy using transfection of the nitric oxide synthetase pathway with INOS (inducible NOS), ENOS (endothelial NOS), and PnNOS (penile specific variant of neuronal NOS) are being considered also.

These gene therapies seek to increase the supply or strength of the erectile stimulus or to make the corporeal tissue more sensitive (the FK506 GPI-1046, h Slo, and calcium rho A factors). Increasing supply includes increasing nitric oxide and nitric oxide synthetase as well as BDNF and VEGF as mentioned above.

Determining Coverage for Penile Therapies

Today most health plans will not cover gene therapies. For the other treatments (e.g. VED, penile injections, or Viagra), case managers should consider their plan language, as well as individual case considerations for medical necessity before deciding to decline coverage for penile rehabilitation therapy. If plans cover these therapies for treatment of impotence (ED), then they should cover early penile rehabilitation because all patients are impotent initially after radical prostatectomy.

Key Resources

Montorsi, F, et al., Efficacy of sildenafil citrate in men with erectile dysfunction following radical prostatectomy: a systematic review of clinical data. *J of Sexual Med* 2(5):658-67, 2005 Sep.

Nandipati, KC et al., Erectile Dysfunction Following Radical Retropubic Prostatectomy: Epidemiology, Pathophysiology and Pharmacological Management *Drugs & Aging*, 23(2):101-17, 2006

Nandipati, KC et al., Erectile Dysfunction Following Radical Retropubic Prostatectomy: Epidemiology, Pathophysiology and Pharmacological Management *Drugs & Aging*, 23(2):101-17, 2006

Raina, R., et al., Rationale for Early Penile Rehabilitation Following Nerve-sparing Radical Prostatectomy, *Curr Sex Health Reports* 2007;4:101-106

Insulin Pumps: Deciding When They Are Medically Necessary

Lyle Mitzner, M.D.

An insulin pump is a medical device that continuously delivers insulin under the skin through a catheter. It usually connects somewhere in the waist area. Now there's a new generation of insulin pump, called a patch pump. Currently patch pumps are only available from OmniPod <<http://www.myomnipod.com/>>. Patch pumps adhere directly to the skin with no catheter tubing showing. It then infuses insulin directly under the skin.

Matches Patient's Need

Either pump delivers insulin at an hourly rate, say 1.1 units an hour. The pump delivers different rates at different times of day depending on the patient's need. Normally, the pump delivers insulin when it notes increased blood sugar. The amount of insulin delivered depends on two things: First, the amount of insulin a patient needs to "cover" the insulin-to-carbohydrate ratio; then by the correction factor, or the ratio of the number of milligrams per deciliter (mg/dl) a patient's blood sugar will be lowered by one insulin unit. If a patient eats 60 grams of carbohydrate at meals and has an insulin-carbohydrate ratio of one insulin unit to 15 grams of carbohydrate, the patient's insulin injection at that meal would be four units. However, if a patient has a correction factor of one unit to 50 points of blood sugar, the pump should give an injection of 2.5 units to lower his blood sugar from 245 mg/dl to needed level of 120 mg/dl.

Pump Candidates' Skill

To use an insulin pump patients must be able to manage it. This involves knowledge at several levels. First, patients must understand how to insert the catheter when using the pump, or how to attach the newer patch pump to their abdomen. They must also be able to push the right buttons on the pump to deliver proper insulin injections and adjust the basic rates. Then patients need to be skilled in carbohydrate counting so they are able to deliver correct insulin injections at mealtimes. Patients should be willing to check their blood glucose levels four to six times a day. This assures that patients detect a pump failure and prevent hyperglycemia and diabetic ketoacidosis (DKA, in Type 1 patients). Patient attention is important because no long-acting insulin is used in Type 1 patients and they need to correct high- or low-blood sugars before they become clinically observable and symptomatic.

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Medical Necessity

Insulin-pump therapy is almost never needed to maintain life because insulin can be easily injected under the skin. Most insurers will cover insulin-pump therapy in situations where it will significantly heighten the level of diabetes care and control over and above multidose insulin (MDI) therapy. This includes cases where:

- The glucose control in multidose insulin therapy is not optimal with glycated hemoglobin (HbA1c) more than the American Diabetic Association recommended goal of seven percent.
- An endocrinologist, who will be able to help the patients learn how to use the pump and adjust basic and injection doses, prescribes the pump.
- The patient has Type 1 diabetes. However, in many situations patients with Type 2 diabetes will benefit from the pump. (See *Diabetes Care*, Sept. 2003, pp. 2598-2603.)
- Presence of hypoglycemia despite adjustments in insulin doses and utilizing carbohydrate counting to help decide pre-meal insulin doses in patients who are using MDI therapy.
- Presence of hyperglycemia — especially as revealed by high morning readings (dawn phenomenon) where increasing basal rates of insulin in the early morning hours would help to better control blood sugar levels.

Resources:

Diabetes Care, Sept. 2003, pp. 2598-2603.

Does Shockwave Therapy Help Plantar Fasciitis?

Skip Freedman, M.D.

Plantar fasciitis is the most common cause of heel pain. The plantar fascia is a broad ligament-like structure that extends from the heel bone to the base of the toes, acting like a thick rubber band on the bottom arch of the foot. With a few extra pounds on board, or with activities such as exercise, the plantar fascia can develop microtrauma at its insertion into the heel bone, or anywhere along its length. This causes pain which can be quite severe at times. Women, heavy individuals, runners and anyone whose job requires a lot of walking or standing on hard surfaces are more likely to get the condition. It is usually most painful when an individual takes the first steps in the morning after getting out of bed, but the pain can recur after sitting for a while or at the onset of any activity. In severe cases, the individual simply cannot bear any weight on the foot.

There are many treatments for plantar fasciitis, including orthotics, splinting, ultrasound, reducing weight-bearing activity and cortisone injections. In many cases, however, these treatment options may not work. The newest treatment touted today is shockwave therapy. The typical costs of this therapy can run between \$6,000 and \$7,000. The cost, combined with mixed reviews of the treatment's success rate, is causing controversy in some medical circles.

While shockwave therapy is advocated by podiatrists as a helpful treatment, orthopedists who look at the same medical literature, interpret the data as inconclusive. This contrast makes shockwave treatment a perfect example of the benefit of independent review organizations. Their orthopedic specialist can determine the medical necessity and viability of new treatment options, because they constantly evaluate newly published medical literature to assure that spending five figures on pain management is medically sound and the best treatment available.

Adult Growth Hormone Deficiency

Lewis Chase, M.D.

Diagnosing isolated adult growth-hormone deficiency is difficult and controversial. Growth-hormone deficiency in adults causes a variety of metabolic abnormalities including muscle-mass loss, fat redistribution, abnormal lipid levels, abnormal cardiac function, decreased bone density, low energy and a reduced sense of well-being. Treatment with recombinant human growth hormone demonstrates improvement of these abnormalities. However, it is not easy to separate uncertain responses from the concurrent treatment of other pituitary-hormone deficiencies. Growth-hormone deficiency in patients having hypothalamic or pituitary disease and multiple other hormonal deficiencies (TSH, ACTH, gonadotropins, vasopressin) provides a better diagnosis than isolated growth-hormone deficiency in an adult.

The anterior pituitary secretes growth hormone episodically. Growth hormone releasing hormone (GHRH) stimulates secretion; and somatostatin and feedback inhibition from insulin-like growth factor-1 (IGF-1) reduces it. The pulsing nature of growth-hormone secretion can result in undetectable serum concentrations between pulses making random measurement of growth hormone useless in diagnosis. Secretion rates of growth hormone fall with age, decreasing up to six-fold between puberty and older adulthood further complicating diagnosis. In obese and older adults, random growth hormone measurements are usually undetectable.

Principally IGF-1, secreted mainly by the liver, mediates the actions of growth hormone. Serum concentrations of IGF-1 do not pulse and generally reflect the overall secretion rate of growth hormone. Serum concentrations of IGF-1 vary with age and sex and require reference to age — and gender — specific normal values. In obese patients, both growth hormone and IGF-1 concentrations are reduced and increase with significant weight loss without hormonal therapy.

In patients with known hypothalamic or pituitary disease growth-hormone deficiency, doctors can establish the condition with high sensitivity and specificity when there are three or four additional pituitary hormonal deficiencies or an IGF-1 less than 84 mcg/liter. To establish the diagnosis in patients without these criteria requires provocative growth-hormone stimulation. Adults diagnosed in childhood with isolated growth-hormone deficiency often have normal growth-hormone secretion after puberty and need retesting before continuing replacement therapy into adulthood. The “gold standard,” an insulin tolerance test, is time consuming,

expensive and potentially dangerous. The next best test combines stimulation with arginine and GHRH. Stimulation with arginine or L-Dopa alone or serum IGF-1 concentrations alone are not considered adequate to establish the diagnosis.

Treating a patient with recombinant human growth hormone is expensive and has significant side-effects including edema, arthralgias, carpal tunnel syndrome and glucose intolerance. Most of the symptoms of adult growth hormone deficiency can be treated successfully with weight loss and medications directed at specific abnormalities such as hyperlipidemia and decreased bone mineral density. Recombinant human growth hormone should be prescribed only in adults with well established growth-hormone deficiency.