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Hawai'i's Role to Increase Public Participation in Health Research

Marjorie K. Mau MD, MS; and Douglas Yee
(on behalf of all Council of Public Representatives members and alumni)

Introduction

The idea of public participation in the biomedical, behavioral and clinical research enterprise has gained new recognition throughout the United States and is most visibly evident at the National Institutes of Health (NIH) through the Council of Public Representatives (COPR). The COPR has been in existence since 1999 and was established to serve as an advisory council to the Director of NIH on the public's perspective on health research and its contributions to improving the public's health. As such, the COPR has had a significant role in advising the Director of NIH, Dr. Elias Zerhouni, on engaging the public and to develop and foster the public's trust in NIH's mission and vision. The COPR is comprised of a diverse group of individuals from across the United States and its affiliated territories that are charged with bringing to light the perspectives and concerns from this diverse public to bear on NIH's research enterprise.

The State of Hawai'i is fortunate to have had two members appointed to the COPR, Mr. Douglas Yee (1999-2003) and Dr. Marjorie Mau (2005-2008). Both Hawai'i residents have served on the COPR under the directorship of Dr. Elias Zerhouni, who is credited with transforming NIH's long term mission into a stronger integration of its 27 Institutes and Centers via the NIH Roadmap. Hawai'i representation on COPR allowed for heightened awareness of the public health and scientific research needs of the Pacific region on a national level. It is this unique contribution to NIH and to the relevant needs of the collective communities in Hawai'i and the Pacific region that provided insight to many NIH leaders and policy makers. Over time, the changes at NIH that have included COPR's input and recommendations have provided for a new concept of how public participation is not only relevant but necessary to advance scientific research to eliminate health disparities and other emerging health issues in the native populations of the Pacific region.

The purpose of this article is to share the collective wisdom of the Council of Public Representatives and to stimulate others in the community to be participatory in the United State's premier health research institution, the National Institutes of Health.

The Future is Now: Enhancing the Role of the Public in Medical Research

The National Institutes of Health is a demonstrated leader of medical research in the United States. Over the past half-century, the NIH's sustained efforts have produced remarkable gains for Americans. This publicly funded research has led to significant declines in heart disease, reduced incidence of many types of cancer, and numerous advances to combat infectious diseases like HIV/AIDS, tuberculosis, and many others. Coupled with better living conditions, education, and nutritional quality, along with improved hygiene, these research activities have nearly doubled the human lifespan since the turn of the 20th century.

This success, however, has brought challenges. With the precipitous drop in acute disease has come a rise in chronic, long-term illness that strains the populace and economy. Even more troubling is that the nation's chronic disease burden is not uniformly distributed, and health disparities remain a vexing problem. The entire health care community recognizes that new and continued efforts are needed to correct this imbalance. Now, more than ever, it is important that the public play an active role in medical research. At this time, stronger, not weaker connections between the public and medical research are vital to progress.

COPR: NIH's Public Voice

The NIH Council of Public Representatives (COPR) was established following the 1998 Institute of Medicine report *Scientific Opportunities and Public Needs*.[1] COPR was created to provide a vehicle for greater interaction among the NIH, its leadership, and the general public. As America's voice to and from the NIH, COPR members play a key role in engaging the public in research.

COPR is a diverse group of 25 people from across the country who have been chosen, through an open application process, to represent the public. They are patients, family members of patients, science and health professionals, communicators, and educators. Representatives advise the NIH Director on an ongoing basis by bringing important matters of public interest to NIH leadership, helping to increase public participation in NIH activities and initiatives, and working to advance public understanding of the NIH and its programs.

The COPR is attuned to current realities: escalating health care costs, an aging population, and many other complexities of modern society that create challenges to preserving the health of the nation. Dr. Elias Zerhouni, Director of the NIH, has posited that a more *"predictive, personalized,* and *preemptive"* form of medicine offers the best chance to alter the current practice of intervening very late in the course of a disease, when it is most expensive in financial and human costs. COPR endorsed this approach, but suggested a fourth "p:" *participatory*. Dr. Zerhouni has incorporated this concept into his vision for transforming medicine.

Realizing this vision calls for a coordinated effort from the government, the scientific community, the private sector, and the American public. To reach the goal of personalized, pre-emptive health,

Table 1.— Examples of Successful Research Dissemination		
Program	**Features**	**More Information**
Be Smart About Your Heart	NIH-ADA partnership promotes heart health for diabetics	www.ndep.nih.gov
Back to Sleep	Health campaign reduced sudden-infant deaths by more than 50 percent	www.nichd.nih.gov/sids/
CityLab Mobile Bus	Engages 7,000 students/year in hands-on biomedical research	www.bumc.bu.edu/citylab
NIDA Community-Based Centers	Educates new doctors to identify and treat addiction and substance abuse	www.drugabuse.gov/
Heart Truth	Health awareness campaign created the "Red Dress" national symbol	www.nhlbi.nih.gov/health/hearttruth/

Table 2.— Examples of Community Engagement		
Program	**Features**	**More Information**
Healthy Vision Community Award Program	Gives seed money for community-based health education programs	www.healthyvision2010.org/
NIAMS Health Partnership Program	Fully engages community in rheumatology research planning and implementation	www.niams.nih.gov/hi/outreach/hpp/chcfact.htm
African American Hereditary Prostate Cancer Study Network	Involves collaborative recruitment centers in seven major urban areas	www.genome.gov/10002040
HIV Vaccination Trial Network	International collaboration of scientists and educators searching for an effective and safe HIV vaccine	www.hvtn.org/
We Can!	Partnership of 154 community sites helping children achieve a healthy weight	wecan.nhlbi.nih.gov
Example of Community Engagement in Hawai'i		
Center of Native and Pacific Health Disparities Research at UH-JABSOM	Partnership of 22 community organizations at 50 sites (Ulu Network) throughout the State of Hawaii, new partnerships (2007) with Anchorage, AK and Los Angeles, CA to conduct research studies, research training and community dissemination aimed at eliminating health disparities in Native Hawaiian, Alaska Native, Pacific Islander and other health disparate communities in the Pacific.	www.hawaiiexportcenter.hawaii.edu

quicker, more reliable ways are needed for discoveries to become practical and effective prevention strategies and treatments in children and adults. For that, the role of the public in medical research is paramount. Better understanding and increased involvement also enhances the public's trust in research.

However, effective public involvement in research is neither simple nor unidirectional. It is long-term and sometimes difficult, and it thrives on many ambassadors to advance progress and sustain momentum. COPR endorses this position and highly values public involvement in research. Their current efforts aim to increase awareness and promote action.

Considerations for advancing the role of the public in research

- *Establish baseline of NIH community participation*
- *Educate researchers about potential roles for the public*
- *Provide guidance to applicants/grantees, enhance training programs*
- *Identify and disseminate best practices of community engagement*
- *Bridge gaps between organizations and research institutions*
- *Build partnerships that expand community involvement in research*

Many Roles for the Public in Research

Public engagement in the research process can lead to beneficial outcomes in several ways. For one, an enhanced dialogue between patients, health-care providers, and researchers can help enable people to take charge of their own health: preventing illness, preserving quality of life, and conserving costs. Second, public involvement at many levels provides underrepresented populations a voice to inform priority-setting endeavors relevant to the broader health research agenda. Third, the public can enrich scientific endeavors by helping to bridge disciplines that do not typically interact and identify cultural and environmental variables that impact research results. Finally, public involvement in research is a critical link in the dissemination of research findings to policy and practice.

Because of creative and effective NIH-sponsored educational campaigns and outreach programs on health trends and diseases, Americans are better informed and empowered to make healthy choices. Successful integration of these programs into communities is a direct result of sustained public involvement (Table 1). Yet, more of these models of success are needed across a broader and more diverse American population to effectively eliminate health disparities.

As a society, Americans cannot rely on a simplistic strategy that assumes that if you tell people something is good for them, they will do it. Public engagement is more than "educating the public", it is also empowering. Complex arrays of cultural and other influences contribute to views about research that go beyond understanding science. Public trust in research depends not only upon knowledge, but also on value systems.

Authentic public engagement requires a solid foundation of public trust, and it needs to be earned and nurtured. Any erosion of public trust can have untoward, multidimensional consequences that impact not only the advancement of health, but also society at large.

With careful planning, public involvement in research can be very successful (Table 2). One common thread for success is open communication between researchers, health care providers, patients, and public participants.

A Voice for Change

The COPR believes a fundamental change in the current medical research paradigm is needed to more firmly conceptualize the public as a true partner in the continuum of research. The benefits of broader community involvement can be far-reaching, providing opportunities for co-leadership, greater availability of resources, enhancement of recruitment, and the development of culturally relevant research instruments. Over time, effective public-researcher partnerships can promote and sustain increased understanding about the context of science in society for all parties.

To accomplish more widespread knowledge and endorsement of increased public participation in research, it is important to develop robust lines of communication and keep them open. The cultural shift promoting greater data sharing and openness currently underway within the scientific community may facilitate progress, although public wariness about sharing personal information is a persistent concern requiring attention. Efforts to identify the benefits, costs, goals, and outcomes of research help non-scientists develop an awareness of and appreciation for medical studies. Thoughtful and transparent communication can also address misconceptions about research.

The scientific benefits of participatory research should be communicated widely. For example, with increased knowledge of culturally appropriate methodologies, scientific investigators may be able to increase the validity of their findings.

The COPR and others recognize that changes cannot take place overnight and that not all research studies will benefit to the same degree from active public engagement. However, an effective framework for change must be multifaceted and should target the public, government agencies, and academia. Now is the time for a philosophical paradigm shift in research towards a larger role for the public.

Academia is the linchpin of this framework. The scientific community must evolve to understand and appreciate the added value of a broader role of the public in medical research. This can only occur if institutional leadership legitimizes and rewards community engagement efforts conducted by investigators.

As a worldwide scientific leader, the NIH plays a pivotal role: any steps the agency takes toward encouraging public engagement will be widely noticed. Providing incentives and developing training programs that encourage clinical researchers to involve communities will send a strong message on the importance of this practice within the research enterprise. Engaging communities takes time and resources, and researchers need assurance that their activities in this realm will be appreciated within the current peer review and funding processes.

Increasing researcher appreciation for public/community engagement

- *Offer incentives*
- *Identify evidence-based practices to involve communities*
- *Develop ways to measure efficacy of public participation*
- *Build effective collaborations and partnerships*
- *Communicate benefits of community involvement in research*
- *Increase public base of support for research*
- *Create tools to educate researchers on community involvement/engagement*
- *Provide guidance to applicants*
- *Promote stakeholder outreach: professional organizations, academic leadership, study sections, Institutional Review Boards*

The Future is Now

The 21st century is an exciting time for medical research–one that holds the promise of achieving predictive, personalized, pre-emptive—and participatory health. Increased understanding of complex interactions between the human body, the environment, and sociological influences will identify strategies to detect disease early and help diminish health disparities. Finding genetic factors that raise chronic disease risk from exposure to environmental toxins offers an opportunity to predict disease before it strikes. In addition, a greater understanding of genetics and of behavioral influences, like stress, has the potential to further improve quality of life.

Yet research does not automatically find its way to application. Several new NIH programs that facilitate participatory research are a good start. The NIH Roadmap for Medical Research, through the Clinical and Translational Science Award initiative, encourages medical schools to team with community-based physicians.[2] Information technology tools currently under development promise to connect researchers, healthcare providers, and patients in unprecedented, efficient ways. It is hoped that these opportunities for connectedness will be endorsed, encouraged, and widely adopted.

Is there a meaningful role for the public in biomedical and behavioral research? As the public voice of the NIH, the COPR offers a resounding "yes." The public and research communities will be vital partners in 21st century medicine and health. As patients, scientists, decision-makers—we are all stakeholders in our health. It is important that we get involved and work together.

http://getinvolved.nih.gov/

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References

1. Institute of Medicine report, Scientific Opportunities and Public Needs. *National Academies Press* 1998. Accessed 5/10/07 at: http://books.nap.edu/html/nih/
2. Zerhouni EA. Translational Research: Moving Discovery to Practice. *Clin Pharmacol Ther* 2007. 81:126–8

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Circulating Blood Volume Measurements Correlate Poorly with Pulmonary Artery Catheter Measurements

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Abstract

Background: *Determination of the intravascular volume status of a critically ill surgical patient is paramount for appropriate fluid and cardiovascular management. Many clinical parameters have been utilized to estimate intravascular volume but none are precise indicators of circulating blood volume. The purpose of this observational pilot study was to compare measured blood volume with hemodynamic parameters obtained from the pulmonary artery catheter and to determine if incorporation of these measurements altered treatment decisions in critically ill surgical patients.*

Methods: *Blood volume measurements were prospectively obtained in twenty surgical intensive care unit patients with a pulmonary artery catheter when intravascular volume status was deemed uncertain by traditional clinical parameters.*

Results: *There was a statistically significant, but weak, correlation between blood volume results and pulmonary artery occlusion pressure, but no correlation with central venous pressure, cardiac index, and stroke volume index. Blood volume information altered treatment in 21% of instances, and 5 of these 6 patients demonstrated a favorable clinical response.*

Conclusions: *Circulating blood volume measurements may be useful in critically ill surgical patients when clinical appraisal of intravascular volume is uncertain. This remains to be validated in a larger, prospective randomized trial.*

Introduction

The ability to directly measure circulating blood volume (BV) has been available for more than 60 years but has not been widely utilized in daily clinical practice due to cumbersome methodology.[1] Historically, many techniques have been employed to measure BV using indicator dilution techniques with radio-labeled substances (albumin, autologous red blood cells), or fluorescent-labeled-colloids (hetastarch, dextran, indocyanine green).[1-9] With technological improvements, a semi-automated analyzer (BVA-100, Daxor Corporation, Inc., New York, NY) became available and was approved in 1998 by the Food and Drug Administration. The I^{131} radio-labeled albumin technique used by this apparatus is the recommended assay for quantitative assessment of plasma volume (PV) by the International Committee for Standardization in Haematology due to its accuracy and reproducibility.[9] This technology has been validated and has made measurement of BV feasible at the bedside due to more rapid turnaround time for results. In parallel, there has been renewed interest in the utility of BV measurements in many clinical settings, such as in the treatment of hypertension, congestive heart failure and renal failure.[10-14]

Determination of the intravascular volume status of a critically ill patient is important for prudent fluid and cardiovascular management. After initial resuscitation, microvascular permeability and capillary leakage initiated by the inflammatory mediator cascade can result in interstitial fluid accumulation and tissue edema. Uncertainty regarding intravascular volume status occurs when patients are edematous and total body fluid overloaded while exhibiting clinical parameters that require treatment, such as tachycardia, hypotension, low cardiac output associated with low mixed venous oxygen saturation or hypoxia, low urinary output, and deteriorating renal function. In these settings, patients may be hypovolemic, hypervolemic, or euvolemic (normovolemic) intravascularly, and it is imperative to distinguish between these various volume categories. This determination is crucial to assure that appropriate therapy is rendered, which bridges the spectrum from fluid boluses; to diuresis and fluid restriction; to the administration of maintenance intravenous fluids, respectively. Conventional surrogate parameters such as vital signs, fluid balance (intake and output), urinary output, peripheral edema, weight gain, jugular venous distention, chest radiographs and laboratory data (hematocrit, lactic acid, base excess, blood urea nitrogen to creatinine ratio, brain natriuretic peptide) have been used collectively to estimate intravascular volume but are not reliably accurate indicators of BV.[15-18] Transesophageal echocardiography and pulmonary artery catheters are common adjuncts used to guide fluid management. However, pressure measurements of central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) reflect volume in relationship to myocardial compliance, cardiac function, and vascular capacitance

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and may not accurately characterize intravascular volume. In practice, assessment of volume status often includes a combination of clinical evaluation, laboratory measurements, and when available, pulmonary artery catheter measurements. The prevailing hypothesis, albeit not unequivocally substantiated, is that measurement of circulating BV will more precisely guide therapeutic interventions.

The purpose of this observational pilot study was to compare measured BV with hemodynamic parameters obtained from the pulmonary artery catheter and to determine if incorporation of BV measurements altered treatment decisions in critically ill surgical patients.

Methods

This study was performed at a University affiliated, tertiary care medical center. The Institutional Review Board approved this study. Consecutive surgical intensive care unit (SICU) patients with a pulmonary artery catheter were identified and BV measurements were obtained if intravascular volume status was indeterminate.

Conventional parameters utilized by the SICU team in evaluating volume status included vital signs, urinary output, fluid balance, peripheral edema, weight gain, chest radiographs, and laboratory data (electrolytes, blood urea nitrogen, creatinine, hematocrit, lactic acid). Clinical parameters requiring treatment included persistent tachycardia (heart rate >100 beats/minute), hypotension (systolic blood pressure <100 mm Hg despite adequate fluid resuscitation to a PAOP of 15 to 18 mm Hg), urinary output of <0.5 mL/kg/hour after fluid replacement, low cardiac output with mixed venous oxygen saturation <70%, poor or worsening oxygenation (PaO2/FiO2 ratio < 200; or intrapulmonary shunt >20%), deteriorating renal function (serum creatinine level increase by >20% from baseline), or a combination of these. Patients were excluded during the first 24 hours of active fluid resuscitation to minimize any impact that rapidly shifting intravascular volume, or vasoactive drug use may potentially exert on blood volume analysis. At the time of blood volume measurement all patients were receiving maintenance intravenous fluids and were not receiving fluid boluses or blood transfusions. Those patients requiring ongoing, active fluid resuscitation beyond 24 hours were not included in the present study, again to ensure that the comparison of pulmonary artery catheter values and blood volume measurements were not confounded by rapidly shifting intravascular volumes seen during the active fluid resuscitation phase. Patients were also excluded if they were pregnant, there was a known iodine or shellfish allergy, or if younger than 18 years of age.

Pulmonary artery catheter measurements were performed according to manufacturer's instructions (Edwards CCOmbo Pulmonary Artery Catheter, Edward LifeSciences, Irvine, CA). Hemodynamic values obtained included blood pressure, heart rate, CVP, PAOP, cardiac index (CI), and stroke volume index (SVI), in addition to simultaneous BV measurements. Laboratory data obtained (at the discretion of the clinical team) included hemoglobin, hematocrit, lactic acid, electrolytes, blood urea nitrogen, creatinine, arterial blood gases, and chest radiographs. Each patient enrolled in this study received at least one BV measurement simultaneously with pulmonary artery catheter measurements.

Blood volume was measured by using a commercially available kit (BVA-100, Daxor Corporation, Inc., New York, NY). After obtaining a baseline sample of 5 ml of blood, I131-labeled albumin was injected intravenously over 1 minute. Serial blood samples were drawn at 12, 18, 24, 30, and 36 minutes from the time of isotope injection. Sample radioactivity was measured in duplicate and a minimum of three samples with a standard deviation of less than 3.9% were used to calculate plasma volume (PV) by extrapolating to time zero. The use of multiple timed samples and extrapolation to zero time is of particular importance in critically ill patients, since many may have capillary leak syndrome attributable to sepsis and other inflammatory conditions. This method can identify and correct for transudation of albumin into the interstitial space.[4,9]

The red blood cell volume (RBCV) was calculated from the PV and the peripheral blood hematocrit, after correcting for plasma packing and mean body hematocrit. Blood volume was then equal to PV + RBCV. This method has been found to be comparable to simultaneous, combined radioisotopic measurement of PV and RBCV.[7,19-21]

The predicted normal BV level was determined from the patient's height and ideal body weight based on the ideal weight method as described by Feldschuh and Enson.[22] This method has been shown to eliminate systematic errors found in norms based on fixed ratios of BV to body weight. Euvolemia was defined as within 8% of the normalized BV. The definitions of mild, moderate, and severe deviations were $\pm$8%, $\pm$16%, and $\pm$32%, respectively, from the predicted normal volumes for that patient.[22] A "normalized" hematocrit measurement is also provided by this method. The normalized hematocrit is an adjusted hematocrit measurement equal to the ratio of the patient's measured RBCV to the predicted normal total BV. Unlike the peripheral blood hematocrit, this measurement provides an accurate indication of the degree of anemia or polycythemia, without being distorted by variations in plasma volume.[18] Blood volume results became available to the treating team one hour after measurement. Once the decision was made to obtain BV analysis, patient therapy was based on the blood volume results. The protocol followed for hemodynamic management was based on prior randomized trials conducted in our Institution and published elsewhere.[23] In brief, patients were treated to a mean arterial pressure of > 65 mm Hg, systolic blood pressure (SBP) of > 100 mm Hg or within 40 mm Hg from known baseline, heart rate (HR) < 100 beats/minute, urine output > 1 ml/kg/hr, lactate level decreasing if elevated, PaO_2/FiO_2 > 200, mixed venous oxygen saturation (SvO_2) > 70%, and oxygen delivery (DO_2) > 600 mL/min/m^2, or > 450 mL/min/m^2 if $\geq$ 75 years of age, by infusing crystalloid or colloid at 250 to 500 ml increments, or blood infusion if the hemoglobin was < 10 gm/dl and if the SvO_2 was < 70% or if the DO_2 was < 600 ml/min/m^2 (or < 450 mL/min/m^2 if $\geq$ 75 years of age), to achieve a PAOP of 15 - 18 mm Hg. Once this PAOP was achieved, or urinary output was > 1 mL/kg/hr, lactate level was decreasing if elevated, or HR < 100 beats/minute, fluid resuscitation was deemed adequate. If the $Sv0_2$ was < 70%, $D0_2$ was < 600 mL/min/m^2 (or < 450 mL/min/m^2 if $\geq$ 75 years of age), and SBP was > 100 mm Hg, dobutamine at doses of 2 to 5 mcg/kg/min was started, titrated to achieve the noted predetermined treatment goals up to 20 mcg/min/m^2 or until patients became tachycardic (defined for this study as HR > 100 beats/minute). All patients received either norepinephrine or epinephrine starting at 1 mcg/minute titrated to predetermined SBP > 100 mm Hg, if patients were hypotensive despite adequate urinary output, lactate

level decreasing if elevated, HR < 100 beats/minute, and if the PAOP was between 15 - 18 mm Hg.

If a measured BV showed normovolemia, no volume-related treatment change was initiated despite what the pulmonary artery catheter results and clinical parameters showed; if the BV was consistent with hypovolemia, crystalloids or blood (if hemoglobin < 10 gm/dl, SvO_2 < 70% or DO_2 < 600 mL/min/m^2, or if age ≥ 75 years DO_2 < 450 mL/min/m^2) was infused; and if BV was consistent with hypervolemia, diuresis was implemented. In this structure, volume infusion would be carried out if a BV measurement showed hypovolemia, regardless of the status of the pulmonary system (i.e., respiratory insufficiency), for example. Moreover, once an intervention was made a subsequent, follow-up BV was obtained, and additional treatment provided until the BV showed normovolemia.

Three of the investigators blinded to each other, independently reviewed patient charts retrospectively after discharge from the SICU. Clinical data evaluated included cardiac (blood pressure, heart rate, CVP, PAOP, CI, SVI, mixed venous oxygen saturation, and requirement for vasopressors or inotropic agents), pulmonary (PF ratio, intrapulmonary shunt fraction, ventilator dependency, and chest radiographs) and renal function (urinary output, blood urea nitrogen, and creatinine level). We operationally defined a positive clinical response as one where there were at least two clinical parameters that demonstrated improvement six to twelve hours after therapy based on BV results, and a negative clinical response if there was no change, improvement in only one clinical parameter, or if there was clinical deterioration. For measured laboratory variables, to be considered a change (either positive or negative) there needed to be a difference greater than the standard error of the test. For example, difference in creatinine levels greater than ± 0.5 mg/dl was considered to be a change; measured values within that range were not considered to be a significant change. This was based on the laboratory's established quality control ranges for the respective assays.

Measured variables were compared using scatter plotting and Pearson correlation. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using OpenStat 3 software.

Results

Twenty SICU patients contributed twenty-nine simultaneous BV and pulmonary artery catheter values. Sixteen males and four females, mean age (± S.D.) 62.5 ± 20.7 years, with mean (± S.D.) APACHE II scores of 21.1 ± 4.8 comprised the study group. Six patients were admitted for severe sepsis/septic shock, nine for hemorrhagic shock, and five for respiratory failure. Mortality rate was 1/20 (5%).

There was no significant correlation between BV and CVP (r=0.27, p=0.13), BV and CI (r=0.24, p=0.21), and BV and SVI (r=-0.29, p=0.45). Blood volume was significantly but weakly correlated with PAOP (r=0.44, p=0.02). For PAOP values ≤12 mm Hg (n=6), BV results showed 2 hypervolemic and 4 euvolemic states. For PAOP values between 13-18 mm Hg (n=14), BV revealed 9 hypervolemic, 4 euvolemic and 1 hypovolemic state. For PAOP values >18 mm Hg (n=9), BV demonstrated 6 hypervolemic and 3 euvolemic states.

In 6 of 29 instances (21%), treatment was changed based on BV information (despite discordant pulmonary artery catheter measurements) with 5 of 6 patients experiencing improvement in cardiac, pulmonary and or/renal function following the change in treatment. Results of BV measurements for all 5 instances demonstrated hypervolemia. All patients received less fluid or diuresis, and three patients also received blood transfusion for correction of anemia, based on low RBCV results, if these results were also associated with decreased oxygen delivery or low mixed venous oxygen saturation, based on our Institutional protocol.[23]

Discussion

Several reports have been published to assess the feasibility and the utility BV measurements. This study was performed to evaluate the degree to which blood volume measurement affects treatment decisions, prior to the design and implementation of a larger prospective controlled study.

The pulmonary artery catheter is not an unequivocally accepted gold standard for evaluating intravascular volume status, particularly based on data from randomized trials demonstrating no significant impact on patient outcome and that pulmonary artery catheter measurements poorly reflects response to fluids.[24] Traditionally, however, pulmonary artery catheter parameters have been used as a guide for fluid management. Our current study showed that there was a statistically significant, but weak, correlation between PAOP and BV. Despite this finding, the utilization of pulmonary artery catheter readings as a surrogate for BV measurement would have resulted in an incorrect treatment approach in six of twenty-nine instances. Five of these patients demonstrated hypervolemia based on blood volume measurements. It is difficult to speculate if our treatment protocols promote hypervolemia and if this represents a selection bias, given the small sample size, although there is a clear trend towards hypervolemia. Notably, our protocols were established based on a prior randomized trial conducted in our Institution that demonstrated that our current protocol was the treatment arm associated with significantly higher survival.[23]

Previous investigators have shown that BV measurements did not correlate with PAOP in 24 hemodynamically unstable ICU patients[25] and in patients during the acute and post-resuscitation phase.[16] This may be related to differences in the study populations and the timing of measurements. Alwari et al reported on a comparative study of BV values and pulmonary artery catheter measurements in 24 intensive care unit patients. Their exclusion criteria included hemodynamically normal or stable patients, and critically ill patients who were managed in an intensive care unit setting without the use of a pulmonary artery catheter.[25] Shippy and colleagues included patients during the acute resuscitation phase.[16] Our study was conducted in patients after the acute resuscitation phase was completed. Similar to our results, Androne et al. showed significant correlation between BV results and PAOP in 17 patients with chronic congestive heart failure.[11] Many clinical situations may alter the pressure-volume relationship of the myocardium resulting in these differences. Measuring pressure to infer volume continues to be problematic.

Furthermore, circulating BV analysis provides distinct measurement of disturbances in the RBCV and in the PV (since BV = RBCV + PV). This precise information, resulting in treatment targeted at improving each individual component of total BV, is not obtainable from pressure measurements provided by the pulmonary artery catheter. Most of the patients in this study were hypervolemic. Notably, in the presence of PV expansion, BV measurement can

quantify the degree of RBCV depletion in relation to the degree of dilutional anemia. Anemia has been associated with poorer outcomes in a variety of conditions,[18] so accurately diagnosing and correcting anemia may be a defining factor in whether or not a patient improves. In those patients with altered treatment based on BV analysis, three patients (10% of the entire cohort) received blood transfusion to correct anemia. Two of those patients showed improvement in two or more clinical parameters, while the other showed improvement in only one parameter but none demonstrated any immediate adverse clinical response. Blood volume measurement is promising and may also be valuable in precisely defining the presence and degree of anemia, and in ultimately determining optimal protocols to treat true and dilutional anemia.

This investigation has a number of limitations. A small number of patients with heterogeneous diagnoses for admission to the SICU were evaluated, limiting the statistical power of this analysis and increasing the risk of a type II error. Treatment responses were evaluated, but in the absence of a control group cause and effect cannot be clearly established; neither, therefore, could outcomes be determined, and our conclusions are limited by the observational design of the present study. Incorporation of BV results into treatment decisions was left to the discretion of the treating team. Despite this uncertainty, none of the patients studied demonstrated an unfavorable or adverse clinical response following treatment changes based on BV results. In addition, three independent reviewers blinded to each other had to agree before categorizing the clinical response as favorable, so this tended to underestimate any immediate benefit. This may have resulted in a study bias, even if the investigators were blinded to patient names and to each other, given that these investigators were part of the study. To minimize bias, any improvement in at least two measured parameters (beyond the standard error of the test parameter being measured if it was a laboratory assay) was defined at study inception as a favorable clinical response.

At this time, there is a paucity of data in the peer-reviewed literature defining optimum intravascular volume associated with survival. Shippy et al recommended, in the critical care setting, resuscitation to greater than normal volumes based on survival characteristics.[16] Other investigators found, in ambulatory heart failure patients, improved outcomes for normovolemic patients compared to hypervolemic patients.[11] The optimal BV in different conditions remains to be determined.[17]

Conclusions

There may be a role for BV measurement in a cohort of critically ill surgical patients after the acute resuscitation phase, when presented with the dilemma of determining intravascular volume status based on conventional clinical parameters. Blood volume measurement may be particularly beneficial to establish fluid management goals and endpoints of treatment in sepsis and septic shock patients. Despite advances in formalized critical care research, sepsis and septic shock are still the most significant cause of mortality in the intensive care unit. Increased microvascular permeability and capillary leak initiated by the inflammatory cascade results in interstitial fluid accumulation and tissue edema, which may also effect changes in venous compliance. Achieving euvolemia is a fundamental principle in fluid management. Clinical surrogates of intravascular volume status and information obtained from pulmonary artery catheters may be deceptive in this group of patients. Early, and clinically appropriate, achievement of fluid resuscitation endpoints to avoid multiorgan system failure may be assisted by BV analysis, which provides an attractive noninvasive alternative for volume assessment. Additional studies, including prospective controlled studies, should be performed to evaluate the effects of utilizing BV measurement on patient outcomes, as well as to determine optimal treatment protocols and to quantify the optimal intravascular volume status for patients in the critical care setting.

References

1. Gray SJ, Sterling K. The tagging of red cells and plasma proteins with radioactive chromium. *J Clin Invest* 1950; 29: 1604-1613.
2. Thomas E, Jones G, de Souza P, et al. Measuring blood volume with fluorescent-labeled hydroxyethyl starch. *Crit Care Med* 2000; 28:627-631.
3. Sakka SG, Reinhart K, Meier-Hellmann A. Comparison of invasive and noninvasive measurements of indocyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable hemodynamics. *Intensive Care Med* 2000; 26:1553-1556.
4. Margarson MP, Soni NC. Plasma volume measurement in septic patients using an albumin dilution technique: comparison with the standard radio-labelled albumin method. *Intensive Care Med* 2005; 31:289-295.
5. Iijima T, Iwao Y, Sankawa H. Circulating blood volume measured by pulse dye-densitometry: comparison with (131)I-HSA analysis. *Anesthesiology* 1998; 89:1329-1335.
6. Haruna M, Kumon K, Yahagi N, et al. Blood volume measurement at the bedside using ICG pulse spectrophotometry. *Anesthesiology* 1998; 89:1322-1328.
7. Fairbanks VF, Klee GG, Wiseman GA, et al. Measurement of blood volume and red cell mass: re-examination of 51Cr and 125I methods. *Blood Cells Mol Dis* 1996; 22:169-186; discussion 186a-186g.
8. Dingley J, Foex BA, Swart M, et al. Blood volume determination by the carbon monoxide method using a new delivery system: accuracy in critically ill humans and precision in an animal model. *Crit Care Med* 1999; 27:2435-2441.
9. Recommended methods for measurement of red-cell and plasma volume: International Committee for Standards in Haematology. *J Nucl med* 1980; 21:793-800.
10. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. *Circulation* 2003; 107:226-229.
11. Androne AS, Hryniewicz K, Hudaihed A, et al. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. Am J Cardiol 2004; 93:1254-1259.
12. Katz SD, Mancini D, Androne AS, et al. Treatment of anemia in patients with chronic heart failure. *J Card Fail* 2004; 10:S13-16.
13. Shevde K, Pagala M, Tyagaraj C, et al. Preoperative blood volume deficit influences blood transfusion requirements in females and males undergoing coronary bypass graft surgery. *J Clin Anesth* 2002; 14:512-517.
14. Mancini DM, Katz SD, Lang CC, et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003; 107:294-299.
15. Biuk-Aghai EN, Yamauchi H, Yu M, et al. Blood volume measurements: Impact on fluid management [abstract]. *Crit Care med* 2006; 33 (suppl):140-S.
16. Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984; 12:107-112.
17. Thorborg P, and Haupt MT. Is it time to use blood volume measurements as a clinical tool? *Crit Care Med* 2000; 28: 883-884.
18. Valeri CR, Dennis RC, Ragno G, et al. Limitations of the hematocrit level to assess the need for red blood cell transfusion in hypovolemic anemic patients. *Transfusion* 2006; 46: 365-71.
19. Moore FD, Hartsuck JM, Zollinger RM Jr, Johnson JE. Reference models for clinical studies by Isotope Dilution. *Ann Surg* 1968; 168:671-700.
20. International Committee for Standardization in Haematology. Recommended methods for measurement of red-cell and plasma volume. *Journal of Nuclear Medicine* 1980; 21:93-800.
21. Dworkin HJ, Premo M, Dees S. Comparison of red cell and whole blood volume as performed using both chromium-51-tagged red cells and iodine-125-tagged albumin and using i-131-tagged albumin and extrapolated red cell volume. *Am J Med Sci* 2007; 334: 37-40.
22. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation* 1977; 56:605-612.
23. Yu M, Burchell S, Hasaniya NW, et al. Relationship of mortality to increasing oxygen delivery in patients > or = 50 years of age: A prospective randomized trial. *Crit Care Med* 1998; 26:1011-1019.
24. Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2003; 290: 2713-20.
25. Alrawi SJ, Miranda LS, Cunningham Jr JN, et al. Correlation of blood volume values and pulmonary artery catheter measurements. *Saudi Med J* 2002; 23:1367-1372.

Acute Interstitial Nephritis Complicating a New Diagnosis of Wegener's Granulomatosis

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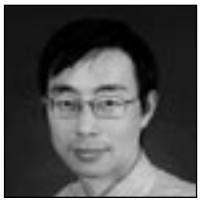

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Abstract

Establishing the underlying diagnosis in acute renal failure is essential in guiding patient management. To our knowledge, this is the first reported case with concurrent diagnoses of Wegener's granulomatosis and non-steroidal anti-inflammatory drug (NSAID)-induced interstitial nephritis. Renal biopsy should be performed in renal insufficiency patients where several concurrent conditions are suspected to obtain the correct diagnosis and institute appropriate treatment.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitides including Wegener's granulomatosis and Churg-Strauss syndrome are uncommon etiologies in patients presenting with acute renal insufficiency.[1] Acute interstitial nephritis is another cause of acute renal failure and is commonly associated with drugs such as NSAIDs, sulfonamides, beta-lactams,[2] rifampin,[3] and ciprofloxacin.[4] Renal biopsy typically reveals edema and inflammatory infiltrate in the interstitium but is usually not performed if the patient responds to discontinuation of the offending drug[5] or corticosteroids therapy.[6]

This case demonstrates a patient with a history suggestive of both Wegener's granulomatosis and NSAID-induced acute interstitial nephritis, in whom the diagnosis was ultimately confirmed by renal biopsy.

Case Report

A 35-year-old Hispanic male with a history of sinusitis presented with headache, sinus pain, and 20-pound weight loss over the preceding month. He noted concomitant fevers, night sweats, arthralgias, along with new onset productive cough, eye redness, and hearing loss of one week duration. Ibuprofen taken intermittently during the past month, including 20 tablets during the preceding week, provided no relief for his sinus pain.

On admission, physical examination showed a temperature of 36.3°C, blood pressure of 143/90, heart rate of 94 beats/min, and respiratory rate of 16 breaths/min. His exam was significant for bilateral conjunctival hemorrhage, tenderness of the nasal sinuses and knee joints, but normal skin, neurological, and abdominal examination. Laboratory studies on admission were significant for a serum creatinine of 2.7 mg/dl, increased from 0.9 mg/dl the prior month. Complete blood count (CBC) was notable for eosinophilia 1,500 cells/mL. C-reactive protein was elevated at 18.4 mg/dL. cANCA was positive at 1:128. C3 167 mg/dL, C4 38 mg/dL, and anti-streptolysin O 112 IU/ml were within normal limits. Serum protein electrophoresis, antinuclear antibodies, and pANCA test results were unremarkable. The only abnormality on urinalysis was hematuria (54 RBC/hpf). Chest radiograph was normal. Otolaryngologic examination revealed bilateral swollen turbinates with extensive mucosal polyps.

Renal biopsy was subsequently performed to evaluate the cause of the patient's acute renal insufficiency. The specimen received for light microscopic examination contained 19 glomeruli, none of which was globally sclerotic. Several glomeruli revealed segmental fibrinoid necrosis of the capillary tuft with a slight cellular reaction in Bowman's space (Fig 1a). Up to five glomeruli displayed varisized cellular or fibrocellular crescents. One glomerulus showed extensive disruption of Bowman's capsule basement membrane with periglomerular granulomatous inflammation (Fig 1b). The remaining glomeruli were largely unremarkable. There was significant interstitial edema with a heavy inflammatory infiltrate composed of lymphocytes, plasma cells and many eosinophils (Fig 1c). The interlobular arteries showed significant intimal fibrosis. The arterioles demonstrated mild hyalinosis. Immunofluorescence studies showed strong fibrin staining in the crescents and areas of fibrinoid necrosis of the glomerular capillary tufts. Stains for immunoglobulins and complements were negative. The specimen submitted for electron microscopy contained three glomeruli, all of which were unremarkable. No electron dense deposits or tubuloreticular structures were noted. Focal foot process effacement was observed. The final pathological diagnoses of pauci-immune necrotizing and crescentic glomerulonephritis consistent with Wegener's granulomatosis, and drug-induced acute interstitial nephritis were rendered.

In addition to discontinuation of NSAIDs, the patient was started on standard treatment of Wegener's granulomatosis with methylprednisolone and cyclo-

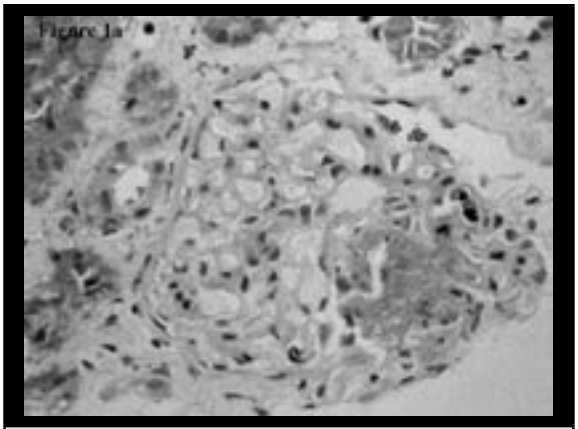

Figure 1a.— Light microscopy. The glomerulus shows a segment with deeply acidophilic, segmental fibrinoid necrosis. The non-necrotic segments are histologically unremarkable (Hematoxyline and eosin; original magnification x400).

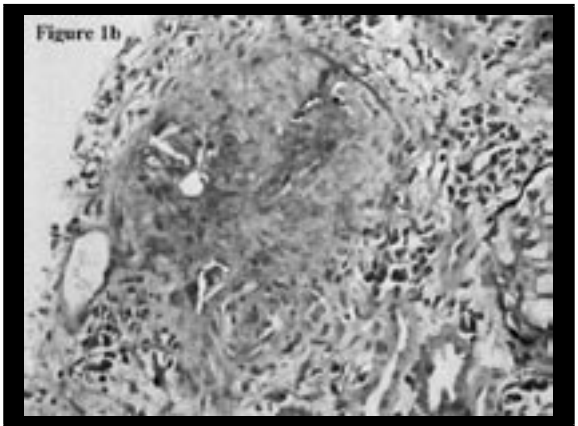

Figure 1b.— Light microscopy. Extensive destruction of the glomerular tuft and Bowman's capsule with a large fibrocellular crescent (Periodic acid-Schiff stain; original magnification x400).

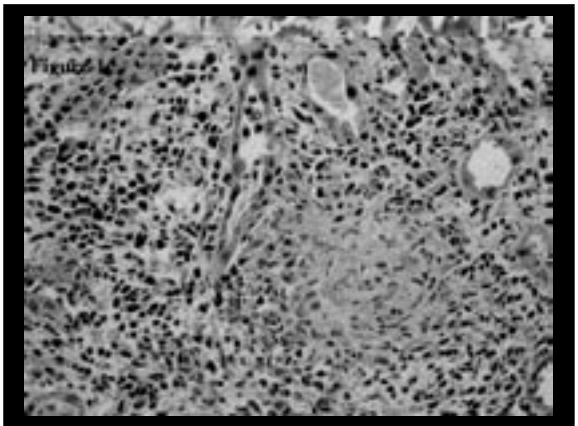

Figure 1c.— Light microscopy. An off-center plane section through a severely injured glomerulus shows intense periglomerular granulomatous inflammation. Also note the significant interstitial eosinophilic infiltrate. (Hematoxyline and eosin; original magnification x400).

phosphamide. He responded well, with resolution of his presenting symptoms over the following week. His serum creatinine was 2.5 mg/dl at discharge on hospital day #7. At a follow-up visit two months after discharge, the patient was asymptomatic with a serum creatinine of 1.3 mg/dl, had no hematuria on urinalysis, and had a negative cANCA.

Discussion

To our knowledge, this is the first reported case of Wegener's granulomatosis occurring concurrently with NSAID-induced interstitial nephritis. Differentiating these diagnoses from other causes of acute renal failure and each other is important due to differences in prognosis and treatment. Making such a distinction on clinical grounds alone can be challenging given variability in patient presentation and requires further testing for a definitive diagnosis. This is especially true considering NSAID-induced interstitial nephritis seldom presents with typical findings of fever, rash, and eosinophilia.[7] While acute interstitial nephritis is a self-limited condition that responds to short-term corticosteroids therapy, Wegener's granulomatosis carries a worse prognosis, and its standard treatment may result in significant morbidity from cyclophosphamide or methotrexate, in addition to long-term glucocorticoids.[8,9,10]

The patient in the case report presented with several features of Wegener's granulomatosis including persistent rhinorrhea, sinus pain, hearing loss, cough, fevers, night sweats, and weight loss. The recent rise in serum creatinine and hematuria were also consistent with this diagnosis. However, the patient's symptoms were not specific, since fever, arthalgia, eosinophilia, and acute renal failure may also occur in acute interstitial nephritis.[11] Churg-Strauss syndrome was also considered because it may present with allergic rhinitis, eosinophilia, constitutional symptoms, and renal insufficiency in the third or fourth decade of life.[12]

Renal biopsy was necessary to provide an accurate diagnosis to determine appropriate treatment given clinical evidence of multiple possible diagnoses. Renal biopsy has relatively low morbidity[13] and was indicated given the differences in treatment toxicity for Wegener's granulomatosis and NSAID-induced interstitial nephritis. Classic acute interstitial nephritis typically reveals edema and inflammatory infiltrate in the interstitium. Pauci-immune segmental necrotizing glomerulonephritis is usually consistent with Wegener's granulomatosis, but its absence does not exclude Wegener's. Wegener's granulomatosis may also present as tubulointerstitial nephritis with predominately normal glomeruli on renal biopsy.[14,15,16] Haqqie et al. reported a patient in whom the clinical presentation was suggestive of drug-induced interstitial nephritis, but subsequent studies revealed positive cANCA and necrotizing crescentic glomerulonephritis diagnostic of Wegener's granulomatosis.[17] Bir et al. previously

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described a patient with azathioprine-induced acute interstitial nephritis undergoing treatment for Wegener's granulomatosis. An initial renal biopsy showed pauci-immune necrotizing glomerulonephritis during active Wegener's granulomatosis. However, a subsequent renal biopsy demonstrated mostly normal glomeruli and an interstitial inflammatory infiltrate of lymphocytes, monocytes, occasional plasma cells, and numerous eosinophils diagnostic of acute interstitial nephritis.[18] Unlike our patient, both pathologic diagnoses were not present concurrently in the same renal biopsy.

Conclusion

The occurrence of both Wegener's granulomatosis and acute interstitial nephritis occurring concurrently in a patient has not been previously reported. Renal biopsy is of relatively low morbidity and may provide important diagnostic information and determine appropriate treatment.

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References

1. Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. *Am J Med.* 2004; 117:39-50.
2. Ten RM, Torres VE, Milliner DS, et al. Acute interstitial nephritis: immunologic and clinical aspects. *Mayo Clin Proc.* 1988; 63:921-930.
3. Nessi R, Bonoldi GL, Redaelli B, et di Filippo G. Acute renal failure after rifampicin: a case report and survey of the literature. *Nephron.* 1976; 16:148-159.
4. Allon M, Lopez EJ, Min KW. Acute renal failure due to ciprofloxacin. *Arch Intern Med.* 1990; 10:2187-2189.
5. Buysen JG, Houthoff HJ, Krediet RT, Arisz L. Acute interstitial nephritis: a clinical and morphological study in 27 patients. *Nephrol Dial Transplant.* 1990; 5:94-99.
6. Galpin JE, Shinaberger JH, Stanley TM, et al. Acute interstitial nephritis due to methicillin. *Am J Med.* 1978; 65:756-765.
7. Kleinknecht D. Interstitial nephritis, the nephrotic syndrome, and chronic renal failure secondary to nonsteroidal anti-inflammatory drugs. *Semin Nephrol.*1995; 3:228-235.
8. Hoffman GS, Leavitt RY, Fleisher TA, Minor JR, Fauci AS. Treatment of Wegener's granulomatosis with intermittent high-dose intravenous cyclophosphamide. *Am J Med.* 1990; 89:403-410.
9. Guillevin L, Cordier JF, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum.* 1997; 40:2187-2198
10. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med.* 2003; 349:36-44.
11. Clarkson MR, Giblin L, O'Connell, et al. Acute interstitial nephritis: clinical features and response to corticosteroid therapy. *Nephrol Dial Transplant.* 2004; 19:2779-2883.
12. Sinico RA, Di Toma L, Maggiore U, et al. Renal involvement in Churg-Strauss syndrome. *Am J Kidney Dis.* 2006; 47:770-779.
13. Parrish AE. Complications of percutaneous renal biopsy: a review of 37 years' experience. *Clin Nephrol.* 1992; 38:135-141.
14. Fannin SW, Hagley MT, Seibert JD, Koenig TJ. Bronchocentric granulomatosis, acute renal failure, and high titer antineutrophil cytoplasmic antibodies: possible variants of Wegener's granulomatosis. *J Rheumatol.* 1993; 20:507-509.
15. Banerjee A, McKane W, Thiru S, Farrington K. Wegener's granulomatosis presenting as acute suppurative interstitial nephritis. *J Clin Pathol.* 2001; 54:787-789.
16. Ernam D, Atikcan S, Yilmaz A, et al. An unusual renal presentation of Wegener's granulomatosis. *Tuberkuloz ve Toraks.* 2003; 51:193-196.
17. Haqqie SS, Phelps KR, Singh J, Urizar RE. Wegener's granulomatosis in a patient with apparent drug-induced acute interstitial nephritis. *Am J Med Sci.* 1998; 315:216-219.
18. Bir K, Herzenberg AM, Carette S. Azathioprine induced acute interstitial nephritis as the cause of rapidly progressive renal failure in a patient with Wegener's granulomatosis. *J Rheumatol.* 2006; 33:185-187.

The Influence of Intravenous Hydration on Hospital Length of Stay in Infants with Hyperbilirubinemia

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Abstract

A retrospective chart review compared data on neonates with physiologic jaundice admitted for phototherapy at a children's hospital. Those infants who received intravenous fluids (IVF) had significantly longer lengths of stay, higher initial bilirubin levels, and were more dehydrated than those babies who did not receive IVF.

Introduction

Hospitalization for phototherapy to treat neonatal hyperbilirubinemia is the most common reason for readmission within the first two weeks of life.[1] Dehydration commonly coexists with hyperbilirubinemia causing further hemoconcentration of serum bilirubin while also delaying excretion of soluble bilirubin.[2] Feeding difficulties also contribute to dehydration in this age group. Furthermore, phototherapy may enhance insensible water losses, exacerbating dehydration and perhaps leading to decreased alertness. Babies with decreased attentiveness may have less success with establishing breastfeeding or with maintaining adequate hydration with oral intake alone, thus potentially prolonging hospitalization for phototherapy. The combination of hydration and adequate oral intake are important components of improving serum bilirubin levels.[3] A review of the literature from 1960 to 2006 revealed only two studies which examined the role of intravenous fluid administration to correct dehydration associated with physiologic jaundice requiring phototherapy.[4,5]

The objective of our study was to compare length of hospitalization for babies admitted for nonhemolytic hyperbilirubinemia who received intravenous hydration to those who did not. We hypothesized that infants with hyperbilirubinemia on phototherapy who received intravenous fluids (IVF) would have a significantly shorter length of stay than those who did not receive IVF.

Methods

This study was a retrospective chart review conducted at a tertiary care children's hospital over a one-year study period (Dec 2003 to Dec 2004). The hospital Institutional Review Board approved the study protocol.

Inclusion and exclusion criteria:

Included were infants >=35 weeks gestation who were admitted within 10 days of life with a primary diagnosis of hyperbilirubinemia, physiologic jaundice or newborn jaundice and who were being admitted for phototherapy. Infants with the following secondary diagnoses were excluded: G6PD deficiency; maternal/fetal ABO incompatibility; Rh incompatibility/isoimmunization; cephalohematoma; hemolytic anemia; sepsis in the newborn; abnormalities of the palate; direct hyperbilirubinemia; urinary tract infection; or any infant requiring exchange transfusion.

Data Collection:

Data was extracted from hospital records, which included the attending and resident physician notes along with the laboratory results. The hour-specific Bhutani nomogram[6] was used to classify the patients as being low risk, low intermediate risk, high intermediate risk, or high risk for developing clinically significant hyperbilirubinemia based on a postnatal age measured in hours.

The following data were collected: gender, gestation, birth weight, weight at hospital on admission for phototherapy, percent weight loss since birth, date and time of birth, time of initial bilirubin and time of admission in hours of life, length of stay in hospital in hours, initial bilirubin (upon arriving at hospital for phototherapy), peak bilirubin, bilirubin on discharge (after phototherapy), Bhutani risk range, whether intravenous fluids were administered, feeding type (breastfed only, breast and formula fed, formula only), whether infants received home phototherapy prior to admission. Dehydration was defined as percent weight loss since birth: mild <5%; moderate 5-10%; severe >10%.

Statistical Analyses (Estimating the sample size):

One goal of the study was to test the hypothesis that the length of stay (LOS) is 12 hours less for the group that received IVF compared to the group that did not receive IVF. A t-test for independent groups with common variance was used as the statistical method of choice to compare the groups.

From a sampling of electronic medical record data for similar patients during the time period of 10/1/2000 to 8/1/2005, the standard deviation for length of stay was found to be 22.8 hours. For an alpha level of 0.05, a delta level of 12 hours, a 1-tailed probability, and a power level of 80% (probability of a type II error is 0.20), the required sample size is 92 for both groups combined.

Results

Of the 120 randomly selected charts reviewed, nine were omitted for not enough data and eight were omitted for erroneous ICD9 codes. One infant whose hospitalization was prolonged (>144 hours) due to reasons unrelated to the hyperbilirubinemia was omitted from the analyses; another was omitted for age >10 days. In addition, one case was omitted due to significant weight gain from birth weight, bringing into question the accuracy of the recorded weight. Of the remaining 100 patient charts that were considered valid, only 6 had gestational age between 35-37 weeks of age, all others (94) were full term. Fifty-four percent of the subjects were men. The mean age of presentation to the hospital or doctor's office for signs or symptoms related to hyperbilirubinemia was 115 hours of life (SD=68).

Comparison of the two groups (IVF versus no IVF) is shown in the Table. The mean percent weight loss from birth to time of hospitalization was significantly different between the non-IVF group and the IVF group, indicating that those who received IVF were significantly more dehydrated than those who did not receive IVF. The IVF group had a statistically significant ($p=0.041$) longer length of stay than did the non-IVF group. However, when the LOS was compared within dehydration groupings (<10% and >10% dehydrated from birth weight), there was no statistical difference between those who received IVF and those who did not. Within each dehydration category, the number of subjects in the group receiving IVF was too small to show a significant difference. The >10% dehydrated group had a significantly longer LOS (45.5 hours) than the <10% dehydrated group LOS (35.3 hours), indicating that the severely dehydrated group had a significantly longer LOS ($p=0.011$).

The initial bilirubin level at the time of hospitalization was significantly higher for the group receiving the IVF (20.9 +/- 4.2 mg/dL) than for the group that did not receive IVF (18.5 +/-3 mg/dL, $p=0.007$). For the cases that were classified as high risk on the Bhutani curve (total 71 in this group), the difference in mean LOS between the two groups was not statistically significant.

The LOS between the group that breastfed only ($N=26$) and that either formula fed only or supplemented with formula ($N=72$) was not statistically significant ($p=0.82$).

Discussion

Our data did not demonstrate a shorter length of stay for infants hospitalized for hyperbilirubinemia treated with IVF. We found that only those patients with >5% body weight loss had intravenous cannulas placed and that they had a statistically significant longer length of stay than those that did not receive IVF. The main contributing reason for prolonged LOS in the group receiving IVF is severity of illness: those infants with higher serum bilirubin levels or with severe dehydration are more likely to get IVF. These infants may have slower excretion of soluble forms of bilirubin, extending the need for phototherapy. Another contributing factor to LOS in severely dehydrated infants may be related to feeding issues (poor latcher, inexperienced breastfeeding mom) or social issues (young mom, poor social support, no established pediatrician in the community), and not directly related to the hyperbilirubinemia or dehydration per se, but compounding both.

When we separated the patients with mild-moderate dehydration from the severely dehydrated patients and compared LOS for those receiving IVF versus those not receiving IVF within each group, there was no significant difference. However the number of infants with severe dehydration was only 15; seven of these patients did not receive IVF so the power to detect a difference was very small.

Our data showed that those patients placed on IVF had a significantly higher initial serum bilirubin level than those that did not receive IVF. In contrast, placement in the high risk Bhutani cohort did not correlate with the likelihood of receiving IVF. This indicates that physicians were more likely to order IVF based upon the absolute serum bilirubin level rather than the risk level on the Bhutani curve.

We observed that most babies with physiologic jaundice come to medical attention between days 4 and 5 of birth. This has been observed by others as well.[7,8] Early postnatal discharge (within 24-48 hours of life) is increasingly prevalent[9] and has been associated with increased severity of dehydration and jaundice in readmitted infants.[10,11] Breastfeeding has also been associated with higher levels of serum bilirubin in infants with physiologic hyperbilirubinemia.[12] With regards to this, our data did not show a statistically significant difference in LOS between those babies who were primarily breastfed versus those who were formula fed or a combination; however we did not have adequate numbers to show a difference if one truly existed.

The combination of early discharge following birth and an increase in breastfeeding rates may contribute to the high readmission rates of breastfed babies with physiologic jaundice.[1] This does not mean we should discourage breastfeeding or extend hospitalization unnecessarily. Instead, it underscores the importance of breastfeeding support (e.g. home visits by a lactation consultant) between days 2-5, the time gap between leaving the hospital and seeing the pediatrician for the first office visit. It also encourages extensive lactation knowledge on the part of the pediatrician or the support staff in the office. As described by Yamauchi et al., establishment of good breastfeeding practice in the newborn and knowledge about the need for frequent feeding practice may help reduce the incidence of readmissions for hyperbilirubinemia[3] by reducing the contributing factor of dehydration in spite of breastmilk's tendency to increase enterohepatic reabsorption of bilirubin.[13]

In conclusion our data indicate that IVF administration does not shorten hospital length of stay, however, dehydration remains a significant consideration in assessing and treating neonatal hyperbilirubinemia. A major limitation of our study was the sample size in the IVF cohort. Ultimately, the issue of whether to use IVF in the standard treatment of babies requiring phototherapy warrants further study. Future studies should look more specifically at parameters quantifying dehydration such as urine output and specific gravity, serum electrolytes and osmolality, total fluid intake, daily weight and feeding patterns.

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Table.— Baseline demographic data and variables			
Parameter	**IV Fluid Group**	**No IV Fluid Group**	**P value**
Number of subjects	18	82	
Gestational Age (weeks) (Mean +SD)	38.5 ± 1.2	37.6 ± 1.4	0.014
Age at admission (hours) (Mean +SD)	114.8 ± 33.5	115.9 ± 73.5	NS
Birth Weight (g) (Mean +SD)	3222 ± 371	3157 ± 527	NS
Percent weight loss (Mean +SD)	8.9 ± 3.0	6.3 ± 3.2	0.002
LOS in Hours - total (Mean +SD)	43.1 ± 16.2	35.5 ± 13.7	0.041
LOS in Hours in <10% dehydration (Mean +SD)	38.8 ± 12.1 N = 10	34.9 ± 13.1 N = 75	NS
LOS in Hours in >10% dehydration (Mean +SD)	48.5 ± 19.7 N = 8	41.9 ± 19.4 N = 7	NS
Initial Bilirubin (mg/dL) (Mean +SD)	20.9 ± 4.2	18.5 ± 3.0	0.007
LOS in hours for Bhutani High risk (Mean +SD)	42.7 ± 14.8 N = 14	36.2 ± 15.3 N = 57	NS
Number of breastfed only	7	19	
Number of Combination of formula and breastfeeding	11	61	

LOS = length of stay; IV = intravenous; g = grams; SD = standard deviation; ± = plus/minus; N = number of subjects, NS = not significant.

References

1. Maisels MJ, Kring, E. Length of stay, jaundice, and hospital readmission. *Pediatrics.* 1998;101:995-998.
2. Tan KL. Decreased response to phototherapy for neonatal jaundice in breast-fed infants. *Arch Pediatr Adolesc Med.* 1998;152:1187-1190.
3. Yamauchi Y, Yamanouchi I. Breastfeeding frequency during the first 24 hours after birth in full term neonates. *Pediatrics.* 1990;86:171-175.
4. Boo NY, Lee HT. Randomized controlled trial of oral versus intravenous fluid supplementation on serum bilirubin level during phototherapy of term infants with severe hyperbilirubinemia. *J Paediatr Child Health.* 2002;38:151-155.
5. Mehta S, Kumar P, Narang A. A randomized controlled trial of fluid supplementation in term neonates with severe hyperbilirubinemia. *J Pediatr.* 2005;147:781-785.
6. Bhutani VK, Johnson L, Sivieri E. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics.* 1999;103:6-14.
7. Martinez JC, Maisels MJ, Otheguy L, Garcia H, Savoraini M, Mogni B, et al. Hyperbilirubinemia in the breast-fed newborn: a controlled trial of four interventions. *Pediatrics.* 1993;91:470-473.
8. Maisels MJ, Kring E. Risk of sepsis in newborns with severe hyperbilirubinemia. *Pediatrics.* 1992;90:741-743.
9. Britton JR, Britton HL, Beebe SA. Early discharge of the term newborn: a continued dilemma. *Pediatrics.* 1994;94:291-295.
10. Lee KS, Perlman M, Ballantyne M, Elliott I, To T. Association between duration of neonatal hospital stay and readmission rate. *J Pediatr.* 1995;127:758-766.
11. Soskolne EI, Schumacher R, Fyock C, Young ML, Schork A. The effect of early discharge and other factors on readmission rates of newborns. *Arch Pediatr Adolesc Med.* 1996;150(4):373-379.
12. Maisels MJ, Gifford K. Normal serum bilirubin levels in the newborn and the effect of breast-feeding. *Pediatrics.* 1986;78:837-843.
13. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med.* 2001;344(8):581-590.

Reflections on the JABSOM Experience for the Incoming Class of 2011

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Keynote at the Class of 2011 Ohana Gathering & Open House, July 21, 2007

First off, let me start by saying congratulations. As I listened to Dean Izutsu discuss the statistics concerning the number of applicants and how difficult it is to get into JABSOM, I am even more impressed with your achievement. You should be proud of what you have accomplished. I am a private practice pathologist and, as a part of my job, I am always around clinical laboratories and laboratory personnel such as medical technologists, technicians, phlebotomists, and pathology assistants. On occasion I am asked for advice on how to get into medical school, what courses to take in college, or how to study for the MCATs. Looking at where they are, I think of what a long road they have ahead of them to just get to where you are today. You have already successfully traveled this long road to make it here. You should be proud.

However, now the work begins again. Medical school will be one of the most difficult things you will ever do, and one of the most exciting. It will be a life-changing experience. When you gather together four years from now as MDs, I guarantee you that you will be different. Medical school is unique because it involves more than just huge intellectual challenges. It demands input from your compassion, your belief system, even your soul and when you come out, you will be different. You won't just have a degree, you will be a physician. Before medical school, I went to graduate school and earned a PhD and I was called doctor for several years before I even opened up a book on medicine. It was a nice title but still just a title to me. When people call me doctor now, it feels different. It is a part of who I am now. You will understand this as the years go by and you join the ranks of our profession.

In preparing for this talk, I spent time reflecting on how best my medical school experiences (which weren't too long ago) could help you. What I came up with is distilled, practical advice five important pearls to remember. Not hallmark sayings like "take time to smell the roses" but hard practical advice that may help you succeed. Take this as advice from one colleague to another.

The first piece of advice was given to me on my first day of graduate school at Princeton. During our orientation, the director of the graduate program in chemistry told us that we are now professionals in our field and to act accordingly. We didn't feel like professional scientists. After all, it was our first day. I only began to understand what he meant after we started juggling classes, study time and research. Unlike college, there were no quizzes to monitor our progress or set hours to work in the lab. Research projects progressed based on the time and effort that people put into them. Those people that saw themselves as professionals put in the time at the lab bench during their free time during the day and usually late into the evenings. The people that had the hardest time were the ones who never accepted this idea. They didn't use the deceptively abundant free time to advance their research. For some of them, by the time they realized they weren't in college anymore, it was too late. You must see yourself as a medical professional starting from today. Treat your studies and your study time like they are your job because now they are. You will transition from here to hospitals and clinics elsewhere where your job will be to apply what you learn now. College is over. You are a professional. You can't drop a course or skip anatomy if you think it doesn't suit you. Look at your book chapters and learning issues not as things that get in the way of your free time, but as things you must know to care for patients. What you learn (or don't learn now) will directly affect the care of your patients. Act accordingly.

The second piece of advice is actually three words: Read, Read, Read! Read like you have never read before. At the end of the first two years, you will take a national exam based on a huge amount of material that should be learned during this time. This material covers multiple medical related disciplines such as pharmacology, pathology, and microbiology. My advice is to pick a book in each area that works for you and READ it. I remember being very frustrated as a first-year medical student trying to get the director of medical education to name the best books for each area. He would tell me to simply choose one that I liked. I would ask "but which one is best" only to get the cryptic reply, "the one that gives you the information you need". I realize now that not every book works for everybody; some are more in depth, some are just reviews, and others are written in a style that might not mesh with the way you learn. Search on the web, talk to the upperclassmen, or go to the bookstore and compare books. However you do it, do it soon. Don't put it off till next year when it may be too late. Identify a book in each area that works for you, buy it, and then READ it.

I know that the size of some of these books can be daunting. I remember during my first week of residency in pathology I went to the medical school bookstore to purchase a general surgical pathology text. As I was standing at the counter, I saw the clerk coming toward me with the largest book I have ever seen outside of a museum. I looked away silently praying that this wasn't mine but sure enough, he came and plopped it down on the counter with a thud and looked up saying, "this is Volume I". "I'll be right back with Volume II." Needless to say, it was a struggle to even get these books home but I will tell you how I got through it.

When I was a medical student, one of my mentors was Dr. John Hardman. Some of you may remember Dr. Hardman as the chair of the pathology department at JABSOM for many years. When people would complain to him about the size of some of the medical textbooks, he would ask them "how would you go about eating a whale on a deserted island". People would look back at him like he was crazy. He would wait a few minutes, smiling at them before

explaining that in order to eat a whole whale, you would have to eat a little bit each day. At the end of a year, you would be surprised at how much you had consumed. The whale analogy isn't so crazy when you consider that I still remember it after all these years. Dr. Hardman was a wise man. Here is how you put this into action. When you get the book, figure out how long you have to read it. For example, let's say, one year. Then divide the book up with Post-it notes into 12 parts, one for each month. I've seen people actually tear the book into 12 parts but I don't recommend this method as it ruins the book. Then divide each of the parts into fourths, one for each week. You now have your weekly reading assignment for that subject for the year. Move onto the next book and do the same. As for the motivation to keep up with your weekly reading assignments, please refer to the first piece of advice. You are a professional now. Act accordingly.

The third piece of advice is straightforward: continue with your personal life. I know this sounds trite but let me give you some practical advice on how to do it. Sit down somewhere quiet and reflect on what is important to you. Perhaps it may be spending time with a spouse or significant other or going out to the movies on Friday night. Be as specific as you can. For example, "sports" is much to vague. Instead, put down exactly what you enjoy about sports such as playing tennis on Saturday afternoons or jogging in the evenings before dinner. When you are done listing everything, prioritize them from the most important to the least. Once you have done this, make the most important things on your list part of your daily week. Schedule time for highest priority items on your list after you have scheduled in your classes, study time and reading assignments. You may only be able to fit in a few of them but they will be the most important things in your personal life that you enjoy doing. The benefit of actually scheduling them is that you will be forced to make the time for them. Medical students who completely give up their personal life in order to study will inevitably become burned out. The reverse benefit of this list is that it will help you to recognize distractions that keep you from your work. When your friends call you up on Wednesday afternoon to go surfing right during your scheduled reading time, if this isn't one of the top items on your list, it becomes easier to recognize it as a distraction and say no. Remember, you are a professional now. Act accordingly.

The fourth piece of advice is to take an active part in the life of the medical school and your classmates. An important part of your life will be spent here with the people around you. You will go through good and bad times together and you will sometimes see each other at your worst and also at your best. You can help each other get through this and, by doing so, you will develop lifelong professional and personal relationships. Some of my closest friends today are former medical school classmates. Take the time to get to know yours. I promise you that you have best friends you haven't yet met sitting in this room right now.

My last piece of advice is to take part in research. It doesn't have to be bench research such as mixing chemicals in a lab. Consider doing a clinical research project or even write up a case report of an interesting patient. You will find many faculty members during your years here who would welcome medical students showing such an interest in their work. Research projects will enable you to explore in greater depth areas of medicine that you may be interested in doing a residency. Another great benefit is that research projects, posters, or papers will enhance your resume when you start to look for residency positions. Years ago, I sat on the admissions committee for a Residency Program. One of the areas they look at in the evaluation of candidates is participation in research. A research project on your resume can enhance your chances of getting the residency position of your choice so get involved.

I hope you will consider these words of advice from a JABSOM graduate: You are a professional now, act accordingly; Read, Read, Read; prioritize your personal life; get to know your classmates and consider taking part in research. Hopefully these ideas will make your time here even more successful. Good Luck.

Glioma: Challenges and New Insights in the Development of Effective Therapies

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Gliomas are the most common type of brain tumors and are among the deadliest of all human cancers. Gliomas are primary tumors that originate in the brain, as opposed to secondary brain tumors, which arise in other regions of the body and metastasize to the central nervous system. They are the second-most common cancer in children and the fourth leading cause of cancer-related mortality in patients over the age of 56. In the United States, more than 20,000 new cases of glioma are diagnosed each year, and for 2007 it is estimated that there will be over 12,000 deaths from brain tumors.[1] In Hawai'i, an average of 40 new cases per year have been diagnosed between 1999 and 2005.[28] The prognosis of gliomas has not significantly changed in decades and remains dismal with the current standard therapy. This article discusses the complexity of glioma cell biology, the limited efficacy of the present treatments, challenges in the development of effective targeted therapies, new insights and issues regarding the origin of gliomas, and future perspectives.

Glioma Classification and Present Standard Treatment

Gliomas are currently classified according to the World Health Organization (WHO) nomenclature, which is based on the work done by Bailey and Cushing over 80 years ago.[2] The WHO grading system correlates histological findings with clinical data and provides histo-pathological criteria to estimate the biological behavior and predict the prognosis of a tumor. The classification comprises all types of brain tumors and designates tumors according to the cell type that the cancer cells resemble: for example, oligodendrogliomas share features with mature oligodendrocytes; astrocytomas resemble mature astrocytes, while oligoastrocytomas have mixed features.[1] Within these classifications, the tumor grading represents a scale of malignancy, which ranges from grade I to grade IV and is defined by the degree of invasiveness, mitotic activity and other specific criteria, such as nuclear atypia, microvascular proliferation, and necrosis. According to this classification, the group of gliomas consists of Low

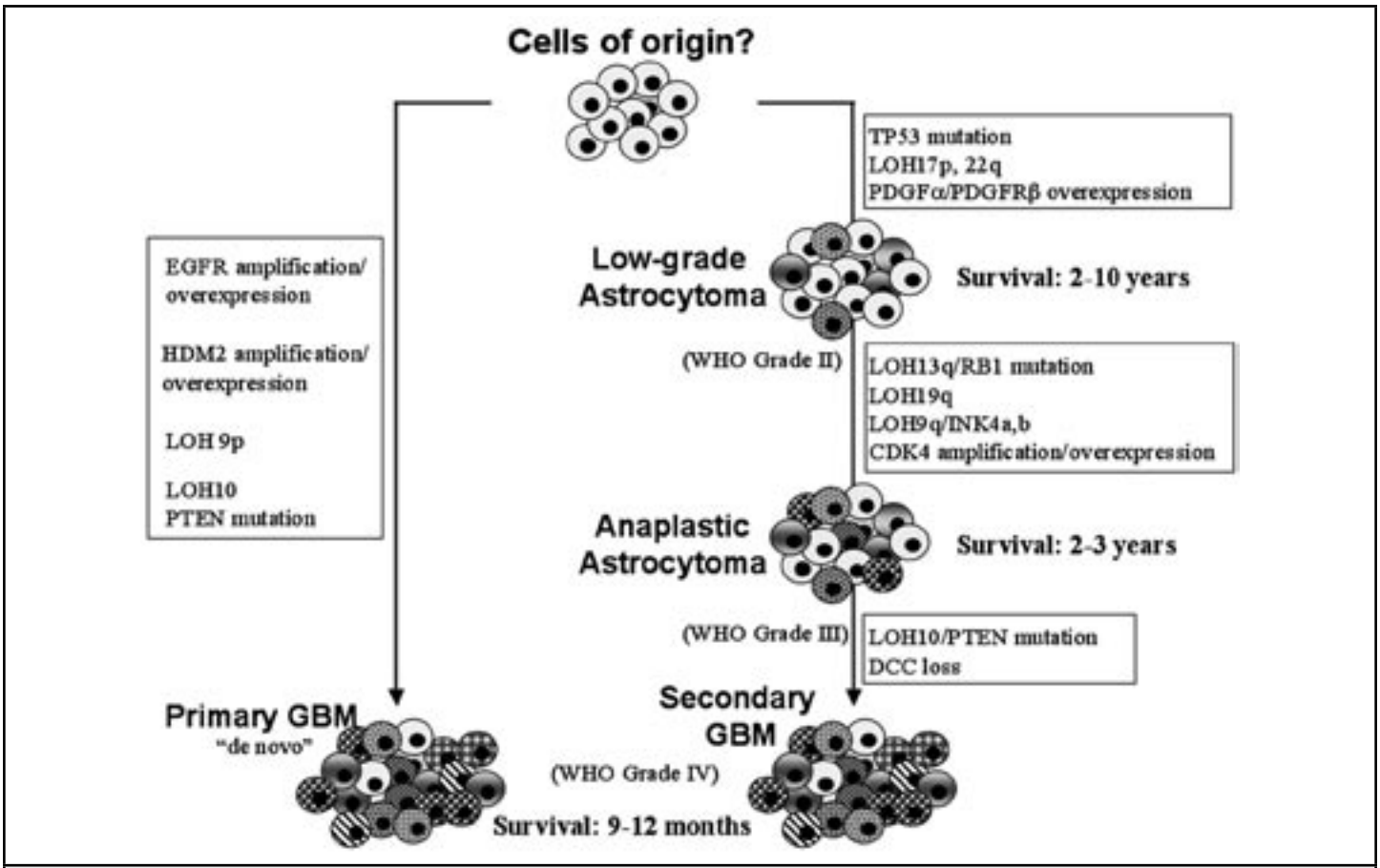

Figure 1.— Molecular alterations involved in the development and progression of gliomas.

Grade Astrocytoma (grade II), Anaplastic Astrocytoma (grade III) and Glioblastoma Multiforme (GBM) (grade IV). Grade I, which is called Pylocytic Astrocytoma, represents a separate disease from all other grades of gliomas. This is because pylocytic astrocytoma has a favorable prognosis and survival rate and is usually curable by surgery. Grade IV gliomas are the most aggressive and account for 30% of primary brain tumors in adults. They are denominated Primary GBMs when they arise "de novo", as opposed to Secondary GBMs, which result from the progression of a lower-grade glioma. With current standard care, patients with any type of GBM have a median survival (MS) of less than one year, whereas patients with Anaplastic Astrocytoma (grade III) survive 2-3 years. Patients with Grade II glioma can survive up to 10 years; however, the patient survival decreases, as these low-grade tumors can often progress to higher grades (Figure 1).

Despite rigorous effort in cancer research and numerous clinical trials, little improvement in overall survival or progression-free survival has been achieved in the last 20 years. Thus far the prognosis for patients with gliomas remains dismal. Surgical resection, followed by radiotherapy has been the mainstay of treatment. Only recently, a regimen of concurrent daily Temozolomide in combination with radiation therapy followed by adjuvant temozolomide unequivocally showed a benefit in newly diagnosed GBMs, by increasing the MS by 2.5 months.[3] Despite the clear benefit, such improvements remain modest from the clinical standpoint. In fact recurrent and progressive GBMs have even less favorable outcomes, reflecting the minimal benefits of the current standard therapies. It is evident that new therapeutic alternatives are needed. This entails a deeper understanding of the origin and development of gliomas, and the molecular mechanisms involved.

Glioma Patho-Biology and Current Clinical Trials

Significant new insights into the molecular mechanisms involved in the pathogenesis of gliomas have been gained over the last two decades. Phenotype and genotype analyses have identified specific molecular alterations characteristic of each glioma type. Genetic and epigenetic changes accumulate as the tumor progresses to a higher grade of malignancy (Figure 1). For example, inactivating mutations or loss of TP53, loss of heterozygosity (LOH) of chromosome (chr.) 17p, and overexpression of Platelet-Derived Growth Factor (PDGF) ligands and receptors are frequently found in low-grade astrocytomas. Anaplastic astrocytomas acquire LOH in chr.9q, 13q, 19q in addition to inactivation of Retinoblastoma susceptibility locus 1 (RB1), inactivation of INK4a and INK4b, and amplification or overexpression of Cyclin-Dependent Kinase 4 (CDK4). Finally, progression to Secondary GBM is associated with loss of chr.10 and acquisition of PTEN mutations. In contrast, primary de novo GBMs are characterized by amplification or overexpression of Epidermal Growth Factor Receptor (EGFR) in association with other alterations common to the Secondary GBMs (Figure 1).

The increasing understanding of glioma biology has led to the development of new anticancer treatments, which are currently being tested in clinical trials. These targeted molecular therapies afford greater specificity for the tumor cells with potentially less toxicity than conventional chemotherapy, which typically does not discriminate malignant cells and rapidly dividing normal cells. Array-based screenings of drug-compound libraries have identified several new small inhibitors, monoclonal antibodies, and ligand-toxin conjugates, which are now in different stages of preclinical and clinical testing. These inhibitors are usually aimed to correct the tumorigenic

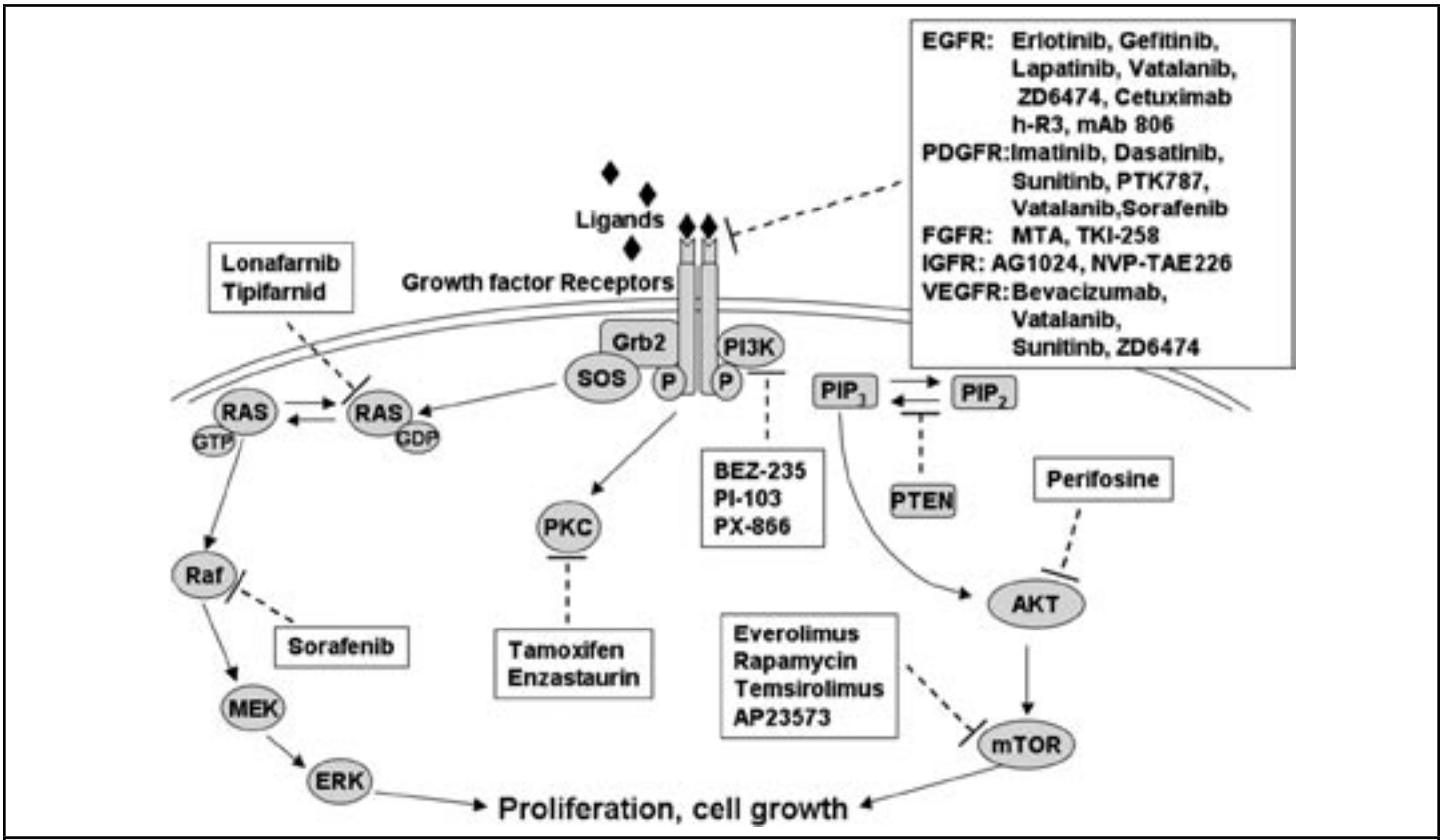

Figure 2.— Schematic representation of main oncogenic signaling pathways and molecular targets of compounds currently tested in the clinical trials for gliomas.

alterations, by targeting molecules within the signaling pathway deregulated by genetic abnormalities (Figure 2). For example, the drugs gefitinib and erlotinib inhibit the tyrosine kinase activity of EGFR,[4] whereas the natural product Rapamycin has been developed to target mTOR (Mammalian Target of rapamycin), which is a key protein in the downstream signaling of both EGFR and PDGF pathways.[5] Phase I and II trials with the two former drugs have been performed in *de novo* and recurrent GBM. Although the agents were well tolerated, the trials showed very little impact on overall patient survival.[4,6] Surprisingly no association between EGFR amplification or expression and response to EGFR inhibitors was found. The outcome is not so different for the mTOR inhibitors. Rapamycin, sirolimus, and its analogs temsirolimus, everolimus and AP-23573 are the most clinically advanced PI3K-Akt pathway inhibitors in malignant glioma. However, despite promising preclinical data, these compounds had minimal efficacy in recurrent GBM phase II trials.[7] PDGFR also seemed to represent an interesting target because it controls both the growth signaling pathway and angiogenesis.[8,9] However, three multi-center phase II trials with the PDGF Receptor-α and $-\beta$ inhibitor imatinib mesilate (Gleevec) reported results similar to historical controls. Furthermore, there was an unexpected rate of intratumoral hemorrhage.[10] As depicted in Figure 2, many other compounds are being tested. However, despite the considerable promise, single agent clinical trials have had low response rates and thus far have not demonstrated clinically meaningful survival benefits.

Challenges in the Development of Targeted Therapies

The reasons for failure of the targeted therapies are many and diverse: including the difficulties in drug delivery, the presence of multiple deregulated pathways, the inadequacy of the preclinical model systems, the heterogeneity of the primary tumors, and the complexity of the tumor niche. Unlike malignancies such as Chronic Myeloid Leukemias, which — in some cases — are driven by a single overactive gene, gliomas harbor many molecular alterations. Therefore, it is unlikely that targeting any single oncogene pathway will be sufficient to control tumor growth. Moreover, cancer cells may escape the treatment by intrinsic resistance to targeted therapies due to the pre-existence or development of multiple parallel and compensatory oncogenic pathways, which permit tumor survival. For these reasons multi-kinase inhibitors and drug-combinations are under development.[11]

The value of the existing *in vitro* and animal model studies in predicting the efficacy of such compounds in human gliomas has been increasingly questioned. Repeated *in vitro* passaging of cancer cell lines results in changes in phenotypic characteristics and genetic alterations. The resulting cell lines may bear little resemblance to those found within the primary human tumor. The authors and colleagues demonstrated that serum-containing media induced major *de novo* genomic alteration and chromosomal rearrangements in human primary GBM cells cultured under standard *in vitro* conditions.[12] After repeated *in vitro* passages, the primary cells do not recapitulate the phenotype of the original tumor, even though they regain tumorigenic potential in later passages.[12] On the other hand, *in vivo* xenograft studies, which are performed to validate intracranial tumor responsiveness to certain compounds, have other problems. The implantation of tumor cells within the brain of an immuno-compromised animal may not reconstitute the complexity of microenvironment, invasiveness, and angiogenesis found in such tumors in humans. Any processes that are dependent on tumor-host interaction affecting the tumor initiation, formation, progression and maintenance, cannot be reproduced in such xenograft systems. Unfortunately, these *in vitro* and *in vivo* cancer cell line-based studies may have led to major misinterpretations regarding the relevance of certain aberrant signaling pathways within cell lines compared to that in primary tumors.[12]

The major challenge faced in the development of new therapies for glioma is its heterogeneity. It has been long recognized that histologically identical brain tumors could exhibit strikingly diverse clinical behavior. Most likely, despite their similar histological appearance, their molecular and genotypic profile is different. Even the same glioma frequently exhibits intra-tumoral heterogeneity in terms of molecular expression.[13] Indeed this fact hampers correlative studies – which are usually based on small biopsy samples – aimed to identify the molecular signature of a tumor type or molecular markers of response to a drug. It is increasingly clear that success in treating brain tumors lies in understanding their origin, their diversity and the complex tumor cell microenvironment.

Intra-tumoral heterogeneity is likely the result of both variation in the tumor microenvironment and the coexistence of many cellular subclones within the same cancer cell population.[14] Whether the cell of origin of these subclones is terminally differentiated or is a stem cell is still a matter of debate. There is data supporting both theories. In support of the origin being differentiated cells, Holland and coworkers showed that viral transfer of the PDGF-B gene into cells expressing the GFAP protein - presumably a marker of terminally differentiated astrocytes - resulted in tumors exhibiting astrocytic and oligodendroglial features. These results would support the hypothesis that gliomagenesis is possibly mediated by de-differentiation of the transduced cells.[8] However because GFAP has been recently found expressed in progenitor cells as well, their conclusion is questionable.[15] On the other hand, it is conceivable that an actively proliferating stem cell, or a transiently amplifying precursor can accumulate enough mutations during its life to undergo neoplastic transformation. The possibility that Neural Stem Cells (NSC) may acquire deregulated self-renewal and differentiation capacities, would exactly explain the brain tumor as a heterogeneous entity made of cells with various degrees of differentiation. Furthermore, some authors suggested that deregulation of distinct progenitor populations may give rise to different subtypes of gliomas.[16]

In support of the hypothesis that the origin of the tumor subclones is a stem cell, Ignatova and coworkers isolated undifferentiated neural precursors from glial tumors.[17] Since then, several groups documented the presence of NSC-like cells with self-renewing and differentiation abilities. These cells are called Cancer Stem Cells (CSC) but to date, no convincing evidence clarifies their origin. Recent work of Jackson and coworkers provides preliminary support to the idea that CSC derive from NSC. They show that NSC express PDGFR-α and that administration of PDGF induces aberrant proliferation of these cells leading to the formation of hyperplastic regions, similar to gliomas, which regress upon withdrawal of PDGF.[18] Indeed molecular pathways involved in the regulation of

self-renewal and proliferation of adult NSC are active in gliomas. For example Notch signaling is required for maintaining the pool of multipotent NSC and their differentiation potential in the adult mouse brain. The authors and colleagues showed that Notch-1 and its ligands are overexpressed in primary human gliomas, and that their down-regulation by RNA interference caused cell death and reduced proliferation both *in vitro* and *in vivo*.[19] Other signaling pathways activated in both NSC and gliomas are EGF, PTEN, Sonic Hedgehog, Bmi-1, BMP, Olig-2 and Wnt.[20] These interesting results provide valuable knowledge, however a causal relationship between NCS and gliomagenesis will have to be further investigated.

A number of investigators have attempted to isolate CSC, on the basis of the expression of surface markers characteristic of stem cells, and to demonstrate their tumorigenic potential. However, several caveats encumber the approach used in these studies. First of all, the isolation of the so-called CSC relies on the CD133 marker.[21] The expression of CD133 has been associated with both NSC behavior and tumorigenic potential. However the CD133-negative population also harbors tumorigenic capacity[23] and not every CD133-positive cell is able to form tumors.[22] It is possible that the "true" CSC fraction requires further purification. In any case, although NSC and CSC share CD133 expression, the presence of this cell surface marker does not prove that the CSC are derived from NSC. Secondly, these studies relied on xenotransplantation to demonstrate the tumorigenic potential of CSC. As discussed above, these models may introduce a selection bias, because the engraftment may depend on homing and evasion of the host immune response: properties that are altered in an immuno-deficient animal. Therefore the xenograft experiments may not adequately reproduce the tumor niche and the complexity of the interaction between the tumor cells and the microenvironment that occurs in the primary tumors.

Another level of complexity is created by the tumor niche. Bidirectional crosstalk between tumor cells and the surrounding tissue has been long recognized.[25] Recently it has been reported that the tumor niche actively contributes to the tumorigenesis by maintaining the CSC population and creating a selective pressure which favors cell transformation.[24] Interestingly, it has been proposed that the tumor stem cell niche could contribute to tumor heterogeneity by inducing transformation of other cell types present within the niche itself, such as newly recruited NSC which possess an exquisite tropism for the tumor environment.[26] Regardless of the ontogeny of the CSC, the recent findings set a solid foundation that supports the hypothesis of the presence of cancer stem cells within the tumor. To carefully evaluate this hypothesis it is fundamental to define the right experimental setting, which will take into consideration the influence of the tumor niche.

Conclusion

The cancer stem cell model has fundamental implications for the development of new cancer therapeutic agents. If CSC give rise to these tumors, it may be necessary to alter the current paradigm in drug development. Eradication of the tumor may require targeting the CSC, therefore require the development of strategies that can affect the CSC, while sparing the normal stem cells. This seems challenging, given that many signaling pathways are common to both cell types. However, a recent study in a mouse model of leukemogenesis showed that modulation of one molecular pathway differentially affects haematopoietic stem cells and leukemia-initiating cells. The authors showed that while treatment with the mTOR-inhibitor, Rapamycin, depleted the leukemic cells, it allowed normal haematopoietic stem cell functions.[27] These data remarkably demonstrated that it is possible to identify selective pathways and therapeutically target CSC in certain types of tumors. A thorough understanding of the signaling pathways that distinguish the interaction of NSC with their niche and the tumor will shed new light on glioma cell origin and on the process of tumorigenensis. This will lead to new therapeutic strategies, which may render malignant brain tumors more amenable to treatment.

For more information about the Cancer Research Center of Hawai'i, visit www.crch.org.

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References

1. Central Brain Tumor Registry of the United Stated (CBTRUS): Statistical report: primary brain tumors in the United States, 1998-2002. Chicago, USA, 2006.
2. Bailey P, Cushing H. A classification of the tumors of the glioma group on a histogenic basis with a correlation study of prognosis. Philadelphia: Lippincott, 1926.
3. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO. Radiotherapy plus concurrent and adjuvant Temozolomide for glioblastoma. *N Engl J Med.* 2005,352:987-96.
4. Rich JN, Reardon DA, Peery T, Dowell JM, Quinn JA, Penne KL, Wikstrand CJ, Van Duyn LB, Dancey JE, McLendon RE, Kao JC, Stenzel TT, Ahmed Rasheed BK, Tourt-Uhlig SE, Herndon JE 2nd, Vredenburgh JJ, Sampson JH, Friedman AH, Bigner DD, Friedman HS. Phase II trial of gefitinib in recurrent glioblastoma. *J Clin Oncol.* 2004,22:133-42.
5. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. *Nat Rev Drug Discov.* 2006,5:671-88.
6. Prados MD, Lamborn KR, Chang S, Burton E, Butowski N, Malec M, Kapadia A, Rabbitt J, Page MS, Fedoroff A, Xie D, Kelley SK. Phase I study of erlotinib HCl alone and combined with temozolomide in patients with stable or recurrent malignant glioma. *Neuro-oncol.* 2006,8(1):67-78.
7. Galanis E, Buckner JC, Maurer MJ, Kreisberg JI, Ballman K, Boni J, Peralba JM, Jenkins RB, Dakhil SR, Morton RF, Jaeckle KA, Scheithauer BW, Dancey J, Hidalgo M, Walsh DJ. Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. *J Clin Oncol.* 2005,23:5294-304.
8. Fomchenko EI, Holland EC. Platelet-derived growth factor- mediated gliomagenesis and brain tumor recruitment. *Neurosurg Clin N Am.* 2007,18: 39-58.
9. Song S, Ewald AJ, Stallcup W, Werb Z, Bergers G. PDGFRbeta+ perivascular progenitor cells in tumors regulate pericyte differentiation and vascular survival. *Nat Cell Biol.* 2005,7:870-879.
10. Wen PY, Yung WK, Lamborn KR, Dahia PL, Wang Y, Peng B, Abrey LE, Raizer J, Cloughesy TF, Fink K, Gilbert M, Chang S, Junck L, Schiff D, Lieberman F, Fine HA, Mehta M, Robins HI, DeAngelis LM, Groves MD, Puduvalli VK, Levin V, Conrad C, Maher EA, Aldape K, Hayes M, Letvak L, Egorin MJ, Capdeville R, Kaplan R, Murgo AJ, Stiles C, Prados MD. et al. Phase I/II study of imatinib mesylate for recurrent malignant gliomas: North American Brain Tumor Consotium Study 99-08. *Clin Can Res.* 2006,12(16):4899-907.
11. Faivre S, delbaldo C, Vera K , Robert C, Lozahic S, Lassau N, Bello C, Deprimo S, Brega N, Massimini G, Armand JP, Scigalla P, Raymond E. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol.* 2006,24(1):25-35.
12. Lee J, Kotliarova S, Kotliarov Y, Li A, Su Q, Donin NM, Pastorino S, Purow BW, Christopher N, Zhang W, Park JK, Fine HA. Tumor stem cells derived from glioblastomas cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines. *Cancer Cell.* 2006,9:391-401.
13. Misra A, Chattopadhyay P, Dinda AK, Sarkar C, Mahapatra AK, Hasnain SE, Sinha S. Extensive intra-tumor heterogeneity in primary human glial tumors as a result of locus non-specific genomic alterations. *J Neurooncol.* 2000,48:1-12.
14. Dalerba P, Cho RW, Clarke MF. Cancer Stem Cells: Models and Concepts. *Annu Rev Med.* 2006,58:267-84.
15. Garcia AD, Doan NB, Imura T, Bush TG, Sofroniew MV. GFAP-expressing progenitors are the principal source of constitutive neurogenesis in adult mouse forebrain. *Nat Neurosci.* 2004,11:1233-41.
16. Girlertson RJ, Gutmann DH. Tumorigenesis in brain: location, location, location. *Cancer Res.* 2007,67(12): 5579-82.

"Glioma References" continued on p. 25

Issues in Medical Malpractice XIX

S.Y. Tan MD, JD, Professor of Medicine, John A. Burns School of Medicine, University of Hawai'i

Question:
Following thyroidectomy, patient developed persistent post-operative hoarseness. The surgery also left an ugly scar. Patient did not ask, and you did not specifically warn, of these complications. She was an anxious patient and you did not wish to upset her. However, she did sign, but did not really read or understand, a consent form that detailed these complications. She now sues you for lack of informed consent, claiming that she would not have undergone the surgery had she known of these risks. Which of the following are valid defenses (none, one, or more)?

A. Patient does not have a case because she signed consent form.
B. Disclosure of risks is not needed, as this is a particularly anxious patient who would be unduly frightened by the information.
C. The medical standard is not to tell patients about horrible complications unless specifically asked, and you are merely following community practice.
D. Consent is unnecessary because the thyroid condition was serious and surgery urgent.
E. Patient is unreasonable because she is using hindsight in claiming she wouldn't have undergone the surgery.

Answer: None Correct
Informed consent is not the same as a consent form. The former bestows a legal right to treat after the doctor has explained benefits and risks of harm to the patient who then gives his/her permission to proceed. The consent form, on the other hand, is merely documentation that such a process has taken place. A signed form where little or nothing was explained to the patient would not constitute informed consent. The patient does not have a duty to ask about risks, whereas the doctor always has an affirmative duty to inform.

However, risk information can sometimes be terrifying to anxious patients, and disclosure may prevent them from benefiting from the proposed treatment. Thus, the doctor has a qualified privilege to withhold such information in the appropriate clinical setting. This exception to disclosure of risks is called the therapeutic privilege, but it should rarely be invoked. The facts must clearly indicate that disclosure would be harmful to the patient's overall well being. This case does not rise to such a level, and the doctor is unlikely to get away with this defense.

The emergency exception does not apply here as there was time for obtaining consent.

Jurisdictions differ as to whether the standard of disclosure should be physician-oriented (also called medical, professional, or community standard) or patient-oriented. This makes a big difference to the defense, as the patient standard is much tougher to meet. Increasingly, states are replacing the physician-oriented standard with the patient-oriented standard. Under this tougher disclosure rule, the information a reasonably prudent person in the patient's situation would have wanted will determine what the doctor needs to disclose.

Patient-Oriented Risk Disclosure

The traditional rule governing risk disclosure is physician-oriented, i.e., what the community of doctors would normally disclose. This tracks the legal standard for medical malpractice where the conduct of the physician is judged by what is ordinarily expected of a similarly situated physician (*"In determining the question of physician's liability for non-disclosure courts generally follow the rule applicable to medical malpractice actions predicated on alleged negligence in treatment which requires the question of negligence to be decided by reference to relevant medical standards…"*— this Hawai'i case has since been overruled).[1]

However, in 1972, the US Court of Appeals in the District of Columbia decided Canterbury v. Spence, an important case which started the movement away from the physician standard. In Canterbury, a 19-year-old young man developed paraplegia the day after spinal surgery. The risk of this happening was 1%, but it was not disclosed to the patient. Declaring *"the patient's right of self-decision shapes the boundaries of the duty to reveal,"* the Court went on to state:

> *"A risk is… material when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forgo the proposed therapy… any definition of scope in terms purely of a professional standard is at odds with the patient's prerogative to decide on projected therapy himself…"*[2]

This decision was quickly adopted by California in Cobbs v. Grant[3] and by other states. Hawai'i too adopted the new standard in Carr v. Strode:

> *"We believe that the patient-oriented standard of disclosure better respects the patient's right of self-determination and affixes the focus of inquiry regarding the standard of disclosure on the motivating force and purpose of the doctrine of informed consent… It also protects against the pitfalls of proof associated with the physician-oriented standard… Moreover, not only should the patient's decision remain at the forefront when assessing the physician's disclosure to his or her patient in each case, but we also believe that, barring situations where the therapeutic privilege exception to the physician's duty to disclose is applicable, what the medical community believes the patient needs to hear in order for the patient to make an informed decision is insufficient, without more, to resolve the question of what an individual patient reasonably needs to hear in order for that patient to make an informed and intelligent choice regarding the proposed treatment…We therefore expressly adopt the patient-oriented standard applicable to a physician's duty to disclose risk information prior to treatment, and, to the extent that Nishi may be construed otherwise, it is overruled."*[4]

In contrast to DC and states like California, Hawai'i, New Jersey and Louisiana, the majority of jurisdictions still apply the physician-oriented standard. However, the legal trend is increasingly towards the harder-to-satisfy patient-oriented standard.

This article is meant to be educational and does not constitute medical, ethical, or legal advice. It is excerpted from the author's book, *"Medical Malpractice: Understanding the Law, Managing the Risk"* published in 2006 by World Scientific Publishing Co., and available at Amazon.com. You may contact the author, S.Y. Tan MD, JD, at email: siang@hawaii.edu or call (808) 728-9784 for more information.

Reference

1. *Nishi v. Hartwell*, 473 P.2d 116 (Haw. 1970).
2. *Canterbury v. Spence*, 464 F.2d 772 (D.C.Cir. 1972).
3. *Cobbs v. Grant*, 502 P.2d 1 (Cal. 1972).
4. *Carr v. Strode*, 79 Hawaii 475 (1995).

Glioma References

17. Ignatova TN, Kukekov VG, Laywell ED, Suslov ON, Vrionis FD, Steindler DA. Human cortical glial tumors contain neural stem-like cells expressing astroglial and neuronal markers in vitro. *Glia.* 2006,39(3):193-206.
18. Jackson EL, Garcia-Verdugo GM, Gil-Perotin S, Roy M, Quinones-Hinojosa A, VandenBerg S, Alvarez-Buylla A. PDGFR alpha-positive B cells are neural stem cells in the adult SVZ that form glioma-like growths in response to increased PDGF signaling. *Neuron.* 2006,51:187-199.
19. Purow BW, Haque RM, Noel MW, Su Q, Burdick MJ, Lee J, Sundaresan T, Pastorino S, Park JK, Mikolaenko I, Maric D, Eberhart CG, Fine HA. Expression of Notch-1 and its ligands, Delta-like-1 and Jagged-1, is critical for glioma cell survival and proliferation. *Cancer Res.* 2005,65:2353-63.
20. Sanai N, Alvarez-Buylla A, Berger MS. Neural stem cells and the origin of gliomas. *N Engl J Med.* 2005,353(8):811-22.
21. Vescovi AL, Galli R, Reynolds BA. Brain tumour stem cells. *Nat Rev Cancer.* 2006,6:425-36.
22. Beier D, Hau P, Proescholdt M, Lohmeier A, Wischhusen J, Oefner PJ, Aigner L, Brawanski A, Bogdahn U, Beier CP.CD133(+) and CD133(-) glioblastoma-derived cancer stem cells show differential growth characteristics and molecular profiles. *Cancer Res.* 2007,67(9):4010-5.
23. Wang J, Sakariassen PO, Tsinkalovsky O, Immervoll H, Boe SO, Svendsen A, Prestegarden L, Rosland G, Thorsen F, Stuhr L, Molven A, Bjerkvig R, Enger PO.CD133 negative glioma cells form tumors in nude rats and give rise to CD133 positive cells. *Int J Cancer.* Oct 22; 2007 [Epub ahead of print]
24. Joyce JA. Therapeutic targeting of the microenvironment. *Cancer Cell.* 2005,7(6):515-20.
25. Calabrese C, Poppleton H, Kocak M, Hogg TL, Fuller C, Hamner B, Oh EY, Gaber MW, Finklestein D, Allen M, Frank A, Bayazitov IT, Zakharenko SS, Gajjar A, Davidoff A, Gilbertson RJ. A perivascular niche for brain tumor stem cells. *Cancer Cell.* 2007,11(1):69-82.
26. Fomchenko EI, Holland EC. Origins of brain tumors--a disease of stem cells? *Nat Clin Pract Neurol.* 2006,2(6):288-9.
27. Zhang J, Grindley JC, Yin T, Jayasinghe S, He XC, Ross JT, Haug JS, Rupp D, Porter-Westpfahl KS, Wiedemann LM, Wu H, Li L. PTEN maintains haematopoietic stem cells and acts in lineage choice and leukaemia prevention. *Nature.* 2006,441:518-22.
28. Dr. Michael Green, unpublished data.

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1. Jones J. Necrotizing Candida esophagitis. *JAMA*. 1982,244:2190-2191.
2. Style L. *Biochemistry*. 2nd ed. San Francisco, Calif: WH Freeman Co; 1981:559-596. [Not CA]
3. Kavet J. Trends in the utilization of influenza vaccine: an examination of the implantation of public policy in the United States. In: Selby P, ed. *Influenza: Virus, Vaccines, and Strategy*. Orlando, Fla: Academic Press Inc; 1976:297-308.

Footnotes

Place footnotes outside of punctuation marks. (e.g. These include diabetes,[5] hypertension, orthopedic complications,[6] asthma, sleep apnea,[7] eating disorders[8] and psychosocial problems.[9])

Acknowledgments

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1.Stryer L. *Biochemistry*. 2nd ed. San Francisco, Calif: WH Freeman Co; 1981:559-596.

References to Website Example

1. Roth AE. Report on the design and testing of an applicant proposing matching algorithm, and comparison with the existing NMRP algorithm [design review of the National Resident Matching Program home page]. December 6, 1996. Available at: http://www.pitt.edu/~alroth/phase.1html. Accessed August 1, 1997.

Table Sample

Table 1.— Age Structure of the Study Population

Age	Ebeye CHC Study Population	%	Ebeye Census	%
30-39	302	43%	1227	45.5%
40-49	206	30%	843	31.2%
50-59	110	16%	391	14.5%
60-74	52	7.5%	193	7.2%
≥ 75	22	3.1%	40	1.5%
Total	692		2694	

Comparison of age structure of study population with age structure of residents of Ebeye as recorded in 1999 Census.

Figure Sample

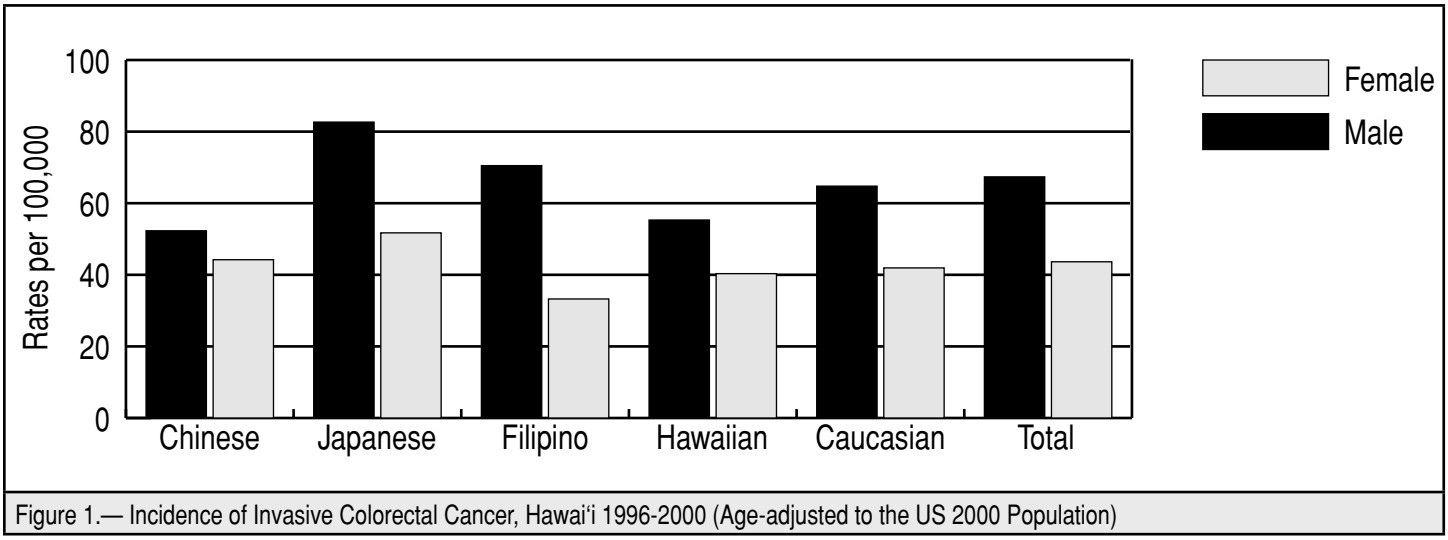

Figure 1.— Incidence of Invasive Colorectal Cancer, Hawai'i 1996-2000 (Age-adjusted to the US 2000 Population)

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Russell T. Stodd MD

❖ **DO I REMEMBER?!? WHY AT THE TIME I WAS...**

Everyone has experienced the recall imprint of a particular event to produce a vivid memory of what one was doing when President Kennedy was shot, the space shuttle Challenger exploded, Pearl Harbor was bombed (a few of us are still around), or when the twin towers came down. This boost in memory is caused in part by a stress reaction to norepinephrine, but scientists have not sorted out how the hormone produces the effect. A team at Cold Spring Harbor Laboratory in New York traced the action to a glutamate receptor (GluR1) attaching to the surface of the nerve cells to strengthen the nerve signals. The significance of the research is that it can lead to new drugs for control of destructive, painful memory problems such as the emotional overload of post-traumatic stress disorders. Sometimes you need to forget.

❖ **YOU CAN BE YOUNG ONLY ONCE, BUT YOU CAN BE IMMATURE FOREVER.**

The good news is that the National Highway Traffic Safety Administration (NHTSA) just released figures for 2006, and found that motor vehicle fatalities (43,642) were at the lowest level in 5 years. Moreover, it was the lowest rate per 100 million miles traveled ever recorded**!** The bad news is motorcycles. The biker fatality rate increased by 5.1% from 2005 accounting for 11% of total highway deaths. That is the highest share ever for motorcycle fatalities, and makes 9 straight years that biker fatalities have increased. Once again, it's the baby boomers. The average age of motorcycle owners has increased to 40.2 years, and more than 25% of bikes are registered to people age 50 and older. Adjusted for miles traveled, bikers were 34 times more likely to die on the highway than occupants of passenger cars. In the meantime sophisticated lobbying by rider groups such as ABATE, have repealed laws requiring helmets in 30 states, and recorded data show that when bikers have a brain protection choice, motorcycle deaths increase. You can lead a biker to a helmet, but you can't make him think.

❖ **THE GREATEST EVIL IS PHYSICAL PAIN. (ST. AUGUSTINE)**

In a survey of 1,700 students at 8 medical schools conducted by the Cambridge Health Alliance (affiliated with Harvard Medical School), J. Wesley Boyd, MD, PhD, found that more than a third of the students surveyed didn't know that the Geneva Conventions prohibit doctors from threatening prisoners or depriving them of food and water. He also posed the three-layered query would you: (1) threaten to inject a detainee with a psycho-tropic drug without intending to, (2) inject a harmless saline solution while saying it was lethal, (3) kill a detainee with an injection. More than 25% said they would perform the first two acts, but not the last, and a frightening 6% said they would do all of the above. The American Medical Association said doctors should refuse all three. The great majority of US military doctors come from medical schools, and the military can call up civilian docs in a crunch, so medical schools have a responsibility to teach the Geneva Conventions. The matter of medical ethics regarding detainees is critical when we have a White House that once believed the President didn't have to recognize the Geneva Conventions, provided an abstrusely worded ban on the use of cruel and inhuman treatment of suspected terrorists, and endorses questionable eavesdropping policies. And we are all supposed to feel safer.

❖ **THE TRUTH WILL COME OUT! EVENTUALLY...**

Outgoing Surgeon General, Dr. Richard Carmona, the Bush appointee who served from 2002 to 2006, reported to a congressional committee that administration people repeatedly tried to weaken or suppress health reports based on political considerations. Specifically, reports about stem cells, sex education, emergency contraception (morning after pill), were marginalized, ignored, or buried because of a theological or partisan agenda. He wrote, "In public health, as in a democracy, there is nothing worse than ignoring science." That is true, doctor, but why did it take you five years to speak the truth to the public?"

❖ **THE BILL OF RIGHTS - VOID WHERE PROHIBITED BY LAW.**

One would believe that a terminally ill patient would have access to a potentially lifesaving drug even if the Food and Drug Administration review process was not completed. Not according to the Court! The US Court of Appeals in Washington, D.C., rejected the argument that such a right to self-preservation was protected by the Constitution. The Oregon law which allows terminally ill people to self-destruct remains intact, but the right to attempt to preserve one's own life is not protected. Thank you, judge!! In the words of Charles Dickens, "if that is the law, the law is an ass – a idiot" Lawyers representing terminally ill patients plan to appeal to the Supreme Court.

❖ **THE MOST COMMON OF ALL FOLLIES IS TO BELIEVE PASSIONATELY IN THE PALPABLY UNTRUE.**

❖ **CONFESSION MAY BE GOOD FOR THE SOUL, BUT BAD FOR YOUR CAREER.**

Dr. James Watson's work in molecular biology led to the discovery of the structure of DNA, and with colleagues Francis Crick and Maurice Wilkins, he was awarded the Nobel prize in physiology and medicine in 1962. This work virtually kicked off the genetic revolution now in full flower. Unbelievably, Dr. Watson recently told the *London Sunday Times* he is "inherently gloomy about the prospect of Africa because all our social policies are based on the fact that their intelligence is the same as ours – whereas all the testing says not really." For an entertainer such as Michael Richards or a television-sponsored bounty hunter like Dog to inadvertently disclose a bigoted mind, is shameful and disgusting, but not really surprising. But, how can one explain "inherent" prejudice in the mind of a scientific giant?

❖ **PERHAPS IT WOULD BE BEST TO ESCHEW ALBERT ARNOLD GORE, IV. TRY SONNY BOY.**

For many reasons, one must be careful with contracts, including bookmakers. In Ireland, Paddy Power PLC rated Al Gore a 14 to 1 long shot on the celebrity list for the possibility of being arrested. What the bookies failed to do was specify Al Gore Jr. When the former vice-president's son, Al Gore III, was picked up for drug possession, the firm had to pay out $13,500. Loss prevention requires proper documentation!

❖ **THERE IS NEVER A RIGHT TIME FOR THINGS TO GO WRONG.**

In Eugene, Ore., a 38-year-old motorist was busy text messaging when he approached a railroad crossing. He looked up to see a train approaching, but could not stop in time. The train crew called 911 and rescuers had to pry the man from his crushed auto. He was trying to text message "Ht trn nd help."

ADDENDA

- ❖ Forty percent of Americans have never known a president other than a Bush or Clinton, and it could happen again and again and again and again and…
- ❖ 80,000 Americans are injured by lawnmowers each year. Most of the damage is caused by flying projectiles, not by contact with moving blades.
- ❖ Overheard in the OR, "Wait a minute. If this is his spleen, what's that?"
- ❖ A padded headboard does not qualify as safe sex.

ALOHA AND KEEP THE FAITH — rts■

Contents of this column do not necessarily reflect the opinion or position of the Hawai'i Ophthalmological Society and the Hawai'i Medical Association. Editorial comment is strictly that of the writer.

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—Mitchell B. Miller, MD, physician member of the AMA and his local and state societies

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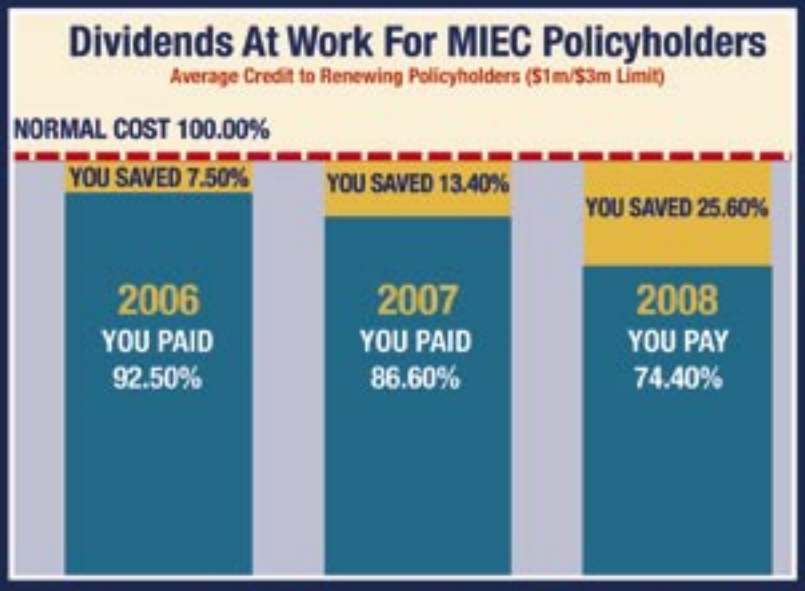

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