ABSTRACT

Comparative Effectiveness of Autologous Platelet Gel in
Coronary Artery Bypass Grafting Surgery
A Formal Decision Analysis

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Coronary artery bypass grafting (CABG) surgery is one of the most common operations performed in the United States. Despite the frequency of this operation, however, it is estimated that surgical site infections (SSIs) occur with a cumulative incidence between 0.5%-7% among CABG patients. In a time of increasing pressure for health care to improve in quality, hospitals must prevent such infections or risk being required to pay for the expenses incurred to treat those infections that arise. Autologous Platelet Gel (APG) has presented itself as an effective method by which to prevent SSIs through the escalation of the immunological response and the growth of new tissue. This decision analysis aims to answer the clinical question: Should Autologous Platelet Gel be used in Coronary Artery Bypass Grafting procedures along with the current standard of care (SOC)? A decision analytic model was used to determine the total expected mortality that is produced from the use of the standard of care (SOC) alone and the SOC along with APG, giving respect to (a) severity of the SSI; (b) development of deep SSI from a superficial SSI; (c) surgical revision of the SSI; and (d) the cause of mortality.

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# COMPARATIVE EFFECTIVENESS OF AUTOLOGOUS PLATELET GEL IN CORONARY ARTERY BYPASS GRAFTING SURGERY

## A FORMAL DECISION ANALYSIS

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# CHAPTER ONE

## Introduction

### *Surgical Site Infections in Cardiovascular Surgery*

Surgical site infections (SSIs) are the second most common type of healthcare-associated ("nosocomial") infection in the U.S. (Anderson 2010). Among surgical patients, 38% of all nosocomial infections are related to the site of the surgical procedure (Anderson 2010). Of all surgeries performed in the United States, it is estimated that between 2%-5% of patients develop SSIs (Anderson 2010). This means that one out of every 24 patients undergoing inpatient surgery in the US develops a SSI following surgery (Consensus 1992; Horan 1998). Due to the high incidence of this surgical complication, the Centers for Disease Control and Prevention (CDC) has developed a standardized and nationally-used system for defining SSIs. According to the system, SSIs are defined as infections relating to an operative procedure that occur within or near the surgical incision within 30 days following an operation (Anderson 2010). As can be imagined, SSIs are a catastrophic complication of surgery, resulting in increased morbidity, mortality, and costs related to their care (National 1998; L'Ecuyer 1996; Lazar 1995; Zoutman 1998; Hollenbeak 2000). Therefore, prevention and better treatment of SSIs should be a major goal in assuring the highest quality of surgical care (Loop 1990).

Cardiothoracic surgery is one of the most common operations performed in the United States. Approximately 470,000 to 600,000 coronary artery bypass grafting (CABG) procedures are performed throughout the country each year (L'Ecuyer 1996;

Hollenbeak 2000). Despite this high rate of surgery, it is estimated that SSIs occur with a cumulative incidence of 1%-2% among CABG procedures (Khalafi 2008; Jonkers 2003). This rate of infection is remarkably low for any surgical subspecialty. It remains, however, that SSIs result in dramatically increased morbidity and mortality. Infection can spread from superficial tissue to the deep structures of the chest, including the sternum, pericardium, lungs and heart (L'Ecuyer 1996). These deep chest infections of the incisional site in a bypass grafting procedure alone result in a 10%-40% greater risk of mortality (L'Ecuyer 1996). With the increasing resistance of microbial organisms to antibiotics and the rising incidence of MRSA and VRSA, a surgical site infection following a routine CABG can easily be fatal.

*Treatment and Prevention*

One of the few treatments for deep surgical site infections is reoperation and debridement of the affected tissue. The infection, along with the associated procedures to remove it, can result in disfigurement. While it has been shown that surveillance of the surgical incision sites for infection has led to a reduction in the rates of incidence on its own, this method is costly—financially and in time. It is vital, then, that better prevention methods become established in cardiovascular surgery in order to increase optimal outcomes within the field (L'Ecuyer 1996).

Prevention methods vary widely, but general principles exist. Antimicrobial soaps and antiseptics, even prior to donning gloves and gowns, have become part of the standard precautions performed before any surgical procedure (Anderson 2010). Sterile drapes are used to add further barriers between surgeon and patient. Antisepsis of the skin

of the patient is a necessary step to the prevention of infection from the already present bacterial flora living on the patient's skin (Anderson 2010). With the development of antibiotics, antimicrobial prophylaxis through antibiotic administration prior to any surgical procedure has become commonplace. Timing of this prophylaxis to within 60 minutes prior to the initial incision has even become standardizedacross the medical profession and enforced by the Joint Commission on Accreditation of Healthcare Organizations(Anderson 2010). Despite these efforts, however, SSIs still occur (Anderson 2010). Additional methods of SSI prevention are needed to reduce the burden these infections have on those undergoing surgical procedures.

*Cascading Effects of Infection*

In any case of an SSI, the initial infection is only the beginning of problems the patient will face. If left untreated, or if the infection is not noticed promptly, a superficial infection can quickly proceed to a deep infection of underlying tissues or even the sternum itself. Due to the proximity of these infections to such vital organs as the heart and lungs, action must be taken immediately in order to reduce morbidity and to prevent the death of the patient. As with any medical intervention, there is risk associated with the treatment of these deep infections. In fact, once infections have progressed so far as to need surgical debridement, the mortality ratefrom the surgery alone is almost 10% (Borger 1998). Even if this surgical revision is not needed, mortality remains extremely high, especially compared to the initial mortality rate of the CABG procedure itself. The complications that ensue from such a routine surgery has effects that can continue to be

felt for the rest of the patient's life, whether through increased morbidity, the high medical costs associated with the infection's treatment, or the infection becoming lethal.

Due to the potentially catastrophic results of developing an SSI, it is important to prevent them rather than treating them retrospectively. While the current standard of care does work to prevent the majority of infections, there are still opportunities for improvement. The prevention of the initial infections has a direct effect on the cumulative mortality of CABG patients, while having an exponential effect on reducing the cost of treatment. Even a minimally more effective prophylaxis measure instituted against SSIs, when multiplied through the vast number of CABG procedures done every year in the U.S. alone, will play a significant role in reducing morbidity, mortality, and the cost of care.

### *Platelet Gel—A New Technique*

Autologous Platelet Gel (APG)—also known as platelet rich plasma (PRP)—has presented itself as a novel way in which to prevent infection through the promotion of growth and healing of tissues. The biological product has been used widely in surgical subspecialties, including: reconstructive, cosmetic, orthopedic, oral maxillofacial and dermatologic surgery (Hom 2007). More recently, cardiovascular surgeons have been incorporating it into their practices in order to improve their postoperative outcomes.

APG is thought to work by accelerating the healing cascade (Khalafi 2008). This is accomplished by concentrating the cytokines and growth factors that are released during platelet activation and degranulation (Khalafi 2008). These cytokines include platelet derived growth factor, epidermal growth factor, vascular endothelial growth

factor and transforming growth factor beta—many of which are present in normal biological immune responses (Khalafi 2008).

Biologically, platelets play a role in the hemostasis of blood following injury. The goal of the use of APG in surgery, however, has little to do with suppressing hemorrhage and more with promoting regeneration of the tissues damaged as a necessary part of any surgical intervention. APG and PRP have been shown in multiple studies to accelerate healing time, increase activity of phagocytes (which play an active role in fighting against microbials), and elevate production of cytokines (Khalafi 2008; Hom 2007; Trowbridge 2005; Englert 2005). As such, investigation into APG's efficacy as a preventive measure in cardiovascular surgery has been conducted and has found it to reduce the odds of infection by as much as 93% (Khalafi 2008). While this is certainly significant, a long-term estimate of the effect of SSI on mortality after treatment with APG was not reported and has not been studied.

Using formal decision-analytic theory, this analysis will incorporate the knowledge previously found on the efficacy of APG and its ability to prevent infection in cardiovascular surgeryin order to estimate the overall expected mortality of patients undergoing CABG surgery who are treated under an APGprotocol in addition to the standard of care (SOC). This calculated expected mortality under APG will then be compared to the expected mortality of the SOC protocol alone, in order to quantify the role of the cascading effects that SSIs have on CABG surgery patients.In addition to the seriousness of these SSIs, the expensive nature of cardiovascular procedures in general is of concern. These facts mandate that in order for a standard prevention of infections to be relevant to the field, it must be as cost-effective as possible. Overall, this decision

analysis was designed to evaluate and compare the immediate and long-term reduction of the incidence of mortality resulting from the use of APG and a SOC for patients undergoing CABG procedures. Furthermore, formal decision analysis will provide the optimal choice (APG vs SOC) that is consistent with valued outcomes by assessing the ability of APG to maximize those outcomes.

*Barriers to Acceptance*

As is often the case in the medical field, few people have all the known information about APG and PRP. Whitlow et al. (2008) studied the factors that barred platelet gel acceptance into cardiovascular surgery as a standard of care. Among the top factors was the apparent lack of reimbursement for the APG's use by Medicare and Medicaid. In fact, the Centers for Medicare and Medicaid Services (CMS) have deemed that there is insufficient evidence to conclude APG is a reasonable form of treatment, likely due to a lack of a randomized control trial(Whitlow 2008). Moreover, no attempts have been made to quantify the number of deaths that can be averted by even a slight reduction in the incidence of SSI following CABG. Additional training and associated costs, along with the costs of the treatment itself, may also be a factor affecting the use of APG. Furthermore, some studies have suggested that the efficacy of APG and PRP is questionable, though these studies were often under-populated and underpowered (Almdahl 2010; Litmathe 2009; Pallua 2009).

*Conclusion and Significance*

Prevention of infection in patients is not something new to the field of surgery. Any invasive procedure has always born significant risk of causing harm rather than good, attested to by any practicing surgeon or any patient who has undergone a surgical procedure and experienced a complication. Since the development of germ theory by Pasteur and the introduction of Lister's idea of antisepsis before surgical procedures, the medical profession has become particularly aware that its members are able to cause as much harm as good. Furthermore, medical knowledge has very seldom stood still. In fact, as we have become more advanced in our knowledge and understanding of the human body and the world in which it lives, we have become increasingly aware of the dangers faced every day and exacerbatedby  medical procedures. One look at a deep surgical site infection of an 85-year-old woman's sternotomy following a coronary artery bypass will make it perfectly clear that a 1%-2% incidence of infection is unacceptable.  Autologous platelet gel has been presented as a way in which to reduce the incidence of potentially lethal surgical wound infections and warrants investigation in order to discern if it merits pursuit as a technique to reduce infection rates or if the medical communities' efforts should be used to find an alternative solution.

# CHAPTER TWO

## Review of Literature

### *Overview*

Surgical site infections (SSIs) occur in the U.S. at a rate between 0.51% and 20% in coronary artery bypass grafting (CABG) procedures (NNIS Report 2004; L'Ecuyer 1996, Khalafi 2008). However, the largest studies show a much smaller range—making it likely that the actual rate is around 1%-2%. The differences in these estimates are huge and likely are related to the sample size of these studies, the expertise of the institutions performing CABG procedures, and the volume in terms of the number of surgeries these hospitals perform. These infections can be either superficial or deep depending on the invading organism and can infect both the sternal incision and saphenous harvesting sites. While uncommon, SSIs can be disastrous when they occur, resulting in higher morbidity, increased risk of mortality and associated costs of care (Hollenbeak 2000, Kachel 2010). Subsequent to the Deficit Reduction Act of 2005, Centers for Medicare and Medicaid Services (CMS) will no longer reimburse for nosocomial infections (BEST Terumo 2008). This has lead to increased efforts by hospitals to reduce the incidence of hospital-acquired infections.

The use of autologous platelet gel is being used as a novel technique to reduce the incidence of SSI in maxo-facial, cosmetic and orthopedic surgery, as well as in sports therapy treatments (Foster 2009). Autologous platelet gel has been shown in several randomized controlled trials (RCTs) to be effective in accelerating healing and promoting

tissue regeneration, although none of these studies were conducted on SSIs of the chest following CABG (Whitlow 2008, Terumo 2008, Hom 2007, Kachel 2010). Cardiovascular surgeons are beginning to realize the potential of this unique biological product in order to protect their patients from acquiring post-operatativenosocomial infections.

*Surgical Mortality in Coronary Artery Bypass Grafting (CABG)*

The National Inpatient Survey (NIS) is the largest all-payer inpatient care database in the U.S., containing an estimated 20% of all discharges from U.S. community hospitals from 44 states. Rathore et al. (2004) used the NIS reports from between 1998 and 2000 (n=228,738) to determine the national surgical mortality of CABG surgery in the U.S., stratified by the volume of the hospitals. From his analysis, he calculated the results reported in the following table.

| Hospital Volume of CABG | Cases/Year | Surgical Mortality |
|---|---|---|
| Low | 12-249 | 4.21% |
| Medium | 250-499 | 3.74% |
| High | ≥500 | 3.54% |

**Table 1 Surgical mortality rates for low, medium, and high volume hospitals**

As high-volume hospitals are likely to be more concerned with the prevention of SSIs due to larger patient populations and because they are more apt at instituting a new technique to prevent such infections due to greater available resources, this analysis will use the estimated surgical mortality of these facilities.

Several studies that report a cumulative incidence of SSIs also report the rate of surgical mortality. Due to the drastically larger sample size of the NIS, however, these

probabilities of surgical mortality from smaller studies will not be used in this analysis so that the results may be more generalizable. Since cumulative surgical mortality is very low in CABG surgery, vast sample sizes are needed to allow enough deaths to accrue to obtain precise estimates.

### *Surgical Site Infections*

According to Anderson et al. (2010), SSIs make up 38% of nosocomial infections among surgery patients. The CDChas determined a national standard of criteria for what qualifies as a surgical site infection. According to these criteria, an SSI is any infection related to a surgical operation occurring at or near the surgical incision within 30 days to one year, depending on whether an implant is left in place during the procedure. The National Nosocomial Infection Surveillance Survey (NNIS) System Report is a national database that reports nosocomial infection surveillance data collected from 300 confidentially participating hospitals in the United States that use the following criteria for determining SSIs.

Infections are classified into different categories (0-3) depending on severity of infection, determined by the number of risk factors present among the following:

> (1) A patient with an American Society of anesthesiologists preoperative assessment score of 3, 4, or 5;
>
> (2) An operation classified as contaminated or dirty-infected; and,
>
> (3) An operation lasting over T hours, where T depends upon the operative procedure being performed. (Culver 1991).

| Risk Index Category | 0 | | 1 | | 2 | | 3 | |
|---|---|---|---|---|---|---|---|---|
| Infection site | No. SSIs | Rate | No. SSIs | Rate | No. SSIs | Rate | No. SSIs | Rate |
| **Leg (Donor Site)** | **20** | **0.74** | **5436** | **1.43** | **2024** | **2.45** | **5** | **2.03** |
| Superficial | 15 | 0.55 | 4203 | 1.1 | 1577 | 1.91 | 5 | 2.03 |
| Deep | 5 | 0.18 | 1233 | 0.32 | 447 | 0.54 | 0 | 0 |
| **Chest** | **14** | **0.51** | **7440** | **1.96** | **2459** | **2.98** | **19** | **7.72** |
| Superficial | 7 | 0.26 | 2796 | 0.74 | 933 | 1.13 | 5 | 2.03 |
| Deep | 4 | 0.15 | 2091 | 0.55 | 627 | 0.76 | 9 | 3.66 |
| Organ/space | 3 | 0.11 | 2553 | 0.67 | 899 | 1.09 | 5 | 2.03 |
| **Total** | **34** | **1.25** | **12876** | **3.39** | **4483** | **5.43** | **24** | **9.76** |
| Denominators for the risk categories are as follows: Category 0 = 2718; Category 1 = 380,340; Category 2 = 82,535; Category 3 = 246. | | | | | | | | |

**Table 2**SSI rates per 100 operations following CABG operation, by risk index category and specific site, Surgical Patient component, January 1992 through June 2004. Adapted from 2004 NNIS report. (NNIS Report 2004)

Data collected between January 1992 and October 2004 in the NNIS System Report were used in this analysis for the baseline rates. The above data was stratified by severity of risk, according to the NNIS. SSI rates change drastically according to the patient's risk category.For the purposes of this study, the separate stratifications made by the NNIS Report (2004) of "Deep" and "Organ/space" will be combined into a group referred to as deep SSIs. "Organ/space" infections include a specific type of deep SSI called mediastinitis, an infection of the sternum itself and the underlying tissue; it has been shown to cause mortality rates of up to 50% in diagnosed patients (Bitkover 1998; Blanchard 1995).

Comparisons of cumulative incidence from similar studies (see Table 3) revealed somewhat lower rates for superficial and deep SSIs. It may be that the NNIS System was more inclusive in its definition of SSIs than the studies presented in the following table.

| Author | Year | Type of Study | Sample Size | Incidence of Superficial SSI | Incidence of Deep SSI* |
|---|---|---|---|---|---|
| Blanchard et al. | 1995 | Retrospective Cohort | 4137 | 1.180% | 0.145% |
| Bitkover et al. | 1998 | Case-Control | 1935 | - | 2.10% |
| Borger et al. | 1998 | Retrospective Cohort | 12267 | - | 0.75% |
| Breyer et al. | 1984 | Prospective Cohort | 870 | - | 0.80% |
| Grossi et al. | 1985 | Prospective Cohort | 7949 | 1.400% | 2.900% |
| Ridderstolpe et al. | 2001 | Retrospective Cohort | 3008 | 6.40% | 3.30% |

**Table 3**Comparison of Cumulative Incidence from Superficial and Deep SSIs in smaller studies

*Superficial Surgical Site Infections*

Superficial surgical site infections are associated with the subcutaneous tissue surrounding and just under the incision site (Cooper 1991). Despite their title, superficial SSIs require timely and assertive action to prevent them from progressing and developing into deep surgical site infections (Cooper 1991). Diagnosis is typically made by observation of erythema, purulent drainage from the incision, fever and sternal instability, but is often difficult as the infection may be occult (Cooper 1991; Kohman 1990; Englert 2005). In these cases the incision appears normal and a mild grade fever may be present, while other, more conclusive evidence is not. As a review of the cardiovascular literature suggests, the incidence of SSIs is between 0.26% and 6.4% (Table 2; NNIS Report 2004). Overall, this level of incidence is somewhat lower than deep SSI incidence when mediastinitis occurrence is included, though this is to be expected, as superficial SSIs entail much less severity than an infection that has invaded deeper into the chest or leg incision site or the deeper organ space. Additionally, according to the NNIS Report

(2004),a smaller portion of infections in CABG patients are superficial rather than deep (26%-50% superficial versus 50%-74% deep), likely due to the apparent and visible nature of superficial infections. The results found by this much larger study (n=465,839) show a significantly different rate of superficial infection than studies done specifically on CABG surgery with smaller sample sizes (n=291) (NNIS Report 2004; Ridderstolpe 2001).

*Deep Surgical Site Infections*

Deep SSIs, as implied by the name, involve the deeper areas around and beneath the sternum and in some case involve the sternum itself (Cooper 1991). These infections go below the upper layers of tissue and can infect organ space if left untreated. In fact, the term surgical site infection replaced the previous term of surgical wound infection once the infections were found to extend to deeper spaces of the body (Anderson 2010). The severity of these infections is often life threatening simply because of the proximity to vital organs such as the heart and lungs. These infections often are of such severity that they require wound debridement, a muscle flap procedure, and possible removal of the sternum to prevent further morbidity and death (Loop 1990). The distinction between superficial and deep SSI is often made by positive culture from suspected infected tissue. A problem remains, however, as deep SSIs can often be occult. These occult infections present with little more than a mild fever and a sternal incision that appears normal (Cooper 1991). As shown by various studies, deep SSIs increase morbidity, mortality, and costs of care due to longer hospitalization and treatments (Hollenbeak 2000).

*Risk Factors*

The mechanism for SSI development is difficult to discern and is not clearly understood; however, it is thought to be associated with a number of factors (Toumpoulis 2005). Risk factors for surgical site infections after coronary artery bypass grafting procedures include: obesity (OR=11); diabetes mellitus (OR=5.5); chronic obstructive pulmonary disorder (OR=1.14);connective tissue diease (OR=25.44); smoking (OR=1.16); peripheral vascular disease (OR not available; p-value=0.007); and,renal dysfunction (OR=3.4) (Toumpoulis 2005, Hollenbeak 2000). Hyperglycemia has also been determined to be a risk factor (OR=2.0) (Anderson 2010). Several factors from the surgical procedures themselves have also been associated with increased risk of infection; although their effects were not quantified in the literature with an estimate of effect, they proved to be statistically significant. Prolonged operation time ($p$ = 0.0013), extended use of cardiopulmonary bypass ($p$ = 0.0072), aortic cross-clamp time ($p$ = 0.0075) and the use of β-adrenergic drugs ($p$ = 0.0037) were all related to the increased incidence of SSI in one case-control study (Bitkover 1998). Borger et al. (1998) and several other studies (Demmy 1990) concluded that being male and diabetic increased the likelihood of the development of an SSI. However, another study (Breyer 1984) found females to have a higher prevalence of infection. Age has been shown to be both protective in some instances and risk-associated in others. The extensive literature on risk factors relating to SSIs provides no clear mechanism for their development. The results varied widely and were only mildly consistent. Studies rarely analyzed the same risk factors from research program to research program and within those studies there was a widely varying range of quantified effects.

*Mortality*

Differing rates of mortality exist depending on the severity of the SSI that develops in each patient. Additionally, many studies only report 30-day mortality, while other report this estimate up to one year after the onset of the infection. Many studies do not even report the mortality rate associated with superficial infections, which have a much lower mortality rate than deep infections or mediastinitis. The largest study (n=1935) found in the literature that reported the mortality rate for deep SSIs was Bitkover et al. (1998) with an estimate of 18.90%. Hollenbeak et al. (2000) found a similar mortality rate from deep SSIs of 22%. Ridderstolpe et al. (2001) (n=291) provides estimates of both superficial and deep SSI mortality rates of 2.1% and 7.2%, respectively. Interestingly, the NNIS report (2004) does not report mortality from the infections that it reports. Inclusion of this data would be invaluable to researchers of SSI prevention.

## *Autologous Platelet Gel – Basics*

Autologous platelet gel (APG) or platelet-rich plasma (PRP) is a novel technique that has been used in surgery since the 1970s. Interestingly, APG has been used primarily in orthopaedic surgery, maxillofacial surgery, plastic surgery, neurosurgery, burns, veterinary medicine and most recently undergone clinical application in sports medicine (Jameson 2007). Its application and benefit to the world of cardiovascular surgery, however, is just beginning to be realized. The reasons for its use lie in its attributed properties of healing. It is widely thought that PRP and APG lead to increased concentration of platelet-derived "growth factors and secretory proteins that may enhance the healing process on a cellular level" (Foster 2009).

The overall effect of the use of APG is to increase bioactivity in specific, localized sites. The following is one such example. Many of the platelet-associated cytokines result in an inflammatory response in a normal, biological setting. The primary purpose of this response is to stimulate an influx of white blood cells into a wound. This further activates platelets, leading to further production of growth factors, some of which activate macrophages—the waste removal cells of the body that play a huge role in immunological defense.

Despite many basic science studies of APG and its derivatives, there have been no clinical randomized controlled trials (RCTs) testing its efficacy in promoting wound healing and preventing infection. Additionally, no RCTs actually examined APG's role in prevention of surgical site infections of the chest. The only estimates that exist of the incidence of SSI after prophylactic treatment with APG come from retrospective studies, both showing that APG significantly reduces infection rates(Trowbridge 2005; Khalafi 2008).

*Platelets*

Platelets play a major role in the hemostasis of blood following injury to the body. Although small and nonnucleated, platelets contain proteins, cytokines and other factors that help promote healing of tissues following any sustained injury. While the normal platelet count within the blood is around 150,000/μL, the premise behind APG is to increase that concentration 4- to 5-fold (sometimes as much as 8-fold) in hopes of boosting the regenerative properties displayed by platelets in the body (Jameson 2007;Khalafi 2008). By concentrating the platelets and adding other biological

components (to be detailed later), physicians are able to apply a high dose of platelets and associated growth factors to specific areas of the body. Chronic, non-healing wounds, incision sites, and difficult to treat wounds have all seen benefits from platelet gel application (Crovetti 2004; Saldamacchia 2004). Many of the growth factors produced by platelets have been shown effective in enhancing formation of new blood vessels (Foster 2009). These growth factors include: platelet derived growth factor (PDGF), platelet derived epidermal factor, and transforming growth factor beta (Foster 2009). Foster et al. (2009) also reported that platelets produce bone morphogenetic protein, insulin-like growth factor, and endothelial cell growth factor; these have various functions—predominately to increase cell growth and proliferation, blood vessel growth, and tissue differentiation.

*Preparation*

To prepare PRP/APG, the first step is to add a citrate to the blood in order to bind ionized calcium and inhibit the clotting cascade. PRP can only be made from anticoagulated blood, so it is often convenient to draw blood from the patient who has already received heparin as part of a cardiovascular procedure. Once the blood is drawn, it is centrifuged one or two times, first to separate the red and white cells of the blood from the plasma and platelets. Then a second centrifugation concentrates the platelets even more.

It is at this point that the platelets must be made to clot, which can be done in several ways. Many systems made specifically for the production of APG exist, including products from Terumo Corporation (Tokyo, Japan). These systems often use bovine

thrombin to activate the clotting cascade. This step is pivotal since clotted platelets are activated platelets, and only activated platelets produce growth and healing factors. Foster et al. (2009) report that around 70% of the stored growth factors of platelets are released within ten minutes of activation, with almost 100% being released in one hour. There are rare complications associated with the use of bovine thrombin, which sometimes trigger immunological responses resulting in the production of antibodies against the thrombin. One way around this issue is to add calcium chloride, which produces the autogenous production of thrombin from prothrombin. The calcium also works to provide a scaffolding to which the platelets may bind, similar to natural fibrin in normal biological processes. The issue with the addition of calcium, however, is that it leads to a minimal amount of thrombin production and, therefore, fewer growth factors are produced. It is often the case that thrombin, either autologous or bovine, is added along with calcium to increase overall production of these growth factors. It has been suggested that collagen can also initiate the production of thrombin. The mixture is prepared through a hand-held applicator system, which places calcium, thrombin and the concentrated platelets in specific ratios on the incision or wound.

While cardiovascular surgery did not initiate the use of APG, it has certainly made use of the potential benefits of this treatment. Cardiovascular surgery now accounts for over 22.8% of all utilization of autologous platelet gel (Whitlow 2008). Orthopedics, where use of APG began, now accounts for only 18.4% of its use (Whitelow 2008). Such high usage within the field of cardiovascular surgery warrants an analysis of APG's cost-effectiveness.

*Efficacy of Autologous Platelet Gel and Derivatives*

Autologous platelet gel has obvious and multifacet clinical applications. It has been widely used across healthcare settings and now has found a new niche in cardiovascular surgery. According to Mazzucco et al. (2007), the healing rate of sternal wounds was increased with application of APG ($p=0.0002$), leading to a decrease in average hospital stay of over twenty days. Englert's data(2005), although a small study ($n = 30$), found significant reduction in chest pain, leg pain around the vein harvesting site, and a decreased level of bruising in the platelet gel group compared to the standard to care. Crovetti et al. (2004) found that platelet gel expedited the healing of cutaneous ulcers in diabetics, while Pallua et al. (2009) used APG as a treatment for burns. Gunaydin et al. (2008) found a significantly higher phagocytic capacity associated with APG use, indicative of decreased risk of infection. Hom et al. (2007) also concluded that APG increased healing of the incision sites, resulting in wound closure several days prior to control groups.

*Estimate of the Effects of APG*

The best estimates of the effects of APG are presented in two studies: a case-control study (Trowbridge 2005)and a retrospective cohort study (Khalafi 2008). Trowbridge et al. (2005), with a large total patient population ($n=2,259$), showed marked reductions in superficial SSI, (0.3% vs 1.8%) with application of platelet gel. A similar relationship was shown with deep SSIs, resulting in no infections in the APG group compared to 1.5% in those not receiving the therapy. Khalafi et al. (2008) followed 1,128 patients as part of a study to determine surgical closure rates. The APG group had one

incidence of sternal infection (0.18%) compared to the eleven cases in the control group (1.98%). Drainage from the incisions was also reduced (0.53% vs 5.39%), meaning that APG was reducing the loss of blood after surgery. Blood loss can create an environment vulnerable to invasion by microorganisms. Similar results were found in the vein harvesting sites in the leg: no infections were reported within the APG group compared to 61 cases or 10.89% of the controls. Excessive drainage was seen in only three cases (0.66%) compared to 212 controls (48.4%). No adverse effects were found in the Khalafi study to be associated with the use of APG as a treatment. Khalafi et al. (2008) concluded that APG application resulted in the "reduced odds of chest wound infection by 93%, chest drainage by 96%, and leg wound drainage by 88%." However, exact estimates of the proportion of deep and superficial infections were not given. Additionally, the cumulative incidence of mortality for each classification was not given, leaving researchers without an understanding of all of the potential effects of APG.

Problems also arise from the small number of infections that actually presented during a study. With an infection that develops so rarely, even in one of the most common surgical procedures in the world, larger sample sizes are required to find precise differences. Inflated reductions of the incidence of SSI could make APG appear much better in this analysis than it actually is.

Despite these remarkable findings, many studies have failed to show a statistically significant reduction in surgical site infections. Almdahl et al. (2010) ,Litmathe et al. (2009), and Pallua et al. (2009) all found no statistically significant reductions in infection or decreased healing time. However, these studies were vastly different. Litmathe et al. (2009), for example, was a study of high-risk patients with a sample size

of only 44. Similarly, Almdahl et al. (2010) had a sample size of 140 and was unable to show a reduction in SSIs.

## *Costs*

It is understandable that surgical site infections, whether superficial or deep, are associated with increased costs of care, usually from longer hospital stays and often from more advanced care, such as multiple surgeries, additional medications and critical care. For platelet gel to be the most effective, it must be applied peri-operatively, leading to increased costs of surgery. In addition to this, special equipment is needed for the proper preparation and application of APG.

### *Platelet Gel and Associated Instruments*

The average cost of the machines needed to produce APG or PRP are $6,000 (Whitlow 2008). The cost of the disposable parts of the equipment, including applicators, range from $350 to $400 per application (Whitlow 2008). In comparison to the price of a coronary artery bypass grafting procedure, this is a minimal addition to cost—resulting in 2.9% to 3.1% increased costs (Taylor 1990). These machines include special centrifuges that allow health care workers to prepare the APG in the operating room. Medetronic (Minneapolis, MN), Terumo (Tokyo, Japan), Sorin (Milan, Italy), and Biomet (Warsaw, IN) all produce these machines. In addition, only 35% of these machines are purchased outright by hospitals, with the remainder being used on a disposable usage provision (Whitlow 2008). The useful life of these machines is 3,000 uses, meaning that for an average volume institute defined as performing 250-499 CABG surgeries each year, a

minimal amount of the original $6,000 can be applied to any specific patient's surgery (Whitlow 2008). The price of the machine is depreciated at a rate of $2 per surgery, with no more than $1000 depreciated in a single year. Therefore, the price of the machinery and equipment necessary to produce and apply APG is relatively minimal.

*Surgical Site Infections*

Surgical site infections have been shown to be huge economic burdens on both hospitals and patients. Increases in costs have been from a few thousand dollars to well over $100,000 per infection (Hollenbeak 2000). In order to determine the societal costs associated with Medicare and Medicaid, fee schedules would have been consulted and costs determined based on average length of stays, medication and pharmacy costs, and any addition surgeries or procedures that were performed in order to treat surgical site infections.

## *Conclusion: the Gap*

No RCTs have been conducted to objectively evaluate the role of autologous platelet gel in its efficacy to prevent infection and, subsequently, reduce mortality. Without a RCT, there is no unequivocal estimate of APG's effects. While the majority of studies show APG to be beneficial in wound healing through increased release of growth factors and reduction in the incidence of infections, some evidence points to platelet gel being ineffective (Almdahl 2010; Litmathe 2009; Pallua 2009). These studies, however, were conducted with relatively small samples sizes.As the overall effect size of surgical site infections is exceedingly small (1%-2% in the U.S.), it will take a RCT with a

considerable sample size to provide conclusive evidence. As the cardiovascular literaturedoes not contain enough evidence on either side, making a decision on the APG's usage seems questionable in the eyes of many. For a number of cardiovascular surgeons, there is simply not enough evidence to warrant even a trial comparing this technique to the SOC.Due to the lack of a conclusive estimate of effect of APG on SSIs, there has been no estimate of the overall expected mortality from using such a protocol in addition to the current SOC. While prevention of infections is the first step, research is still needed to estimate the overall impact that APG has through the cascading effects ofon mortality. This gap in the literature has resulted in physicians defending opposite sides without conclusive evidence based on either cost-effectiveness or in relation to reduction in infections or consequent mortality, leading to controversy among the elite of the field. Although a formal decision analysis cannot replace the clear picture provided by a RCT of statistical significance, it is able to model complex issues with clinical relevance. By integrating relevant data into the problem at hand, this formal decision-analytic model potentially offers evidence to hospitals and surgeons in order to inform their judgement on the implementation of APG for the management of financial and biological risk associated with surgical site infection in cardiovascular surgery by dealing with the uncertainties of the underlying problems.

# CHAPTER THREE

## Hypothesis

### *Research Question*

*Should Autologous Platelet Gel be used in Coronary Artery Bypass Grafting (CABG) procedures along with the current standard of care?*

### *Hypothesis*

With the general objective of investigating the efficacy in preventing surgical wound infections and subsequent mortality in a cost-effective manner for cardiovascular patients, this analysis proposes to test:

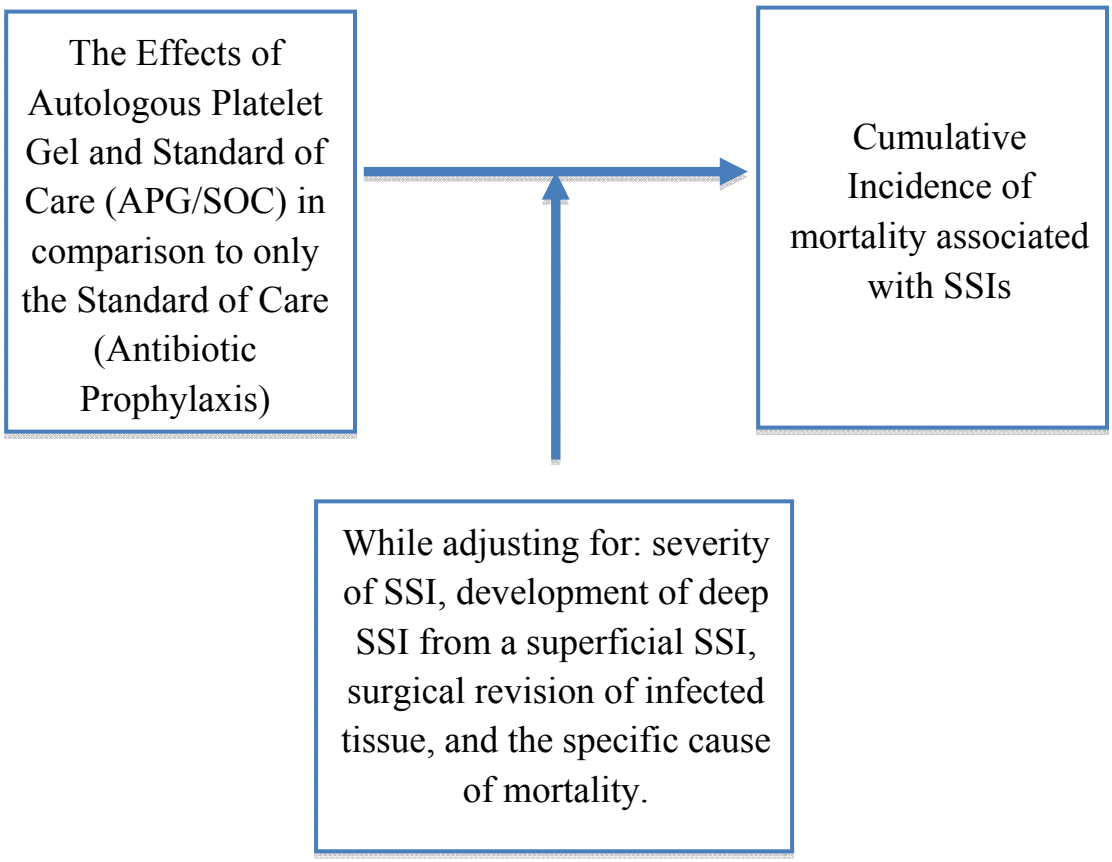
> The hypothesis that autologous platelet gel application to patients, along with the standard of care, will result in a lower mortality following the CABG procedure.

after adjusting for the cascading effects of surgical site infections; specifically—(a) severity of the SSI; (b) development of deep SSI from a superficial SSI; (c) surgical revision of the SSI; and (d) the cause of mortality. This hypothesis will be tested using the methods of formal decision analysis on a hypothetical sample patient group from Bethesda Heart Institute all undergoing coronary artery bypass grafting procedures from the same surgeon.

In this analysis, consideration will be given to the efficacy of the current standard of care, as well as to the differences effected by the use of APG. It will include data concerning complications from the APG application, as well as the rates of superficial

and deep surgical site infections, and relative treatments for such outcomes—such as further surgical procedures and extended hospital stay.

Diagrammatically,



# CHAPTER FOUR

## Methods

### *An Overview of Formal Decision Analysis*

Certainty can never be achieved when evaluating the appropriateness of a decision to be made. Nevertheless, one faces decisions every day of life. In order to progress, we must have a way in which we take account of this uncertainty the world presents while making confident decisions. Such a process must be methodical and exhaustive, employing all possible alternatives with the aim of making an informed, though sometimes intuitive, decision.

The same premises hold true for decisions made within science. An indecisive clinician is rarely one that pleases the patient or adds to the profession in meaningful ways. Good science requires a methodical approach that allows the decision maker to see the options clearly and to make a decision without undue delay. Such a process should require intentional and attentive thought that results in a decision that can be made with confidence.

Yet, in the world of medicine, rarely do clinicians have complete knowledge about any given decision. In a field using intellect, experience, and instinct, how can decisions be made that go beyond "just a gut feeling"? Even with the tools of scientific and biological reasoning, our decisions are prone to errors, and medicine is a high stakes game; the decisions to be made involve the lives of others. It remains that decisions are

often made without clarity of understanding or consistency in thought (Skinner 2009). So how can clinicians reach decisions that they are secure in making?

Formal decision analysis provides a systematic manner in which to make good decisions while in the presence of uncertainty. A good decision is "one that is logically consistent with our state of information" (Skinner 2009). It is exhaustive in creative alternatives and it integrates the likelihood of each with its potential outcome, while providing the opportunity to adjust for the decision-makers' feelings toward risk—whether one is risk-adverse, risk-prone, or neutral.

The tools employed by decision analytic theory should be explicit. They should provide the framework with which clinicians are able to make consistent decisions. Decision analysis should illuminate the decision maker and his team through the facilitation of rational discussions of excellent quality about the issues faced within a specific decision (Skinner 2009). The methodology is one of prescription and normativity, meaning that acting against the model is equivalent to acting against one's stated beliefs. As such, decision analysis attempts to answers the "should questions" of healthcare and medicine: should this treatment be used for this patient? Should this woman receive this surgery? Should this drug be put on the market? Should this treatment method be prescribed to all similar patients? Decision-analytic models "provide a higher level of thinking that allows for a better understanding of the decision" to be made (Skinner 2009:11).

As described by Skinner (2009), formal decision analysis involves a Scalable Decision Process. This allows for the matching of the process to the complexity of the problem at hand. If there is a point in the decision-making procedure when it becomes clear that one choice is obviously more beneficial, or at least less harmful, than all other possibilities, then the methodology calls for a decision to be made at that point. Decision-analytical techniques are best suited for problems of great complexity with no clear or apparent course of action. Well understood problems, for example, are not best suited for the formal decisional process and should not be undertaken.

In any decision analysis model, the goals are brevity and clarity, without sacrificing the complexity of the true issue at hand. The model should match as closely to the real world issue as is possible with the available information. To fully model any issue, numerous variables and outcomes must be considered. These variables include the possibility of death, other treatments (medications and surgical procedures, etc.), morbidity, complications, cost, and quality of life. The variables included within the model are determined by the problem that is being modeled. Without comprehensive inclusion of all issues relevant to the issue of interest, the risk-benefit tradeoff cannot be wholly described and the model and subsequent decision will suffer.

### *The Process of Formal Decision Analysis*

Decisions are made every day but rarely are they so complex that a model of the issue is required. Decision analysis attempts to make the process as clear-cut and straightforward as possible. Therefore, the methodology of decision analysis is forthright;

it simply involves an explicit model rather than making the decision intuitively, as is done for everyday questions.

The decision-maker using FDA begins the process by first indentifying the problem or issue to be solved. She then has to understand and acknowledge the objectives of making this decision. In order to make the optimal choice, she must create potential and unique alternatives, in order to determine a preference. The previous steps are all part of the framing of the decision. At this point the decision-maker can create a diagrammatic model, which is often helpful in making the decision compelling to oneself and others. Evaluation of the alternatives follows, resulting in a quantitatively preferred strategy. However, it is important to ask the question "what if?" Analyses should be performed in order to identify how much better one decision is over one of its alternatives; this is to answer the question of "how do we know that we know this decision is correct?" Once the decision-maker is certain the model accurately reflects the evidence, the preferred strategy should be implemented.

Figure 1 provides a flow-chart representation of the decision analysis process.

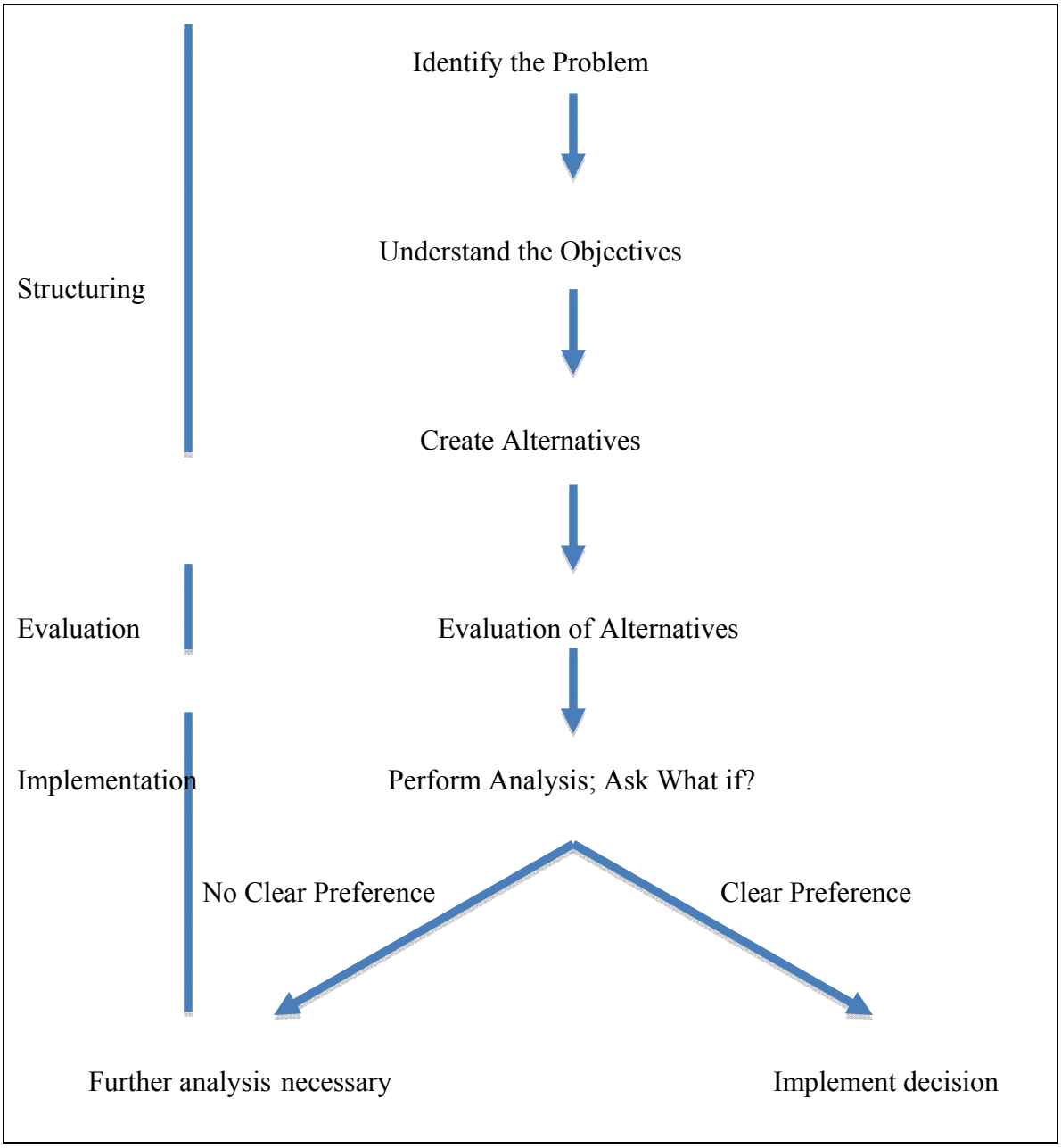



**Figure 1 Decision Maker Process, adapted from Skinner 2009:8**

Clarification of the decision to be made is an essential step, as it ensures that the correct problem is solved. As decision analysis is best used for complex issues, it can often be the case that the effects of a problem are what is focused on, rather the

underlying issue. The decision-maker must be able to clearly and succinctly state the problem to be solved (Skinner2009).

Similarly, the stated objectives, or what the decision-maker values, must also be unambiguous:

- Why do we care about this issue?
- What can we gain from clearer knowledge of the issue?
- What do we care most about (cost, quality of life, reduced infection rates, low mortality rate, etc.)?

Clear and stated objectives in the beginning will ease the decision process later, especially in creating alternative solutions and in the structuring of the decision model.

It is improbable that any model will perfectly reflect the real-world issue. Any model a decision team frames will be merely a surrogate of the true issue. In order to make the model resemble the real-world question as closely as possible, it is important to employ a content expert in the area or field of study of the issue, as well as gathering information from other sources. By doing so, the decision team lessens the chance of missing important complexities or placing undue weight on unimportant factors of the problem. The subjectivity of this type of information is what makes decision analysis different from the rest.

After the decision-maker and her team have framed an accurate model, an optimal alternative strategy, or a different course of action, that meets stated values and objectives should be determined. Once established, this optimal alternative should be evaluated for reliability through sensitivity analysis. *If factor X were different, what would be the*

*outcome? What if our probability of infection risk reduction is too high? What if it is too low?* Sensitivity analysis (to be discussed below) allows the investigator to vary different factors within the model in order to determine thresholds, or points at which our decision would change. The analyses could be used as incentives to further research specific factors if they prove to be driving factors of the model. If the model offers a clearly preferred alternative strategy, then implementation of the decision can begin.

While the methodology of decision analysis attempts to reduce uncertainty about a specific question, it can only do this within the model. Ultimately, the decision maker must assume the risk and act to implement the decision strategy or to reanalyze. The intention of decision analysis is to provide the decision makers with a logical and systematic approach to viewing uncertainty in order to make a strategic decision based on previously stated values. The value of the model is directly reflected in the accuracy of the information put into it. The role of decision analysis is to provide the decision-maker with a clear and enlightened view of the complexities within an issue in order for her to take action.

### *Statistical Analysis: Framing Decisions*

To better see the complexity of the issue, decision trees often are useful when modeling decisions to be analyzed. These diagrammatic representations follow a logical progression with a sequential nature related to the question being investigated—providing visual clarification of the decision to be made, the factors affecting that decision and the outcomes related to each alternative strategy. Decision trees allow analysis of problems that involve a series of choices under uncertainty that are restricted by the decisions made

beforehand. They impart a convenient way to show consequential effects of choices and the significance of those events on the related outcome (Henderson 2009). Investigators should choose the alternative strategy that has the highest expected value that is based upon previously stated values. Simply, this means that the optimal decision is determined by the highest probability associated with the desired outcome.

Each of the factors within a decision tree that affects the outcome is quantified with a probability of that event occurring, providing the decision analyst with a quantitative measure of comparison. A probability is defined as the likelihood of an event occurring given all possible outcomes. In this way, analysts are able to quantify the uncertainties concerning an issue.

*Bayes' Theorem*

Decision-making is often a difficult process, exacerbated by uncertainty. Uncertainty about an issue implies that an optimal and a sub-optimal choice exists. Without uncertainty, questions would have clear answers and optimal decisions would be inherent and obvious. The level of uncertainty surrounding a decision is directly related to the difficulty of making that decision. Uncertainty is merely a lack of knowledge. Risk, therefore, is uncertainty that matters.

It is rarely the case that all knowledge is attainable about any issue. This is especially true in a field such as medicine. Physicians can never know the actual condition of any patient; perfect information is likely not to exist. Thermometers may estimate the temperature of the body, but it is merely an indirect measure of the true temperature of that patient. Sphygmomanometers may measure blood pressure, but the

true blood pressure of the patient will remain unknown. Thankfully, we have strategies that help us deal with this lack of true knowledge.

The Bayesian approach allows clinicians to deal with uncertainty in a mathematical and logical way. Bayesian statistics attempts to reduce the amount of uncertainty within any issue by taking a prior probability (data previously collected) and updating that probability in light of newly obtained information. In order for the Bayesian process to take place in a medical context, we must know (1) the prevalence of disease and (2) conditional probabilities of the test result given disease status, known as sensitivity and specificity. **Prevalence** is the prior probability of disease. It is a marginal probability and is entirely independent of other probabilities. **Sensitivity** and **specificity** are both conditional probabilities that are measures of how well a test can predict disease. Conditional probabilities rely on two separate factors, in this case the test and the disease. Sensitivity is the probability of a positive test given a patient has the disease. Specificity is the probability of testing negative for a disease given a patient truly does not have the disease.

The following chart provides formulas for these specific terms and probabilities:

| Term | Formula | In Words |
|---|---|---|
| Prevalence | P(D+) | Probability of having a disease |
| Sensitivity | P(T+ \| D+) | Probability of a positive test given that a patient has the disease |
| Specificity | P(T- \| D-) | Probability of testing negative given that a patient does not have the disease |

**Table 4: Probability formulas**

To visualize the relationship between a test and a disease, analysts can employ the use of a 2x2 table. In such a table, we are comparing the state of the world (disease) to an action (a test) (Winkler 2003:202). This table is composed of four distinct cells—**A, B, C,** and **D.** Each cell contains a joint probability, or a probability of event X *and* event Y, or the product of two or more events. Joint probabilities, consequently, are composed of the quotient of two separate probabilities, in this case (marginal probability x conditional probability). Prevalence, a marginal probability, can be found on the bottom left margin of the 2x2 table.

| | Disease + | Disease – |
|---|---|---|
| Test + | **A**<br>Sensitivity<br>X<br>Prevalence | **B**<br>1 - Specificity<br>X<br>1 - Prevalence |
| Test – | **C**<br>1-Sensitivity<br>X<br>Prevalence | **D**<br>Specificity<br>X<br>1 - Prevalence |
| | Prevalence | 1 - Prevalence |

**Figure 2. 2x2 Table (Contingency Table)**

Bayes' Theorem uses the above joint probabilities to bring into account newly obtained information. Bayes' attempts to update prior probabilities relating to uncertainty by adding new information into the probability. As previously stated, uncertainty arises from a lack of knowledge, so by updating our probabilities with new information, we are

able to reduce uncertainty. By using Bayes' Theorem, analysts attempt to predict the probability of future events (i.e. create a posterior probability).

Bayes' Theorem is defined mathematically below:

$$P(D+|T+) = \frac{P(D+)\,P(T+|D+)}{P(D+)\,P(T+|D+) + P(D-)\,P(T+|D-)}$$

The Bayesian approach of allowing clinicians to update probabilities in light of new data is a valuable asset to the medical field. Clinicians are trained to gather data, synthesize and make a diagnosis. However, human brains are not exceptional at correlational thinking. By providing a systematic approach to correlational thinkng that allows quantifiable revisions by taking into consideration new data, decision-analytic methods ensure clinicians can obtain better outcomes in practice. To put it simply, clinicians can gain greater confidence in diagnoses while running fewer tests and procedures.

*Formal Decision Analysis*

Formal decision analysis (FDA) is chiefly concerned with the gains or losses associated with the consequences of decisions. The estimates of these consequences are called *utilities,* which can be payoffs or losses (decreased morbidity or increased mortality, for example). By using these utilities, which are assigned specific values, decision-makers are able to determine preferential courses of action that meet their stated objectives for making the decision.

To understand utilities, we must first understand values. Values are simply outcome measures stated in "natural metrics" such as the percentage of patients with

decreased morbidity or the percentage of mortality. Utilities are outcomes that have added a) a decision-maker's attitude toward risk (risk-adverse, risk-prone or risk-neutral) or b) incorporated a decision-maker's appraisal of quality of life. Therefore, utilities can be quantified in several different ways, but in either case they are quantified between 0 and 1.0.

Attitudes toward risk can be determined through standard gambles. In this situation, a person is offered a fifty percent likelihood of winning $1,000,000 and a fifty percent likelihood of losing $250,000. The amount of money the gambler is willing to accept in order not to take the bet determines the risk attitude. If this number is higher than $250,000, they are said to be risk-prone; if the dollar value is lower, they are risk-adverse. If the amount is equal to $250,000 then the person is risk-neutral in that situation.

An appraisal of quality of life utility is achieved through a panel's assignment of values to various outcomes. The panel is typically composed of experts on the issue who are able to give reliable data concerning the outcome. Utilities reflect the preferences of the decision maker with regard to risk relative to each other utility. In this analysis, we will use values for the outcomes of interest, specifically the cumulative incidence of surgical site infections.

Every decision has outcomes, or consequences. Outcomes are exhaustive and mutually exclusive. To accurately model a real-world situation, all possible outcomes that have an affect on the decision maker's values must be included in the analysis. In medicine, it is often the case that treatments have side effects that occur alongside the

actual treatment. These side effects should be included. Take, for example, the treatment of a patient with a certain surgical procedure X.

Outcomes from this procedure would include:

1. Full recovery following the procedure
2. Death from the procedure
3. Severe complications from the procedure
4. Minor complications
5. Allergic reaction to drugs administered during the procedure

Perhaps the procedure often leads to reduced mobility or an extended recovery period. These issues could be major factors in the determination of a quality of life estimate that could be used as the outcome of interest. Cost, a hotly contested issue in medicine, can also be analyzed using FDA. Perhaps the procedure is exorbitantly expensive but leads to a higher cure rate, while another procedure is a less expensive treatment but has somewhat inferior results. All of these outcomes can be analyzed using FDA.

### *Decision Trees*

Decision trees are diagrammatic representation of real-world problems. Decision trees consist of many branches, emanating from nodes, that reflect different probabilities of various events or factors that influence a decision. Characteristic of all decision trees are three separate types of nodes: one decision node (usually symbolized with a square), several chance nodes (usually symbolized with circles), and many outcome nodes (symbolized as triangles). To begin a decision tree, analysts must know the question they wish to solve, as the decision node is the first node of the tree. From this node emanates the various paths that can be taken to reach the outcomes. The decision node possesses neither a probability nor a utility; it simply begins the tree and the decision pathways that

follow. The intermediate nodes, which manifest from the decision node, pertain to the factors that contribute to the outcomes. These chance nodes lie between the decision to be made and the possible outcomes. Associated with each of these nodes is a probability that quantifies the uncertainty associated with that particular event occurring. It is for this reason they are called chance nodes, as they represent likelihoods of events that can occur at each node. The number of chance nodes typically directly correlates with the complexity of the issue. It is important to integrate all pertinent action and events that could take place within a decision pathway. Similarly, incorporating too many chance nodes overwhelms the model with detail that is unimportant, in comparison, to the main issue. Doing so adds very little to the accuracy of the model, especially when the event is negligible, while making it more demanding to understand. Adding too many possible events that have little effect on the outcome leads to a sacrifice of clarity.

The nodes on the far right of the tree, denoted by triangles, represent the exhaustive and mutually exclusive outcomes. Each is assigned a value, dependent on the pathway with which it is associated. These outcomes may be percent mortality, quality of life estimate, percent morbidity or infection, cost, or others. Below is a simple version of a decision tree. Note the separate nodes with their corresponding shapes and the associated probabilities with those nodes ("#" represents the reciprocal probability for that node). No outcome data has been input at this time.

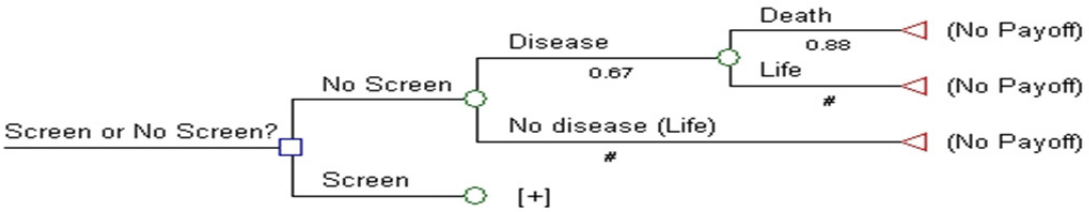



**Figure 2. The Anatomy of a Decision Tree**

Once the decision tree has been structured and all branches assigned probabilities, the analyst can begin evaluating the individual decision pathways. The typical method of evaluation is the calculation of expected value for each node, which traces through the tree in each decision pathway, giving the investigator an expected value for each possible decision. Simply, expected value is a method of integrating uncertainty and its related significance. For that reason, one may define **expected value** as the sum of weighted-averages of the uncertainty for each decision pathway. The method of calculating the expected value of a decision pathway is termed **folding** or **rolling back.** This is the method by which a decision scientist is able to determine a preferential option in a decision analysis. As an example, consider the previous outlined situation, this time with utilities associated with each branch:

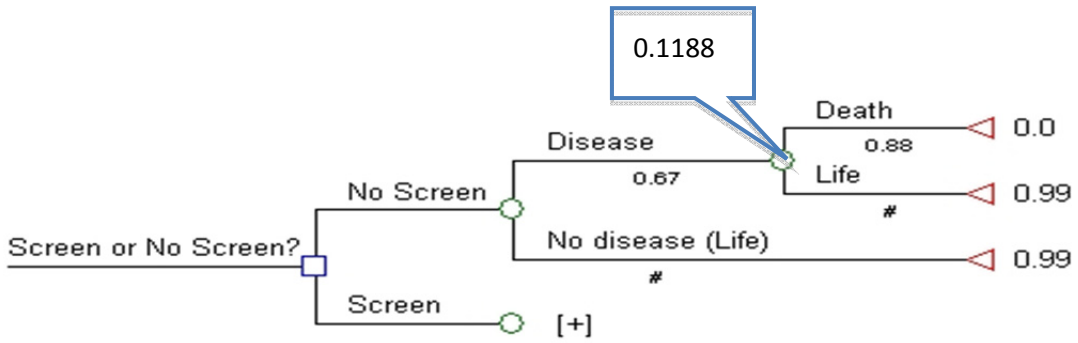



**Figure 3. Expected Value Calculation**

To calculate the expected value of this node, sum the products of the outcomes and their

specific probabilities of occurrence. For this example:

Expected value = (0.0)(0.88) + (0.99)(0.12) = 0.1188

This process continues until the tree has been rolled back to the decision node, revealing an optimal decision based on the stated values of the decision maker.

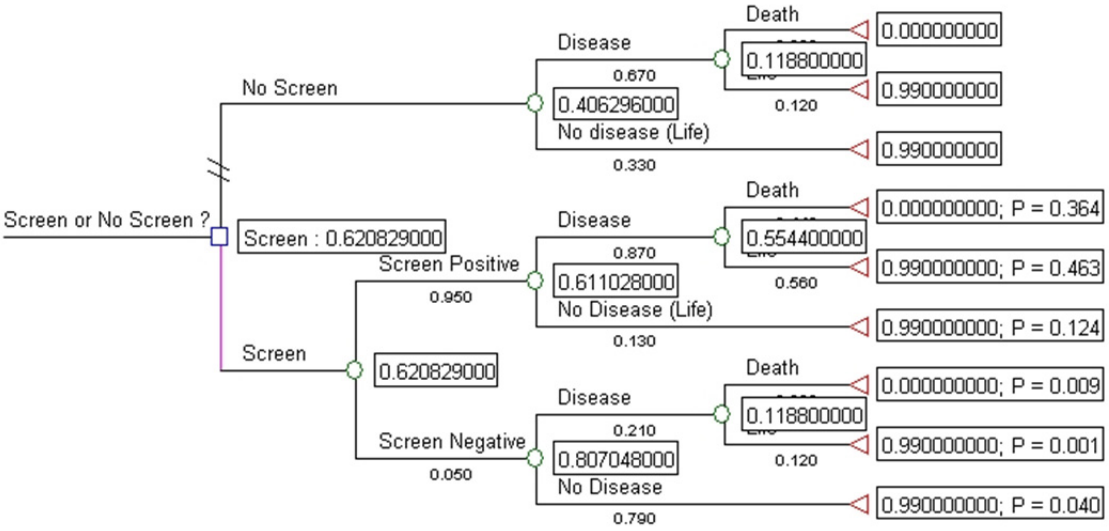



**Figure 4. Folded Back Decision Tree**

Figure 2 depicts a rolled or folded back decision tree, revealing the optimal decision that should be implemented. In this example, the expected value (EV) tells the analyst to choose to screen (EV= 0.620829000) rather than to forgo screening (EV= 0.406296000) and assume the risks. In the above tree, one is able to see the progression of expected values as the tree is being rolled back from right to left. One can also see the advantage of using computer software for this task, as it quickly can become difficult to keep account for each branch's expected value.

Notice that quality of life is the outcome in this example. The outcome could have easily been cost (calculated based on hospital length of stay) or a reduction in percent of people who develop the disease. Again, the outcome is based upon the values and objectives set by the decision maker.

Decision analysis is able to compare more than just a "yes or no" or "Screen versus No Screen" question. Indeed, as many nodes as a decision maker has alternative decision strategies can be produced. In such a case where several different strategies are being evaluated, it may be that several EVs are similar and a clear choice is not available. If such a case arises, continued analysis and research could be done to see if the EVs change. Additional outcome values may also be analyzed, such as cost. Perhaps one surgical procedure or treatment produces excellent results but is prohibitively and unrealistically expensive and another has a somewhat lower expected value and is reasonable in cost. One alternative may produce excellent results overall but is risky to a degree that makes the patient unsure. These difficulties will likely arise but, without the decision analysis, the issue may not have been evaluated. FDA also allows for creative ways to continue analysis to determine the optimal strategy.

Whatever the case, the decision-maker will now have the tools to address the risk-benefit ratios and tradeoffs associated with alternative solutions. Overall, formal decision analysis allows for clarity of thinking that rises above a physician's intuition and experience and provides a systematic approach to dealing with the uncertainty of the field of medicine. In the way that Bayes' theorem updates prior probabilities to posterior probabilities, FDA updates a clinician's initial way of thinking and clarifies the path to be chosen.

### *Sensitivity Analysis: The "Inferential Strategy" of Decision Analysis*

Sensitivity analysis is the inferential strategy of formal decision analysis (FDA). It is an evaluation technique that allows a decision-analyst to vary an estimate from its highest to lowest value, in order to find a threshold at which a preferred decision could become sub-optimal. A threshold value is a value at which two decision strategies have the same value for a variable. *Will this factor ever change my course of action?* This method tells the investigator which variables in the analysis are the driving forces and gives a quantified value for that strength. Similarly, it tells the analyst if decisions are susceptible to slight variations in value. This is a significant benefit to any decision-analyst as the problems that FDA attempts to solve are typically the "high-stakes issues." FDA is far too time-consuming and specialized to use for each clinical decision and, as such, tends to focus on crucial issues of morbidity and mortality. Sensitivity analysis is akin to confidence intervals in bivariate analyses. As our probabilities in FDA are quantified uncertainty estimates, sensitivity analysis allows a decision-analyst to see just how much an estimate can vary before a change in expected value would cause an opposing decision strategy to become optimal. Overall, sensitivity analysis provides confidence in the robustness of the decision-analytic model.

### *Cost-effectiveness Analysis*

Cost-effectiveness analysis (CEA) is a method to quantify the trade-offs between the use of limited resources and the health benefits achieved (Henderson 2009). It is an attempt to maximize health outcomes given financial limits. In this economical sense, it provides a framework for choosing treatments and procedures when unlimited resources

are not available in order to achieve the greatest level of health. CEA associates the cost of treatment strategies to a single outcome. In this way we can compare a standard of care within cardiovascular surgery to the use of a novel technology like Autologous Platelet Gel against the common outcome of reduced surgical site infections.

The effectiveness of any treatment is determined by the improvement of health that it produces. These improvements can be indicated by three kinds of measurements: indirect, intermediate, or with final measures (Henderson 2009). Indirect measures, or surrogate measures, are those such as blood pressure and cholesterol. Intermediate measures are stated in terms of events, such as heart attacks and strokes. As final outcomes are measured by economic effectiveness, we are able to state them in terms of infections avoided, events cured, years saved or quality-adjusted life years saved (Henderson 2009).

If a new treatment is discovered that is much cheaper and more effective than any other treatment available, the cost-effectiveness is easy to determine. The difficulty arises when a treatment is made available that is more expensive and more effective. (Obviously, if a treatment is more expensive and less effective, it is not considered.)

The formula for cost effectiveness is as follows:

$$CE = \frac{C_2 — C_1}{E_2 — E_1}$$

where $C_1$ and $C_2$ are the costs of treatments 1 and 2; and $E_1$ and $E_2$ are estimates of the effectiveness of each treatment.

Cost-effectiveness can be determined on either an individual or societal basis. For an individual, a clinician may wish to determine the economical effects of a preoperative test, comparing the benefits of lessened uncertainty with the increase costs, in an attempt

to eliminate the cost of the possibly unneeded test for a certain diagnosis. *Will this test change the treatment I pursue?* In the case of a societal question, a CEA may be necessary to determine the potential economical benefits of screening all men over the age of fifty for elevated PSA (prostate-specific antigen) versus screening men at age seventy. In either case, the use of Medicare/Medicaid reimbursement fees are an excellent way of standardizing the cost inputs in the calculations.

### *Limitations of Formal Decision Analysis*

Without perfect knowledge, we must make decisions every day with varying levels of uncertainty. Some decisions require very little thought, and intuition is more than enough to make an optimal decision. However, there is often the case when a rational and systematic approach to making a decision is both useful and necessary. In medicine, clinicians are presented with these types of decisions daily. What must be understood is that no amount of modeling and analysis will ever give us absolute certainty.

Formal decision analysis is not without its limitations. To begin, decision-analytic models are only as useful as the data that is put into them. As FDA relies heavily on the research of others, there is some inherent error that cannot be prevented. Judgment of the quality of the data is a requirement for any potential decision analyst. These quality judgments are a source of subjective information that are included in the analysis; while this is a strength of FDA, it can cause vulnerability. There is also the potential for manipulation of the analysis if the results do not fit the decision-maker's expectations. Furthermore, no model or decision tree will ever wholly reflect the real-world issue. This is an example of systematic error in the study design. Real-world issues are composed of

intangible complexities that skew our knowledge. Similarly, clinicians and analysts alike are working with imperfect information.

In the medical world, time is often of the essence. As such, there rarely is enough time to run further analyses, to gather more data, to generate additional alternatives, or to address concerns fully. The time to act may come before a clinician is ready to make such a decision. FDA can be a time-consuming process despite its apparent simplicity, and clinicians will rarely have time to conduct such a study before they are called to act. Thus it is essential that formal decision analyses be done on important and frequent questions so that the clinician has access to the results of this strategy instead of relying only on intuition or remembered experience. While a company might be able to conduct analyses for several months before gaining an acquisition or starting a new investment, clinicians may have only seconds to decide how to act.

### *Strengths of Formal Decision Analysis*

Despite these limitations, formal decision analysis is a way to raise our thinking above the level at which our problems were created. It can be an enlightening, though time-consuming, process, the goal of which is to lead to a rational and informed decision that has dealt with the uncertainty of the issues at hand. Its systematic approach allows clinicians to see past the obvious factors related to the problem and to notice the potential confounders that, in medicine, can quickly lead to sub-optimal decisions.

Decision modeling allows clinicians to see problems clearly, in both a logical and sequential way. The ability to see all the alternative strategies along with associated outcomes and possible confounding or risk factors is a valuable tool to physicians as they

take action. Clarity of decision rationale will aid a physician's intuition and experience, providing better-informed decisions while allowing personal flexibility.

Consider the advantages of seeking the solution to a problem in a methodological approach. Even if an expected value is not clearly the preferential and optimal strategy, the insight gained from the analysis, the determination of factors driving the issue, the ability to quantify uncertainty—all are invaluable components to making a decision that best fits the needs of an individual patient. Any process that raises a clinician's level of clarity about a decision above where he or she began will benefit the patient greatly.

Formal decision analysis provides a method for a quantitative synthesis beyond what our human brains can perform. The human brain does not excel at finding relationships between different sets of data; measuring five to six different variables for fifteen different patients and making correlations between these variables is almost impossible without a systematic or diagrammatic approach. Whether a formal process is viewed as necessary or not is for the individual to decide in the context in which the decision is to be made. Formal decision analysis does nothing more than facilitate the ability to think critically about an issue and to provide a rational decision based on a synthesis of information, while being explicit about the analysis of the methods by which one arrived at his or her decision.

# CHAPTER FIVE

## *Analysis and Results*

### *Strategic Search*

Web of Science, PubMed, ScienceDirect and UpToDate were searched methodically using all possible combinations of the following key terms: "autologous platelet gel," "platelet-rich plasma (PRP)," "surgical site infection rates," "platelet derived growth factors," "cardiovascular surgery," "autologous blood products," "sternal wound infection," "mediastinitis," and "wound healing." Clinically relevant articles, published in the English language, that concentrated on the impact of autologous platelet gel and its derivatives (PRP, platelet concentrate, etc.) on surgical wound healing and prevention of infection in the surgical sites were used. Studies determining infection rates without the use of autologous platelet gel were used to establish baseline estimates under the standard of care protocol. Studies conducted on animals were excluded as well as those not addressing risk of infection in some form.

### *The Chagrin Factor*

One of the goals of any decision analysis is to make explicit what information is known and what is left to be discovered. Decision analysis is particularly adept at exposing gaps in the literature that research has yet to fill, while providing a means to bridge such gaps as well as possible without performing large, expensive randomized control trials of medical treatments and interventions. During this analysis, it became clear that all of the data needed to perform a thorough decision analysis was not

available. While a multitude of researchers have studied surgical site infections (SSIs) in cardiovascular surgery and the subsequent impact on both patient outcomes and cost of care, few actual trials of autologous platelet gel (APG) have been conducted in cardiovascular patients: Khalafi et al. (2008) and Trowbridge et al. (2005). Indeed, even within these two studies of APG's impact on SSIs in cardiovascular surgery, there are severe limitations. Khalafi et al (2008) fails to stratify patients according to severity of infection into the deep and superficial classifications needed to conduct this decision analysis. While Trowbridge et al. does record these strata, his study is massively under-populated to provide an estimate of risk as low as those of SSI's in cardiovascular surgery, which has been estimated to be as low as 0.0051 in low-risk patients by the National Nosocomial Infection Surveillance System Report (2004). Trowbridge et al. (2005)found no deep surgical site infections in his population of 382 who received platelet gel. In medicine, there is rarely a 0% probability of an event occurring. It seems more likely that the study simply missed possible infections due to a narrow sampling of patients undergoing the APG treatment. Nevertheless, these data points are our best estimates of surgical site infections in patients undergoing coronary artery bypass grafting (CABG) procedures and are the ones used in this analysis.

This decision analysis is aimed at estimating the probability of mortality while controlling for treatment method, infection severity, and surgical revision. Neither clinical study of platelet gel followed their patient populations long enough to determine mortality rates from either the revision surgeries or from the infection classifications. Neither did the studies record the number of surgical revisions that were performed nor the number of initially superficial infections that proceeded to become deep

infections/mediastinitis. These estimates are all critical factors for this analysis. Currently, such estimates are not available in the cardiovascular literature.

### *Solution*

Without the estimates needed for the APG treatment of CABG patients, a complete analysis cannot be performed. While science generally attempts to provide an estimate for some effect, it is just as useful to identify where those estimates are lacking. The decision analysis performed here not only identifies exactly what data are missing, but attempts to give anestimate of APG's impact to prevent cascading mortality.

In order to overcome the problem of the data that does not exist in the medical literature, the model used heremade certain assumptions in the analysis. The difference between the estimate of SSIs in the two treatments being investigated (APG vs. Standard of Care (SoC)) is vast (0.004 vs 0.097). Due to this and the almost complete lack of knowledge of the side effects of APG, this decision analysis assumes that all the estimates obtained for SoC treatment protocol can be used as high estimates for what the estimates would be under a APG treatment protocol. The only probability estimates that differ within the tree between APG and SOC are the estimates of the incidence of SSIs. It is important to note that this is not a full decision model. In effect, we are conducting a sensitivity analysis on the estimate of SSIs under different treatment protocols, while holding all other estimates constant. In all actuality, this assumption is not far from the truth, as many of the estimates are likely the same for both protocols. APG produces its effects on the patients during and subsequent to the initial operation. APG application, therefore, is only driving the estimates of SSI and the severity of the infection. It has no

effect on whether a surgical revision is performed, besides the initial prevention of the SSI that would lead to the revision surgery. Nor does APG affect the mortality rate of the revision surgery. The APG treatment protocol, however, does likely effect the probability of whether a superficial infection proceeds to a deep infection.

Given these assumptions, the following decision tree branches contain the probability estimates used in this analysis.

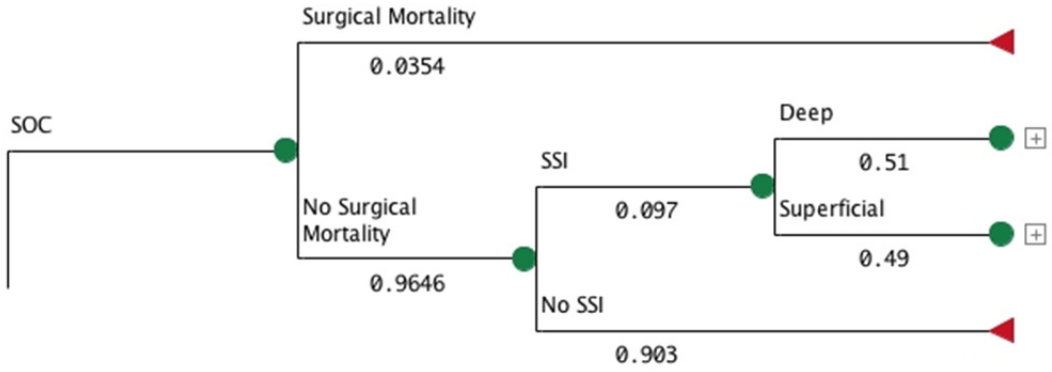



**Figure 5.SSIs under the Standard of Care treatment protocol.**

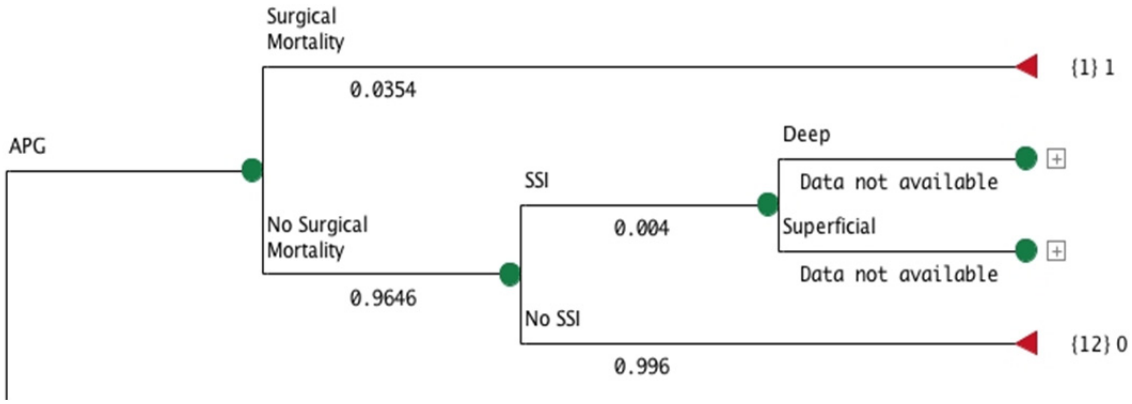



**Figure 6.SSIs under the Autologous Platelet Gel treatment protocol.**

The following tableprovides all of the probability estimates used in the final decision analytic model, along with the plausible range of these estimates that were used in our sensitivity analysis. The source for each value is listed in the far right column. Let it be noted that the estimate used in this analysis of the probability of mortality due to superficial infection is less than the probability of surgical mortality. In order to

| Node | Variable Name | Estimate | Plausible Range | Source(s) |
|---|---|---|---|---|
| 1.G | Surgical Mortality - Gel | 0.0354 | 0.001-0.1 | Rathore 2003 |
| 1.S | Surgical Mortality - SoC | 0.0354 | 0.001-0.1 | Rathore 2003 |
| 2.G | Surgical Site Infections - Gel | 0.004 | 0.001-0.99 | Trowbridge 2005 |
| 2.S | Surgical Site Infections - SoC | 0.097 | 0.001-0.99 | Ridderstolpe 2008 |
| 3.G | Deep Infections - Gel | 0.51 | 0.001-0.99 | NNIS 2004 |
| 3.S | Deep Infections - SoC | 0.51 | 0.001-0.99 | NNIS 2004 |
| 4.G | Proceeds to Deep Infection - Gel | 0.1202749 | 0.001-0.5 | Ridderstolpe 2008 |
| 4.S | Proceeds to Deep Infection - SoC | 0.1202749 | 0.001-0.5 | Ridderstolpe 2009 |
| 5.G | Surgical Revision - Gel | 0.4536083 | 0.001-0.99 | Ridderstolpe 2010 |
| 5.S | Surgical Revision - SoC | 0.4536083 | 0.001-0.99 | Ridderstolpe 2011 |
| 6.G | Mortality from Revision - Gel | 0.109 | 0.001-0.99 | Borger 1998 |
| 6.S | Mortality from Revision - SoC | 0.109 | 0.001-0.99 | Borger 1998 |
| 7.G | Mortality from Deep Infection - Gel | 0.22 | 0.001-0.99 | Hollenbeak 2000 |
| 7.S | Mortality from Deep Infection - SoC | 0.22 | 0.001-0.99 | Hollenbeak 2000 |
| 8.G | Mortality from Superficial Infection - Gel | 0.021 | 0.001-0.5 | Ridderstolpe 2008 |
| 8.S | Mortality from Superficial Infection - SoC | 0.021 | 0.001-0.5 | Ridderstolpe 2008 |

**Table 5. Probability estimates used in decision tree model.**

understand this, one must understand that a superficial infection is just that, superficial. While all infections are important to manage vigilantly, superficial infections are highly treatable. Superficial infections also are much more easily diagnosed than deep infections due to their high level of visibility. It is likely, therefore, that patients who develop superficial infections are likely to be given a very high level of care in order to prevent the death of the patient or a more serious infection proceeding from the initial superficial one. Due to this, there is a smaller probability of death for patients with a superficial infection than the estimate for surgical mortality—which often has to do with error in the operating room or differences in individual patients.

Figures 7-10 contain the entire decision tree used in this model with variable names in place of the probability estimates. Figure 7 is the entire tree.Figure 8 &9 are each half of the tree in order to aid visualization. Figure 10 is the tree folded back. The node numbers in the above chart correspond to the placement of the nodes in the tree. Those numbers with a "G" following the number are associated with the APG treatment, while those followed by an "S" are part of the standard of care treatment.

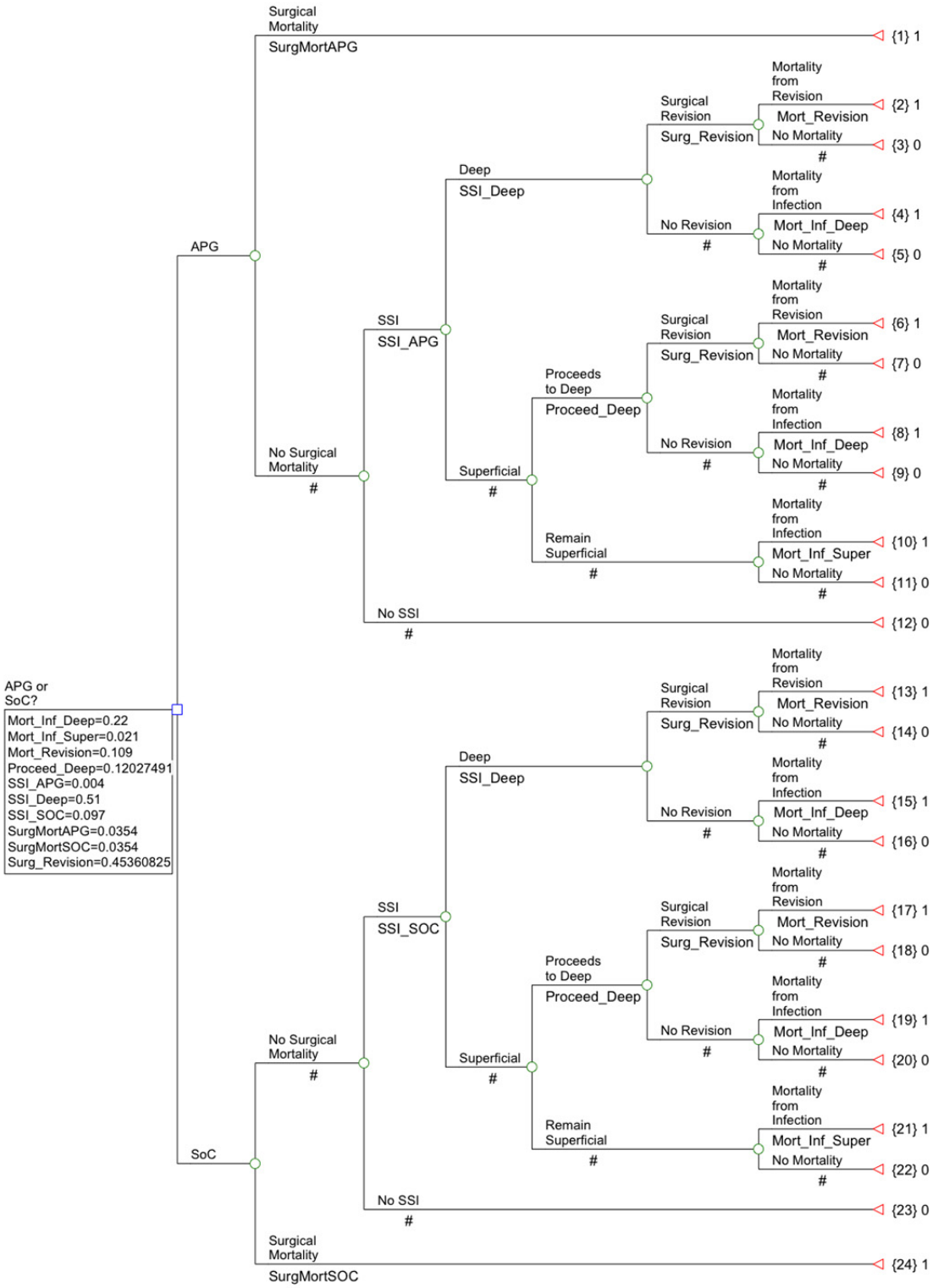



**Figure 7. Entire Decision Tree**

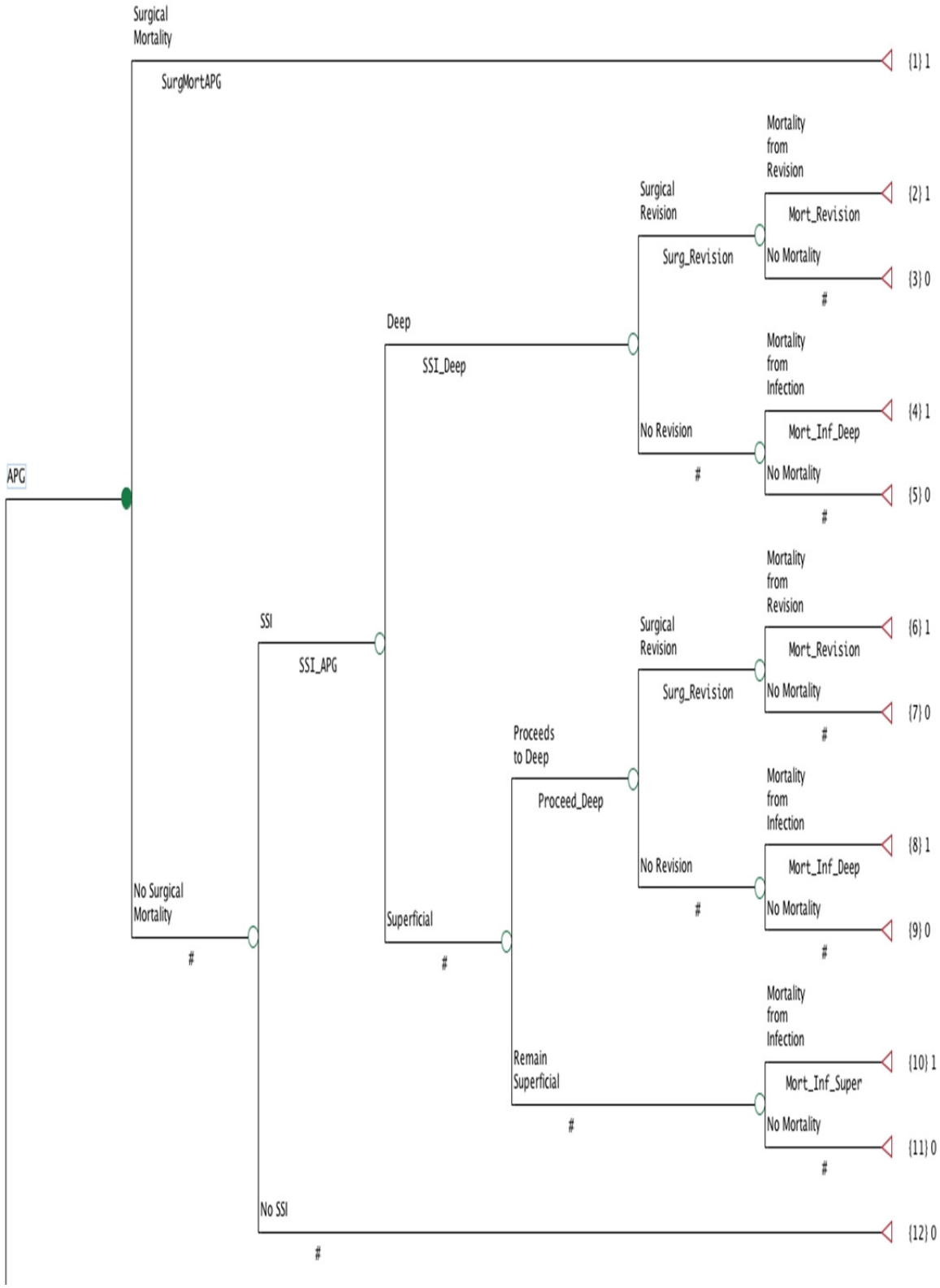



**Figure 8. APG branch of Decision Tree**

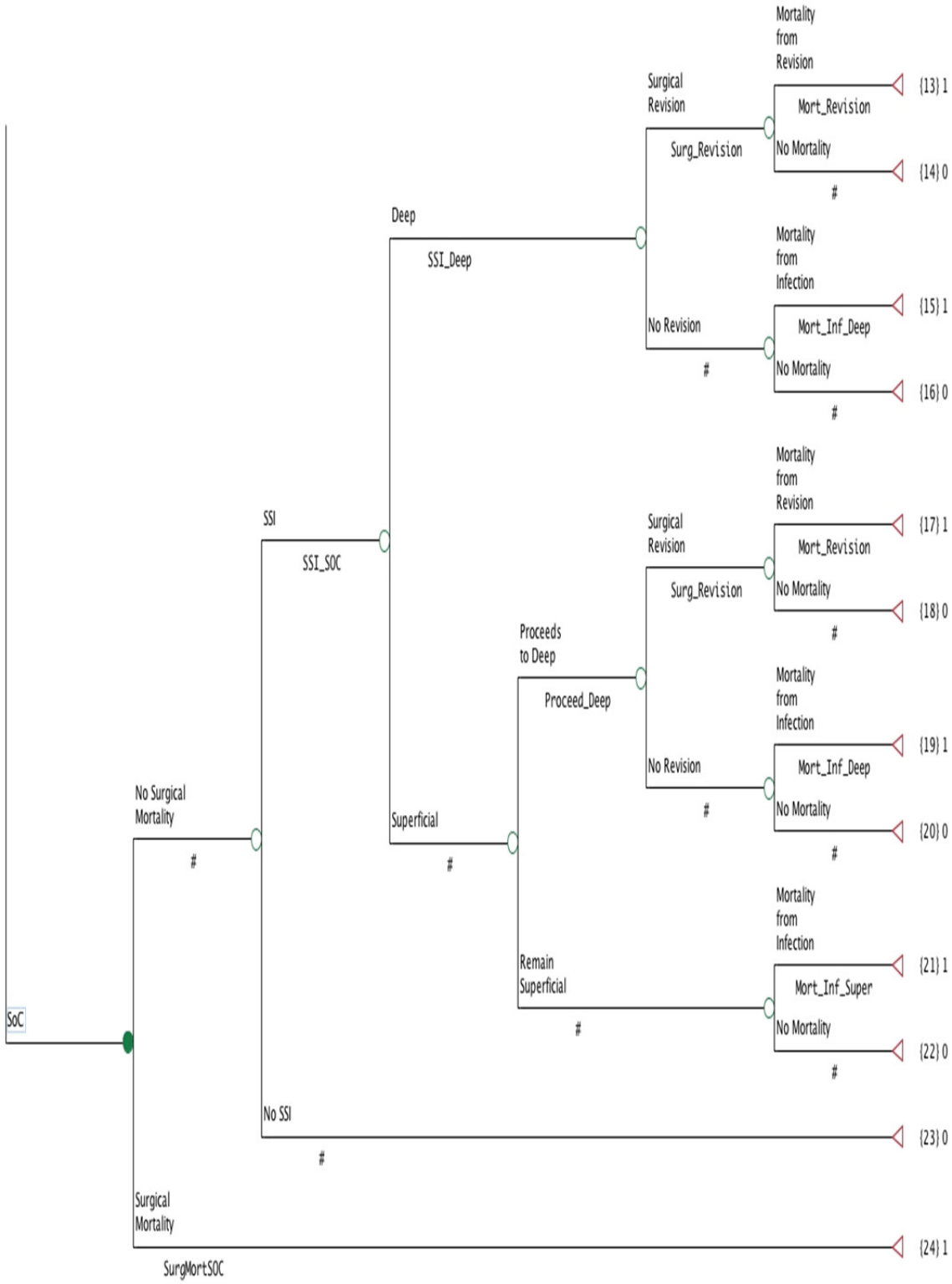



**Figure 9. SOC branch of Decision Tree**

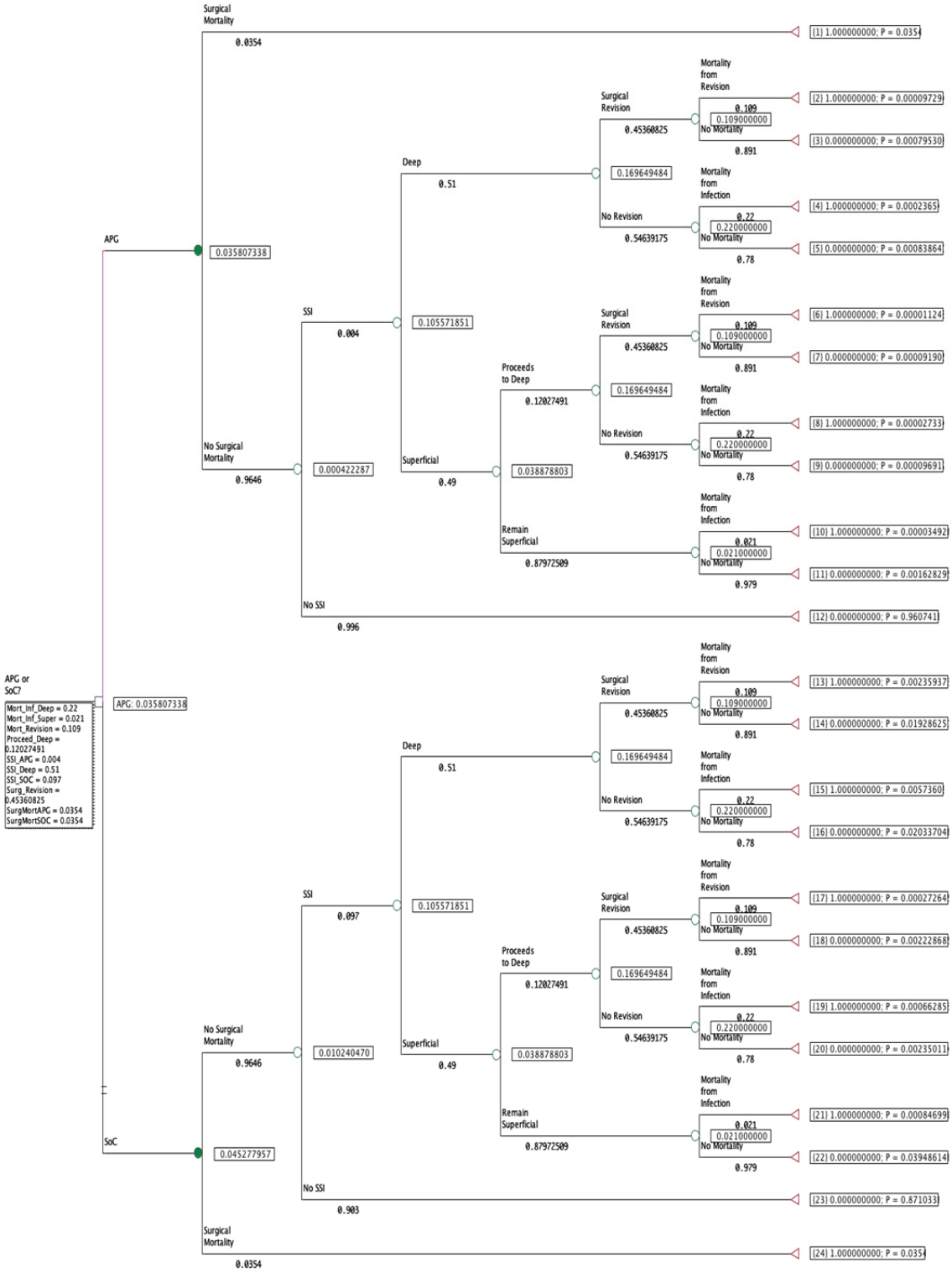



**Figure 10. Decision Tree folded back**

## *Results*

### *Decision Tree*

Folding back this (incomplete) decision tree with the known estimates of surgical site infections, under both the APG and SoC treatment protocols, produced the expected values of treating coronary artery bypass grafting patients with each protocol in terms of mortality. The following table illustrates the results of the analysis.

| Treatment | Total Mortality |
|---|---|
| Autologous Platelet Gel | 0.0358 |
| Standard of Care | 0.0453 |

**Table 6. Expected values of different treatment protocols compared to estimates of surgical mortality.**

As Figure 10 makes apparent, autologous platelet gel, on average, reduces the mortality of patients undergoing CABG procedures in comparison to SOC. This calculated expected value is driven entirely by the estimates for the incidence of SSIs, as all other estimates in the model are held constant between APG and the SOC. For those patients who do not initially experience surgical mortality, the probability of mortality in the subsequent twelve months was 0.000422287 for APG patients and 0.010240472 for SOC patients. The overall mortality (both surgical and subsequent) was 0.035807339 for APG patients and 0.045277959 for SOC patients.

These are crude, but fair, estimates of the expected value of mortality due to APG. If anything, the expected value of mortality following the use of APG may be inflated due to the use of standard of care estimates for mortality in the tree.

*Sensitivity Analysis*

Sensitivity analyses were conducted on each of the variables in the model in order to determine the robustness of the final decision. The following table lists each of the variables, their best current estimates, the range in which they were tested, any thresholds that were obtained, and if these thresholds are clinically plausible and relevant.

| Node | Variable Name | Estimate | Low | High | Threshold | Clinically Plausible |
|---|---|---|---|---|---|---|
| 1.G | Surgical Mortality - Gel | 0.0354 | 0.001 | 0.1 | 0.0449 | No |
| 1.S | Surgical Mortality - SoC | 0.0354 | 0.001 | 0.1 | 0.0258 | No |
| 2.G | Surgical Site Infections - Gel | 0.004 | 0.001 | 0.99 | 0.097 | No |
| 2.S | Surgical Site Infections - SoC | 0.097 | 0.001 | 0.99 | 0.004 | No |
| 3.G | Deep Infections - Gel | 0.51 | 0.001 | 0.99 | None | - |
| 3.S | Deep Infections - SoC | 0.51 | 0.001 | 0.99 | None | - |
| 4.G | Proceeds to Deep Infection - Gel | 0.12027491 | 0.001 | 0.5 | None | - |
| 4.S | Proceeds to Deep Infection - SoC | 0.12027491 | 0.001 | 0.5 | None | - |
| 5.G | Surgical Revision - Gel | 0.45360825 | 0.001 | 0.99 | None | - |
| 5.S | Surgical Revision - SoC | 0.45360825 | 0.001 | 0.99 | None | - |
| 6.G | Mortality from Revision - Gel | 0.109 | 0.001 | 0.99 | None | - |
| 6.S | Mortality from Revision - SoC | 0.109 | 0.001 | 0.99 | None | - |
| 7.G | Mortality from Deep Infection - Gel | 0.22 | 0.001 | 0.99 | None | - |
| 7.S | Mortality from Deep Infection - SoC | 0.22 | 0.001 | 0.99 | None | - |
| 8.G | Mortality from Superficial Infection - Gel | 0.021 | 0.001 | 0.5 | None | - |
| 8.S | Mortality from Superficial Infection - SoC | 0.021 | 0.001 | 0.5 | None | - |

**Table 7. Sensitivity analyses: ranges, thresholds, and plausibility**

Sensitivity analyses performed on each of variables in the decision model found four threshold values. None of these thresholds, however, are clinically plausible. For example, surgical mortality for both APG and SOC were shown to have thresholds. Nevertheless, it is not plausible that surgical mortality would differ between the two

treatment groups since surgical mortality is primarily a measure of the number of deaths occurring from anesthesia and APG has no effect on this type of mortality.

Threshold values were found for incidence of surgical site infections under APG and the SOC treatments, as shown in Figures 11-12.

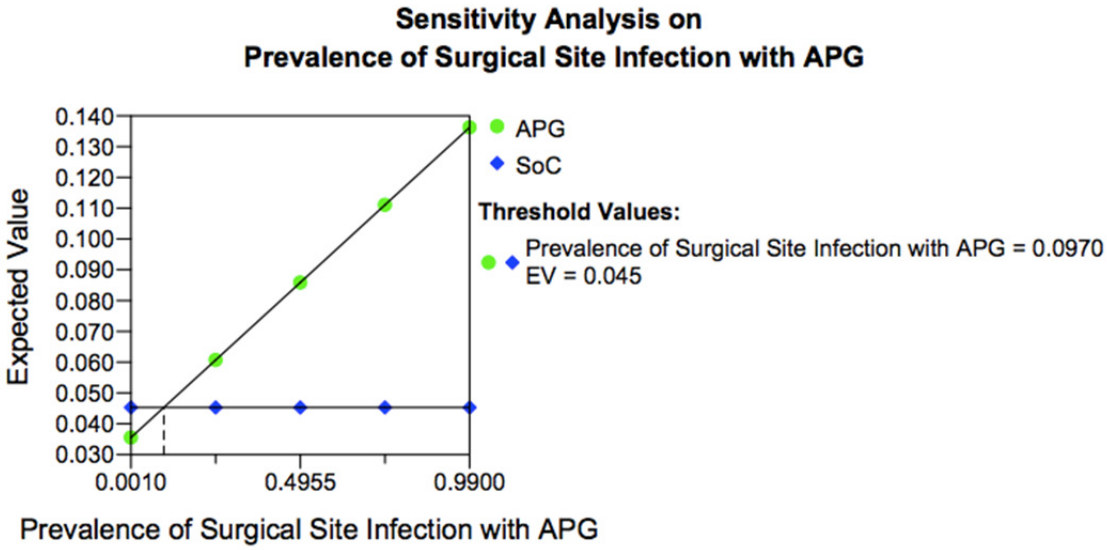



**Figure 11. Sensitivity analysis on the prevalence of surgical site infection under APG treatment**

The threshold value for the cumulative incidence of SSIs under APG treatment was 0.0970 while holding the expected value of SOC constant. This shows that when the incidence of SSIs that occur under APG rises to 9.7% or higher it becomes more beneficial to not use APG. This threshold value is actually the estimate of SSIs under the SOC. The intuitive meaning of this analysis is that if APG were to only reduce the incidence of SSIs to 9.7%, then there is no reason to use it along with the SOC—if APG is not better than current prophylaxis measures then there is no point in its use.

Nevertheless, this threshold holds no clinical plausibility as no study that has shown APG to be beneficial has estimated its effect to be no better than the SOC. The real insight that this sensitivity analysis provides, however, is that it gives face validity to

the tree. Because the trade-off relationship between the incidence of SSIs under APG and SOC shown in this analysis, the tree is proven to be running correctly.

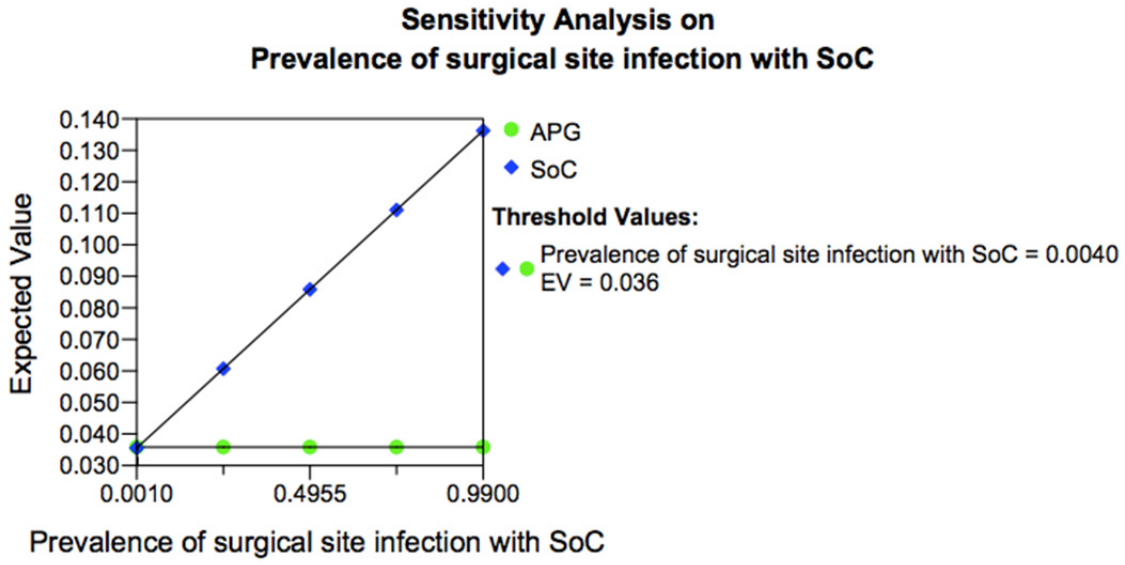



**Figure 12. Prevalence of SSI under the SOC**

A threshold was also found in the sensitivity analysis of the prevalence of SSI with the SOC. If the SOC ever became so effective as to only allow four SSIs in one thousand patients (0.004) then APG would no longer need to be utilized in order to reduce the total expected mortality. This threshold is not clinically plausible, however, as current estimates show that as many as 9.7% of patients develop SSIs following CABG when treated with the SOC. Again, this sensitivity analysis proves the face validity of the tree.

No other variables in this analysis were shown to have threshold values. Figures 13-15 are examples of these analyses, each providing validity to the decision that the use of APG reduces overall expected mortality from the cascading effects of SSIs.

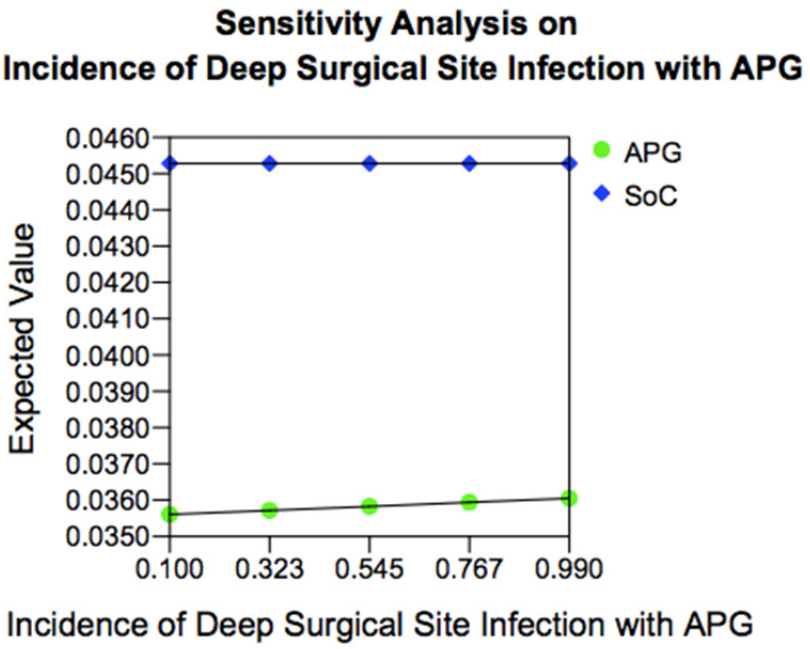



**Figure 13 Sensitivity Analysis of the incidence of deep SSI with APG**

Figure 13 shows that even if all SSIs that occur following CABG are considered deep infection APG will still reduce the expected mortality far more than the current SOC.

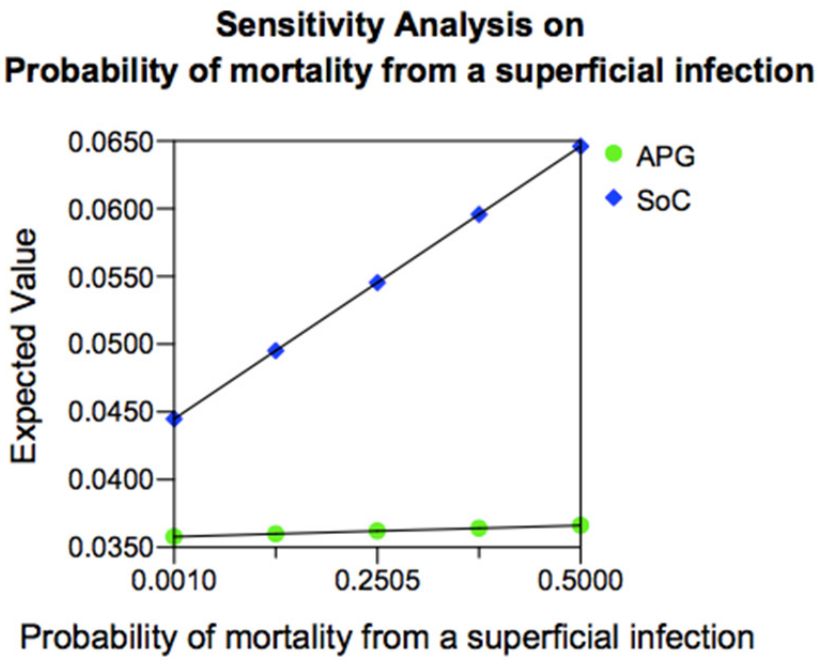



**Figure 14. Sensitivity analysis on the probability of mortality from superficial SSIs**

Figure 14 shows that even if as many as 50% of superificalSSIs result in death, APG produces a better overall expected mortality.

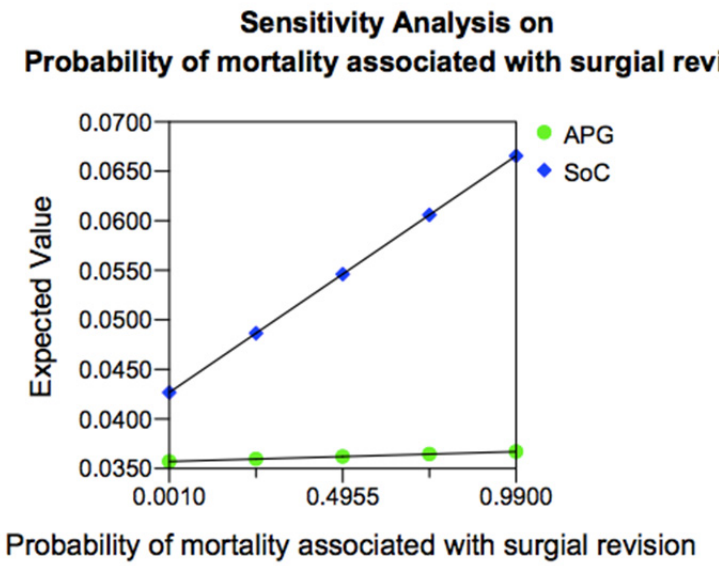



**Figure 15. Sensitivity Analysis on the probability of mortlaity associated with surgical revision**

Figure 15 shows that even if all surgical revisions of SSIs result in the death of the patient, APG continues to produce the best overall expected mortality. These results are likely driven by the low initial incidence of SSIs with APG.

*Summary*

From this analysis, a calculated expected value of APG in terms of mortality was obtained. The different rates in mortality between APG and SOC could have far-reaching effects. Treatment of patients with autologous platelet gel result in expected mortality very close (0.0008) to that of surgical mortality from CABG. Standard of care, while clearly working to prevent infections, is shown to be less effective in terms of mortality. By making the APG the new SOC, there could be an almost 2% prevention of mortalities associated with CABG surgery and SSIs. When this estimate is taken along with the fact that almost 500,000 of these operations occur annually in the United States, almost

10,000 lives could be saved each year by using APG along with the current standards of care—according to the estimates provided here.

It cannot be stressed enough that many assumptions, though certainly plausible, were incorporated into this decision analysis. By using the same set of data for all probability estimates except for SSIs, we incorporate some error into the model. These estimates, however, serve as upper bounds for future data concerning APG treatment. By making these assumptions, we are conceding that even an inflated estimate of mortality under APG treatment will still result in a significant reduction in the expected mortality that will occur.

To be equally stressed is that this is not a balanced or complete decision tree. Most decision trees consist of some equilibrium of pros and cons for each treatment being evaluated. There are many advantages to platelet gel, leading to a much lower estimate of SSIs with its use. APG, however, currently has no known side-effects besides extremely rare allergic reactions that can be prevented with a specific preparation of APG. Further research on APG is needed. Indeed, one goal of this decision tree is to encourage such research. One area that may serve some of these purposes would be collection of accurate cost data concerning SSI, APG and CABG surgery so that cost efficiency can be calculated. Another possibility is to incorporate quality of life into the model, as this is likely to differ between patients with no infection compared to a patient with mediastinitis. Due to these issues, we cannot currently build a balanced decision tree. This tree simply serves to estimate the cascading mortality effects of SSI under both APG and SOC treatment protocols with the results being expressed in expected mortality, with

the hope that future research will be conducted in order to better model this real-world and complex problem.

# CHAPTER SIX

## Discussion

### *Strengths*

There have been no previous estimates given for the expected mortality resulting from treating coronary artery bypass grafting (CABG) patients with autologous platelet gel (APG). This model is the first that undertakes such a task. Once empirical mortality data are available it will take minimal effort to calculate the cost-effectiveness of APG. The cost of APG itself is a strength, as it is slight, especially when compared to the overall cost of CABG surgery. The next step of a complete analysis will be to quantify how effective APG is in terms of the societal costs of mortality and the overall costs of the use of this intervention.

The purpose of this analysis was to determine the cascading effects of surgical site infections (SSI) on mortality and estimate how those effects can be mitigated through use of APG. Moreover, as with any decision analysis, there was both a goal and a requirement to determine what information exists and to make such information explicit; by doing so, this study made explicit where the data are lacking. This decision analysis performed the second goal, while also providing a good estimate for the first. As such, it meets both of its goals.

### *Limitations*

In order for this analysis, in its current state, to produce the estimates that it does, assumptions were made about some of the data that now are known to be missing. All of

the estimates used in this analysis concerning APG, except for the probability estimate of the incidence of SSI under the APG protocol, have been assumed to be the same as the estimates from the standard of care (SOC) data for the same factors. Due to this, the estimates presented are crude approximations of what the actual expected total mortality associated with SSI under a APG prevention protocol. In fact, this estimate is likely to be inflated since APG is known to lower drastically the risk of SSI following surgery. APG may, in fact, be much better than this analysis shows. There is the chance, however, that it does not perform as well as hoped. This cannot be determined until further research of APG use in CABG surgery is conducted and analyzed.

Again, it is important to note that this decision tree was not balanced as it did not include any down side for either the SOC or APG. Because of this, we are not giving autologous platelet gel its hardest test. This is due in part to the fact that APG is a relatively new innovation that has only been recently applied to cardiovascular surgery. Its use is also very limited, and its efficacy tested even more rarely. Any negative effects, though doubtful that they exist, have not been made known. There are very few medical interventions that produce no side-effects whatsoever and until we fully understand how APG works, there is a potential missing factor in this analysis.

### *Future Research*

In future research, this model can only be enhanced. It is likely in future research that the probability of SSI will continue to be the driving factor, as this is the variable on which APG has the greatest and most direct effect. As the estimates for the proportion of deep and superficial infections, the proportion of superficial infections that proceed to

deep infections, and the mortality rates due to infections are studied and revised, a more accurate expected value will be obtained. With that being said, the current estimate is more than enough of a reason to pursue further research into the novel infection prevention technique of autologous platelet gel.

### *Conclusions*

A review of the cardiovascular surgery literature shows that surgical site infections occur in the U.S. at a rate between 0.51% and 20% (NNIS report 2004). Due to new legislation that is being put in place, Centers for Medicare and Medicaid Services will no longer reimburse hospitals for treatment of such infections. It is vital, therefore, for a way to be established that continues to reduce the incidence of SSIs.

Autologous platelet gel has presented itself in a variety of ways as a potential solution to this problem of surgery-associated infections. Its uses seem obvious and it has application not only in the field of cardiovascular surgery but far beyond as well. Its efficacy has been shownto reduce the cumulative incidence of SSIs to a mere 0.04% (Trowbridge 2005). Nonetheless, its adoption by surgeons has been slow, potentially resulting in the loss of hundreds, if not thousands, of livesof CABG patients each year.

With all that we know of APG, there is much that is still being determined. Taking this model as an example, we can state explicitly what remains unknown:

1) It remains unclear how APG affects the distribution of SSI between severity classifications (deep and superficial). It is likely that this factor may be a driving force for any decision tree modeling this problem.

2) Overall, we do not know explicitly how many superficial infections proceed to deep infections. This may be a rare occurrence, although it is known that many deep infections are occult. Data are needed to determine the probability of this occurring.
3) Nowhere in the cardiovascular literature concerning APG is surgical revision of infections quantified. Additionally, it is unclear who exactly is given such a revision.
4) The studies that were conducted to determine APG's efficacy only looked at the incidence of infection rather than continuing in time to determine mortality. The following mortality rates are needed to further evaluate APG:
    a. The mortality rate of patients undergoing surgical revision;
    b. The mortality rate of patients who have developed superficial infections; and,
    c. The mortality rate of patients who have developed deep infections.

This decision analytical model quantifies the expected mortality of patients undergoing CABG by using previous studies of both APG and the current SOC. Despite the assumptions that have been made, APG was shown to reduce significantly the cumulative incidence of mortality of these patients. It is the hope of this study that more research will be funded and conducted in order to continue to evaluate this method of preventing surgical site infections so that we may give autologous platelet gel its hardest test.

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