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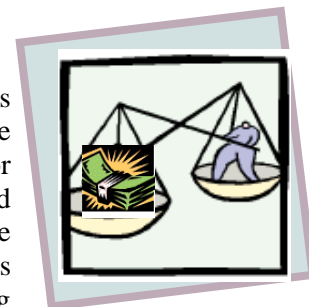
Mini-Transplants for Everyone?



A relatively new technology, non-myeloablative hematopoietic stem cell transplantation, causes less toxicity than standard bone marrow transplantation, and it may allow older and more infirm patients to benefit. If more patients may be eligible receive marrow transplantation, how significant are their costs likely to become, and are mini-transplants also mini-cost?

Health Care Cost Drivers at the End of Life

Recently, in underwriting a new account, we reviewed medical disclosures to identify the patients with high claims risks. Sadly, we encountered five cases aged in their 40's and 50's with terminal cancers, either metastatic or of unknown stage, all having already incurred more than a hundred thousand dollars in claims for 2002. It remains to be seen to what extent the families, the patients, and the medical system will work and spend resources toward every possible avenue to prolong the lives of these relatively young people, despite their terminal conditions, perhaps even when death is imminent. This is an issue that we will continue to face over time. The Annual Report to the Nation on the Status of Cancer released this past May predicted that the number of Americans diagnosed with cancer each year will double by 2050. How does one estimate the anticipated costs associated with such cases?



Nitric Oxide: Better Outcomes for Newborns



Most people have heard of laughing gas, or nitrous oxide (N_2O). In fact, it was one of the earliest anesthetics. Nitrous oxide is even used in auto racing to provide additional oxygen to fuel more efficient engine combustion! In contrast, only a few of us are aware of another gas called nitric oxide (NO - molecule of the year, Science 1992), despite its pivotal role in our own bodies immune and circulatory systems. Now, doctors may use nitric oxide in newborns to treat babies with severe hypoxia, an inability to provide sufficient oxygen to the blood.

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Mini-Transplants for Everyone?

Let's begin with a review of the traditional bone marrow transplant. Bone marrow transplants were developed as a means to allow the delivery of more potent chemotherapy regimens. Higher doses of chemotherapy are believed to destroy more tumor cells, and therefore provide a greater chance of cancer remission or cure. However, while high-dose chemotherapy regimens may achieve more remissions, they are destructive to other tissues. Most often, the bone marrow, which is responsible for the body's immune function, is most sensitive to high-dose chemotherapy. Therefore, prior to the advent of bone marrow transplants, high dose chemotherapy was too high risk in most cases because it severely compromised the body's ability to fight infection, and, in fact, to survive.

After the body metabolizes and clears the toxicity from high-dose chemotherapy, a rescue of the bone marrow and the immune system by bone marrow transplantation allows chemotherapy concentrations not otherwise compatible with survival. Donor bone marrow is most often obtained from another person (an allogeneic transplant) to prevent reintroduction of the malignancy. Occasionally, the patient's own marrow may be used (an autologous graft). The cost usually ranges from \$250,000 to \$550,000, with the autologous transplants usually being the lesser cost, for reasons that we will discuss. This traditional form of replacement of the bone marrow is called myeloablative hematopoietic stem cell transplantation (HSCT).

Unfortunately, the substitution of one's immune system through bone marrow transplantation often involves various complications. The immune system of the patient (the host) may actually compete with the newly transplanted bone marrow graft, and this can trigger several complications.

A complication called *Graft versus Host Disease* occurs when the new bone marrow's immune response attacks the patient's own body cells as foreign. This can cause severe sickness, or even death.

Historically, bone marrow transplants have been restricted to young, less than 50-55 years of age, and otherwise healthy patients. This limits treatment to those best able to tolerate the many

side effects of high-dose chemotherapy and those able to endure *Graft Versus Host Disease* (GVHD). Unfortunately, many cancers that benefit from bone marrow transplantation typically arise after the age of 50, thus limiting eligibility for transplant.

Another possible complication of bone marrow transplants is *Host Versus Graft Disease* (HVGd). This is the exact opposite of *Graft Versus Host Disease*! It can actually cause rejection of the bone marrow transplant itself and/or leave the patient rather sick without effective immune defenses. These complications are treated by immunosuppression, expensive medications used to diminish these undesirable immune responses.

Mini-transplants are different in that they are non-myeloablative, meaning that they do not completely destroy the patient's bone marrow, in contrast to the full ablation of a standard bone marrow transplant. Although this means that less chemotherapy can be administered, this technique leverages an important additional tumor fighting benefit, the *Graft Versus Tumor* effect. It turns out that this is a very important reason for success in mini-transplants, and it is correlated with chemotherapy doses low enough to retain some of the patient's own bone marrow.

Mini-transplants are now understood to offer several benefits:

- 1) There are less side effects in the early phase of transplant as less chemotherapy is administered, meaning less immune system compromise as the marrow is not fully ablated
- 2) There is less concern for acute rejection
- 3) There is less concern for limiting application by age or other conditions
- 4) The active immune reaction to the tumor causes additional tumor destruction, particularly advantageous in chronic leukemia and low-grade lymphoma

The most common applications involve leukemia, lymphoma, multiple myeloma, myelodysplastic syndrome, and renal cell carcinoma. There has also been some activity in the areas of amyloidosis, breast cancer and Richter Syndrome. The most successful, least expensive, and least complicated cases involve siblings with matched genetic markers to reduce the *Graft versus Host* and *Host Versus Graft*

Disease issues. Therefore, these, and autologous transplants, using the patient's own marrow, are the least expensive.

Concerning coverage, some insurers have adopted the position that non-myeloablative allogeneic stem cell transplantation may be considered medically necessary in patients who would otherwise meet patient selection criteria for traditional high dose chemotherapy and stem cell transplantation, and that other applications of non-myeloablative stem cell transplantation are considered investigational. Under these guidelines, the cost for these procedures may on average be somewhat less due to the lesser chemotherapy complication rates and possibly less infectious complications, but the primary driver of cost for transplant costs and *Graft Versus Host Disease* are likely to remain somewhat comparable. Other insurers maintain the position that this is considered experimental or investigational in any circumstances.

Health Care Cost Drivers at the End of Life

To estimate health care costs at the end of life in aggregate would seem at first glance to be the domain of the actuary. However, to do so accurately for a specific case or a small group of cases requires substantial clinical information, clinical review, and clinical judgment to determine where on the actuarial distribution that individual case or small group is most likely to fall. Many contributors drive medical cost:

- The type of disease
- Its stage of advancement or severity
- The likelihood of the treatment to induce harm and further complications and expense
- The response of the patient and their disease to any of the various therapies that have already been provided
- The state of the industry concerning various available therapies, and their associated costs
- Possible complications
- The likelihood for success or retreatment
- The will of the patient and that of the family to treat aggressively.
- The impact of hospice, advanced directives, do-not-resuscitate orders, and power of attorney status.

In reviewing this list of variables, one can sympathize with the clinician or actuary who is asked to project the future cost of any given case.

Unfortunately, there is no good data on total health care costs for the last year of life for patients either over or under age 65. Reliable cost data can be found, however, for patients 65 or older in the Medicare sector. In fact, Medicare data on mortality and expenditures may be the only reliable figures available, but they cannot be extrapolated to the whole health care system without adjustment. Why? Medicare patients are older, sicker, and die more often in a given year. Less than 1 percent of the total American population dies each year, yet 5 to 6 percent of Medicare beneficiaries die. Over the past two decades, the proportion of United States Medicare spending attributable to beneficiaries in the last year of life has remained stable at approximately 25%, but it is improbable that the less than 1 percent of the American population at large who die account for 25% of the total national spending on health care.

2.2 million Americans die annually and most likely account for more like 10-12 percent of health care expenditures. The costs of the final year (fees, costs of accommodation, blood, implants and medication) are mainly determined by the number of days spent in skilled nursing,



long-term acute care, or a hospital. When this year is spent in a hospital rather than at home, costs will increase by a factor of thirty.

Moreover, payments for dying patients increase exponentially as death approaches. Payments during the last month of life constitute forty percent of payments during the last year of life. These trends have been consistent since the early 1960's, but no one can predict the time of death to manage them.

Physician communication and patient perception are key drivers of end-of life expenditures as well. For example, it seems that physicians rather consistently overestimate the prognosis of terminally ill patients. One study showed the median prognosis at 75 days from hospice admission, but mean survival was only 26 days. In another study, the physician reported

communicating the real prognosis to the patient in only 37% of the cases.

Patient perceptions are equally problematic. One study found that one of three of patients with incurable metastatic cancer actually believed that they were receiving treatment to cure their condition. In another study of terminal cancer, patients overestimated their probability of survival (and made treatment decisions accordingly). Prognosis correlated well with preference of life-extending therapy over comfort measures. Therefore, the perception displayed by both physician and patient often drive utilization of more aggressive therapy. Studies also consistently show that family members are more hesitant to withhold or withdraw life-sustaining treatment than the patients themselves. So a durable power of attorney may actually increase utilization.

Moreover, people request treatment even if they should become incompetent or have a low chance of survival. Approximately 20% of patients want life-sustaining therapy even if they develop a persistent vegetative state. 50% of AIDS patients request aggressive life-sustaining treatment, including intensive care and resuscitation, in circumstances in which they had a relatively poor chance of survival, and studies show only 50% of HIV patients discuss some aspect of end-of-life care with their practitioners.

Although the decision to give a DNR (do-not-resuscitate) order or to withdraw life-sustaining treatment is usually made late in a patient's illness, most dying patients in tertiary care hospitals have DNR orders. Interestingly, 'do-not-resuscitate' does not translate to 'do not treat'. Heroic and multiple therapies are often initiated in intensive care areas for these patients.

It may be difficult to reduce substantially the percentage of health care expenditures spent on patients who die, because humane care at the end of life is also labor-intensive and therefore expensive. Even when patients refuse life-sustaining interventions, they do not necessarily require less medical care, just a different kind of medical care. High-quality palliative care – providing pain medications, help in the activities of daily living, radiation therapy for pain relief, and so on – require costly, skilled personnel. This relatively lower technology health care that is administered outside of hospitals to terminally ill patients is not cheap.

The amount that might be saved by reducing the use of aggressive life-sustaining interventions for dying patients has been estimated to be 3.3% of total national health care expenditures. As these tend to be costly patients, one might expect potentially somewhat greater amounts on the excess layers, savings that could seem to make a significant difference to insurers in premiums or in loss ratios, even if these costs seem to be swallowed up by recent double-digit medical trend increases.

It may not be possible to accurately determine before death the patients who will benefit from intensive interventions versus those who will receive 'futile care'. However, it should be possible, perhaps through care management if by no other means, to assure that each patient has a realistic understanding of their disease, that they understand the options available to them as well as their likely outcomes and side effects, and that they have been given the opportunity to review and evaluate their end-of-life plans when appropriate.

Regardless of any economic opportunities, the truly important objectives should be to respect patients' wishes, to empower patients with the tools they need to become educated masters of their own destiny, to reduce pain and suffering, and to provide compassionate and dignified care at the end of life.

Nitric Oxide: Better Outcomes for Newborns



Nitric oxide had once been considered to be an atmospheric pollutant, however, more recently, medical science has found that nitric oxide can enlarge blood vessels. Now, nitric oxide gas is being directly supplied to newborns on ventilators with refractory hypoxemia (inability to maintain arterial oxygen > 50 millimeters of mercury). This new discovery may help thousands of newborns each year to survive, to avoid aggressive, expensive, mutilating therapies, to prevent complications leading to future lung disease, or simply to breathe easier when the lung is not working correctly.

Most newborns are born with the natural urge to take that initial wonderful breath of life! Their

bodies display a symphony of responses to the delivery process in those initial seconds. Beginning with their first life-giving breath, among many other things, blood vessels in the lung enlarge to enable the infant to provide its very own oxygen to the body. Sometimes, however, with prematurity or lung disease, this symphony of life is interrupted. The ability to move blood through the lungs never really pulls together, meaning an infant in respiratory distress, with little the external world, including doctors, can do to help. This condition is called persistent pulmonary hypertension of the newborn (PPHN).

Doctors use ventilators to move more air and even pure oxygen into the lung, but they cannot overcome nature's course if the blood is not moving properly through the lung. The doctor forces in air with the ventilator and further abuses the young lungs. The baby tires, and it loses the fight to thrive without oxygen. Even when successful, aggressive ventilator management techniques have resulted in chronic lung disease and neurodevelopmental delays.

In the late 80's, medical science developed Extracorporeal Membranous Oxygenation (or ECMO) to deal with this inability of the lung to provide oxygen to the body. It essentially combined the technology of the cardiac bypass machine with an artificial lung (a membrane) that diffused oxygen into the cardiac bypass flow. It involves a highly invasive and expensive surgical procedure to insert large tubes into the carotid artery and jugular vein. While it offered great hope to solve a problem that had not been otherwise solvable, it also brought tremendous cost and morbidity in the process of saving only some. Babies treated with ECMO are subject to large amounts of blood products and are at risk for intracranial hemorrhage because their blood must be treated with heparin to prevent clotting, and about thirty percent die.

About 40% of nitric oxide treated neonates must still proceed to ECMO, a decision that must often be made within eight hours. One study in 1993 reported that the average hospital cost for an ECMO therapy patient was

\$97,000, excluding the cost of the ECMO system and physician time. However, nitric oxide (NO) significantly reduces the need for ECMO and decreases the risk of chronic lung disease. Nitric oxide can save lives from refractory hypoxemia bypassing ECMO.

The FDA approved Nitric oxide (NO) in December of 1999 for use in term and near-term infants (> 34 weeks gestation) with hypoxic (too little oxygen) respiratory failure due to meconium aspiration, respiratory distress syndrome, pneumonia, and idiopathic pulmonary hypertension. Nitric oxide is delivered in very small amounts to the lungs through a ventilator. It costs anywhere from \$2,000-\$3,000 per day in addition to ventilator charges. However, it prevents ventilator-associated morbidities such as air-leaking and chronic lung changes. Nitric oxide responders also spend less time on the ventilator, and they require less ventilator associated interventions such as respiratory treatments, blood gas assays and chest x-rays, which help decrease overall hospital charges.

Although it has side effects and requires careful monitoring, nitric oxide appears to offer an innovative, common sense, and cost-justified alternative to ECMO for neonates unable to maintain arterial oxygen over 50mmHg. It is expensive, but it offers a mechanism to save lives and reduce complications, acute care time, and downstream costs. Nitric oxide may also become a standard therapy in coronary care units for its ability to enhance pulmonary blood flow.

Brief News Items

The largest clinical trial in hypertension ever conducted, ALLHAT, shows diuretics are the best choice to treat hypertension and prevent its complications. They are also most economical.

In West Virginia, doctors went on strike to protest the high price of malpractice insurance.

As in West Virginia, trauma centers in Nevada, Mississippi and other states are in danger of being downgraded or closed because doctors are steering clear of high-risk practices.

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