Emphasis Program

Biomedical Informatics

Community Health

Global Health

Healthcare and Public Health Research and Management

Laboratory-Based Biomedical Research

Medical Education

Medical Humanities, Ethics and Policy

Medical Scientist Training Program

Patient-Oriented Research

Poster Presentations Forum VIII

April 26, 2013

10:00AM - 11:30AM
and
11:45AM - 1:15PM

School of Medicine

VANDERBILT UNIVERSITY

Message from Bonnie M. Miller, M.D., Senior Associate Dean for Health Sciences Education

The Vanderbilt University School of Medicine is firmly committed to training future leaders and scholars in medicine. This includes the ability to recognize and understand the various challenges facing medicine as well as the vision and skill to address these challenges. That's why we've created the EMPHASIS PROGRAM – an opportunity for our students to acquire specialized knowledge and experience in a focused area of their choosing.

The EMPHASIS PROGRAM is a unique mode of self-directed study, which takes place during the first two years of medical school. We match the students' area of interest with those of committed faculty mentors, providing them the opportunity to draw from seasoned professionals. Students cultivate knowledge and skill through these mentorship experiences, as well as hands-on research and study in desired areas of focus.

There are eight EMPHASIS focus areas in which students can choose projects: Biomedical Informatics, Community Health Initiatives and Outreach, Global Health, Healthcare and Public Health Research and Management, Laboratory- Based Biomedical Research, Medical Education, Medical Humanities, Ethics, and Policy, and Patient-Oriented Research. Students choose their areas, mentor, and projects during the fall semester of first year, and then use the spring semester to acquire general knowledge and skills within their EMPHASIS area. During this semester, they also work with mentors to design their studies. All students devote a minimum of eight weeks to their projects during the summer between their first and second year while supported by an EMPHASIS stipend. Projects are completed during the second year and, in the spring; students display their work as a poster presentations at our Spring EMPHASIS Forum.

Students who are part of our Medical Scientist Training Program also participate in the poster presentation event and are also featured in this publication. By the time they have completed the second year of medical school, these students will have selected research areas that will lead their doctoral degrees in biomedical research. The abstracts they have provided will serve as roadmaps for their future full-time doctoral studies.

In this publication, you will find abstracts of all projects carried out by the Class of 2015. The broad range of projects reflects the diversity of interests our students chose to pursue during their early years in medical school.

Message from Lillian Nanney, PhD, Director of the Emphasis Program

In devising the EMPHASIS PROGRAM, the Vanderbilt University School of Medicine sought to channel the diverse skills and passions of our students into the pursuit of scholarship and leadership. Believing that this aim is best achieved in the context of a relationship with a mentor, we sought the assistance of faculty in many different disciplines across the medical school, the university, the community, the country, and the globe. The response from faculty mentors has been extraordinarily generous, in terms of both time and commitment. Each student has been able to work closely with a mentor for the duration of the program, spanning the first two years of medical school and including eight weeks during the intervening summer. As Director of the EMPHASIS PROGRAM, I want to express my thanks to those faculty in the Nashville area and several around the globe who willingly accepted the responsibility and interactive opportunity to mentor these students. The quality of the work reported in this volume is evidence of the effectiveness and creativity of this collaboration.

The 108 abstracts herein represent the posters that will be presented at the EMPHASIS Forum at Vanderbilt University School of Medicine on April 26, 2013 Of these abstracts, 95 represent the work of students who entered the EMPHASIS PROGRAM in the fall of 2011. Thirteen abstracts describe one of the research rotations performed by students in Vanderbilt's Medical Scientist Training Program as they learned techniques and tested their interests prior to selecting a dissertation advisor.

Consistent with the aims of the EMPHASIS PROGRAM, the topics covered in the abstracts are wide ranging. Students explored innovative projects as diverse as medical informatics and healthcare policy. Students carried out complex, cutting edge laboratory investigations and undertook projects on healthcare delivery in developing countries and among the urban poor.

Many of these projects will soon be reported at scientific meetings and in peer-reviewed publications. Some students plan to continue to work on their projects as they move to the next phase of their medical education. Others may take their newly honed skills and apply their scholarly skills to push forward other frontiers in medicine. Regardless of the future directions these projects take, it is clear the collaboration between students and mentors has provided significant benefit to students, faculty, and the advancement of knowledge. For many, the opportunity to work closely with a faculty member over the past 18 months has forged a relationship that will endure in the incoming years.

The EMPHASIS PROGRAM was the result of many years of discussion and planning. Experiential learning with an opportunity to make a difference in one small area of medicine was an overarching objective of Vanderbilt's scholarly research concentration opportunity Once initiated, refinement has continued as we have learned from the experience of students and their mentors. However, if we judge the work presented herein, the overarching goal of nurturing scholarship and leadership in our students has been a win-win experience for student and mentor alike and many project will eventually translate into pivotal gains for patients.

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Cindy Gadd PhD, is an Associate Professor of Biomedical Informatics. She has been the Director of Graduate Studies for Department of Biomedical Informatics graduate degree programs since January 2006 and is the Principal Investigator on an NLM Biomedical Informatics Training Grant. She is an elected Fellow of the American College of Medical Informatics and an active participant in the informatics education initiatives of the American College of Medical Informatics Association. Her primary area of research and publication is the implementation and evaluation of integrated clinical information systems, including electronic health records (EHR) systems, in large health care networks. Since joining Vanderbilt, Dr. Gadd has become a co-investigator in the evaluation of the development, and sustainability of a regional health information exchange and is co-developing ePrescribing evaluation research focused on surrogate prescribers.

Biomedical Informatics

Biomedical Informatics is the scientific field that deals with the storage, retrieval and optimal use of biomedical information for problem solving and decision-making. Vanderbilt Biomedical Informatics is the largest academic department of biomedical informatics in the country, with more than 50 faculty members, a graduate training program, and a portfolio of research and development projects that spans from computational biology and bioinformatics applied to the understanding of biological molecules, through advanced clinical information systems that care for hundreds of thousands of patients at Vanderbilt, to regional health information projects that span many states. Research is focused on all areas of healthcare ranging from computer programs that alert physicians about patient problems to tools that assist basic scientists with bench research. The students' educational focus is in three general areas of biomedical informatics:

1. Developing, evaluating and refining the computer tools available to clinicians caring for patient
2. Using computer applications and techniques to better enable clinicians to assemble evidence for patient care and research.
3. Managing biologic or genomic information in ways that support discovery of new therapies or that guide basic science research.

"It has been very exciting to observe students as they learn about the field of biomedical informatics. We have had students with a wide range of technical backgrounds who have made landmark contributions to the field. The Emphasis Program is facilitating an exchange of knowledge among our medical students, our faculty, and our graduate students, in a way that has enhanced the intellectual capabilities of all three groups."

ICD-10-CM CROSSWALKS IN THE PRIMARY CARE SETTING: ASSESSING RELIABILITY OF THE GEMS AND REIMBURSEMENT MAPPINGS

Robert W. Turer
Biomedical Informatics

Background Problem

On October 1, 2014, the Department of Health and Human Services mandates that all HIPAA covered entities must transition from ICD-9-CM (I9) to ICD-10-CM/PCS (I10) in all electronic transactions. Providers, payers, and researchers are scrambling to upgrade software and train personnel to handle the new coding systems. The Centers for Medicare and Medicaid Services (CMS) published the general equivalence mappings (GEMs) and reimbursement mappings (RMs) as guidelines for organizations seeking to develop forward and backward crosswalks during the transition. Studies in reimbursement settings have shown that the GEMs and RMs can be used as foundations for these crosswalks, but blind use as true crosswalks leads to significant reimbursement changes.

Objectives

No independent studies have assessed the GEMs and RMs in a real-world clinical setting. To address this gap, we contracted 3M Consulting/SourceHOX (Lexicode) to natively dual code one hundred cases from an adult outpatient clinic into both I9 and I10, and compared those codes to mappings in the GEMs and RMs.

Materials and Methods

Each diagnosis was characterized as being derivable or non-derivable from the I9-to-I10 GEMs, I10-to-I9 GEMs, and RMs. Diagnoses represented by one I9 and one I10 code were more carefully characterized based on whether they matched an entry in the GEMs and what type of entry they matched in the GEMs. Unmatched one-to-one diagnoses were analyzed to explain why they did not match the GEMs.

Results

More than 80% of diagnoses were derivable from the GEMs and RMs. However, that leaves a significant portion that were not. Of those unmatched diagnoses, only between 14 and 18% could be explained by blatant coder error.

Conclusions

The combination of these results demonstrates the importance of cautious use of the GEMs and RMs and the need for organizations to perform their own analyses to prevent significant impacts on reimbursements and longitudinal data collection.

Acknowledgements

Theresa Zuckowsky, Jennifer Causey, and the entire ICD-10 Transition team at Vanderbilt contributed both data and insight to this project. Rischelle Jenkins from DBMI has been extremely supportive with scheduling and resources throughout the Emphasis program.

Mentor / Department

S. Trent Rosenbloom MD, MPH has been integral to this project and to this mentorship program. This work would have been impossible without his extensive assistance. Cynthia S. Gadd, Ph.D., MBA, MS has provided support and guidance throughout the Emphasis program.

Barbara Clinton, M.S.W. is Director of the Center for Health Services at Vanderbilt University. Ms. Clinton is an Adjunct Assistant Professor in both the medical schools and nursing schools at Vanderbilt and has worked as a counselor, a community organizer and a therapist with children. Ms. Clinton helped develop a system of alternative health services for seniors for the state of Georgia and has served as an advisor to former Vice President Al Gore, the Tennessee Commission on Aging, the National Center for Children in Poverty at Columbia University, the Appalachian Rural Science Initiative of the National Science Foundation, and several private foundations.

Community Health Initiatives & Health Outreach

Through the Community Health Emphasis Program, medical students develop a substantial set of products that address an unmet community health problem. As they do this, they develop skills in community leadership and scholarship, and helping patients practice positive health behaviors. Students receive training from Center for Health Services in community research strategies including focus groups, in-depth interviews, community needs assessments and grant writing. Nonprofit organizations serve as community partners, helping students develop a strong relationship with the community.

Community Health Emphasis Enduring Understandings

- The health of the community plays a critical role in the health of the individual.
- Health may be strongly influenced by a person's physical, social, political, economic, psychological, or cultural environment
- You think you know the full answer, but you don't. There are non-medical explanations, resources, and solutions to consider.
- Successful community health programs are interdisciplinary, built from the community level up.

Community Health Emphasis student projects may address

- Health risks/diseases that disproportionately affect underserved populations.
- Obstacles to health and healthcare for the underserved.
- The socio-cultural, historical and medical aspects of caring for an underserved population.
- Principles, approaches and skills needed by medical providers in an underserved community.
- Skills and strategies that motivate patients to practice positive health behaviors
- Diagnosing the health needs of a community and designing plans to meet those needs.

"These students who selected Community Health were, not surprisingly, advocates by nature. They demanded the support of the school in full measure, so that community people would not be left behind in the excitement over bench research or more glamorous emphasis areas. Thus group of Community Health Emphasis students are brilliant, energetic, and helpful to each other step of the way. It was pure pleasure to work with them and to share in their pride as their objectives were met, their papers were accepted for publication, they achieved funding for their community projects, and in some case, became award winners for service to the community."

THE IMPACT OF IMMIGRATION ON THE DEVELOPMENT OF RESILIENCE AMONG LATINA MOTHERS

Gretchen Edwards
Community Health Initiatives and Health Outreach

Objectives

Despite extensive history of trauma, undocumented status, economic instability, and disruption of the core family unit due to immigration and/or deportation, not all Latina women and their children face poor health outcomes. This project seeks to understand and evaluate how the immigrant experience shapes both personal and family resilience among first-generation Spanish-speaking immigrant mothers, with the ultimate goal of incorporating these skills and attitudes into local health and social service resources.

Summary

After establishing partnerships with two community organizations—the Maternal Infant Health Outreach Worker (MIHOW) Program and Conexión Américas, twenty in-depth individual interviews were performed and major themes were identified. The primary source of stress among participants was revealed to be undocumented status, contributing to depression, isolation, and anxiety. This stress was compounded by extensive history of trauma as well as geographic and linguistic isolation. Despite these barriers, qualitative analysis revealed two major factors contributing to resilience and improved mental health status: early establishment of support networks as well as a high level of participation in group-centered, culturally-sensitive educational programs. Finally, first pregnancy within the US was identified as a key intervention interval for involving Latina immigrant mothers in community health and social service resources.

Brief Description

This study utilized community-based participatory research to identify the impact of immigration upon the development of resilience among Latina mothers in Nashville, TN.

Conclusions

These qualitative findings will provide continued support for existing programming and form the basis for future mental health intervention programs among Latina immigrant mothers.

Acknowledgements

Adriana Bialostozky, MD; Maternal Infant Health Outreach Worker (MIHOW) Program; Conexión Américas; Catholic Charities of Middle Tennessee – Hispanic Services

Mentor / Department

Barbara Clinton, MSW (Center for Community Health Solutions); Tonya Elkins, MSW (Maternal Infant Health Outreach Worker Program)

REDUCED SPORTS PARTICIPATION IN CHILDREN WITH EPILEPSY

Richard Latuska
Community Health Initiatives and Health Outreach

Objectives

Understand potential drivers of non-participation in after school sports activities among children with epilepsy.

Summary

In light of the declaration on January 25, 2013 by the Department of Education (DOE) that "schools should make 'reasonable modifications' for disabled students who want to play on traditional sports teams or in their own leagues", this analysis provides important current data on the activity participation levels of children with epilepsy. We analyzed data from the 2007 National Survey of Children's Health; a population-based, cross-sectional, random-digital-dialing survey using a complex, multi-cluster, probability sampling design. Potential confounders were selected for clinical/statistical significance. Multivariate logistic regression was used to examine the association between epilepsy and sports participation. Of 48,649,074(weighted) respondents, 306, 209 parents (0.6%) reported their child currently having epilepsy/seizure disorder (with 66.7% with having a "mild" and form compared to 33.3% having a moderate/severe epilepsy form). Only 34% of children with epilepsy participate in after school sports. After controlling for other variables (age, highest household education level, insurance status, presence of a medical home, functional limitation status, and feelings of safety at school) children with epilepsy were found to be 2.0 times more likely not to participate in after school sports compared to children without epilepsy (95% CI: 1.03, 3.92). Among those with mild epilepsy, for whom participation would be recommended, not feeling safe at school was the only covariate independently associated with lack of participation.

Brief Description

This study utilized data from the 2007 National Survey of Children's Health to determine if sports participation among children with epilepsy is less than children without epilepsy and if so, to identify potential drivers of non-participation in after school sports activities for children with epilepsy.

Conclusions

Misconceptions around the degree to which epilepsy should result in limited activity participation continue to exist despite recommendations to the contrary. Given the well documented physiological and psychological benefits of physical activity for children, parents should receive adequate education from physicians about this disease and the degree to which activities should be adapted.

Acknowledgements

Richard Latuska was supported by Vanderbilt University School of Medicine. There were no funds involved in this study. Shanthi Krishnaswami and Melissa McPheeters work for the Evidence-Based Practice Center of the Institute for Medicine and Public Health at Vanderbilt University Medical Center and served as faculty mentors for this project and played a role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, and approval of the manuscript. Melissa McPheeters and Richard Latuska had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors involved with the production of this manuscript have no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations

Mentor / Department

Melissa McPheeters, Evidence-Based Practice Center of the Institute for Medicine and Public Health at VUMC

THE INFLUENCE OF ISLAMIC VALUES ON THE LIVES OF CHILDREN WITH AUTISM

Jasia Mahdi
Community Health Initiatives and Health Outreach

Objectives

The objective of this project was to examine the specific influence of Islamic values on the way in which the diagnosis of Autism Spectrum Disorder is regarded and how it affects the way families perceive, treat, raise, and educate their children.

Summary

In traditionally Islamic countries, Autism Spectrum Disorder is often ignored and misunderstood. Accordingly, children with autism in these societies are sometimes neglected and ostracized despite the Islamic precedent that promotes the acceptance and respect of these children. Through a series of interviews we examined the specific influence of Islamic values on the way the diagnosis of autism is regarded and how it influences the way families perceive, treat, raise, and educate their children. Additionally, we looked at the influence of Islamic values on the way children are integrated into their families, social and religious circles, and academic community. In the course of our study we discovered that even though faith served as a source of strength for parents with children with autism and was emboldened upon taking care of their children, these families were often isolated from their religious circles and extended families and met great intolerance as well as a lack of proper understanding, acceptance, and support from these communities.

Brief Description

A series of qualitative, two hour, one-on-one interviews were conducted over the phone and at the homes of Muslim parents with children with ASD in order to gain insight to the stories and experiences of these parents.

Products Developed

A virtual support group was created for the participants of the study and the findings will be presented to local Imams in order to educate them on the nature of the problems faced by Muslim parents of children with ASD. We hope that these educational initiatives will help ameliorate the discrimination and alienation these families encounter in their religious communities.

Conclusions

Thus, although Muslim parents turn to their faith to face and overcome the struggles they encounter in raising children with autism, they remain largely ostracized from the religious community itself due to the lack of awareness and acceptance of children with special needs, which in turn leads to the alienation and discrimination of children with autism within Muslim communities.

References

References Available Upon Request

Acknowledgements

Professor Barbara Clinton, MSW

Mentor / Department

Dr. Nirupama Madduri, Department of Pediatrics

ASSESSING THE NEEDS AND STRENGTHS OF A KAREN REFUGEE COMMUNITY FROM BURMA

Ian McGuinness
Community Health Initiatives and Health Outreach

Objectives

One religious congregation in middle Tennessee has served as a hub of social support for a particular Karen refugee community from Burma by employing two bilingual refugees from the community to work as church lay workers (CLWs) to meet their community's needs. The objectives of this project included characterizing the needs and strengths of this refugee community with the goal of developing an intervention to mobilize community strengths to meet key needs.

Summary

Needs and strengths were characterized by shadowing and describing the activities of church lay workers (CLWs) and by interviewing key members of the refugee and church community. The CLWs were found to transport people to, interpret for and schedule medical, legal and social service appointments. Key strengths found included the competency of the CLWs in meeting community needs, a community wide trust in the CLWs and other community leaders, and a small group of involved, bilingual youth. Key needs included English competency, adequate transportation, further training for the CLWs, and more people with CLW-like training.

Brief Description

The needs and strengths of a church-associated refugee community were characterized and assessed by shadowing employed church lay workers (CLWs) and interviewing community members, where key strengths included CLW competency and bilingual youth, and key needs included English competency and more trained CLW-like personnel.

Products Developed

The intervention sought to equip a group of bilingual youth to more effectively navigate medical clinic visits. A workshop was developed in which youth learned how to use a patient appointment card and how to ask good questions at a doctor's office visit.

Conclusions

The key needs of this community are similar to many newly established refugee communities studied, the primary limiting needs being English competency and more CLW-like personnel working in the community. However, the strengths of the community, such as the CLWs and congregation members' competency and generosity, offer innovative means of meeting these needs, means that appear to be unique among recently resettled refugee communities. This example of a religious entity using its resources to empower an associated refugee community presents itself as a translatable model for assisting similar communities elsewhere.

References

References Available Upon Request

Acknowledgements

I would like to thank the generosity and cooperation of the staff and members of All Saint's Episcopal Church. Without their help, this project would not be possible. Also, thank you to the staff of Siloam Family Health Center, and Amy Richardson and Carol Etherington of the Vanderbilt Institute for Global Health for their advice and direction, as well as Elizabeth Bradley in helping to format the patient appointment card.

Mentor / Department

Barbara Clinton, Academic Advisor Director, Center for Community Health Solutions Fr. Randy Hoover-Dempsey, Community Advisor All Saint's Episcopal Church

Doug Heimburger, MD, MS, directs the Education and Training portfolio of the Vanderbilt Institute for Global Health (VIGH) and conducts research on nutritional influences on antiretroviral therapy outcomes in HIV/AIDS. Before joining VIGH in 2009, Dr. Heimburger served on the faculty of the Departments of Nutrition Sciences and Medicine at UAB, where his titles included Senior Scientist in the UAB Clinical Nutrition Research Center, Center for AIDS Research, and Comprehensive Cancer Center; Director of the Clinical Nutrition Fellowship Program; and Associate Director of the UAB Sparkman Center for Global Health. During a Fulbright Scholar award-supported sabbatical in Zambia in 2006-7, he initiated nutrition research in a population of Zambians starting antiretroviral therapy for HIV/AIDS. He has served on the Advisory Board of the Fogarty International Center (NIH), the governing Council of the American Society for Clinical Nutrition, a standing Review Group for the National Cancer Institute, the U.S. FDA's Food Advisory Committee, and a Test Materials Development Committee for the United States Medical Licensing Examination.

Marie Martin, M.Ed., joined the Vanderbilt Institute for Global Health in 2009 as a Senior Program Manager in the area of Education and Training. In this capacity, she manages curriculum development, international academic and service programs for Vanderbilt students in global health, and other educational initiatives for VIGH. Prior to VIGH, Marie worked for three and a half years as the Assistant Director of the Global Education Office at Vanderbilt, developing international service-learning programs for undergraduate students. Her professional background includes seven years as an assignment editor for CNN and four years in the Czech Republic, primarily managing a parliamentary internship program for Czech university students under the direction of the European Union. Her academic interests include comparative and international education, public administration, global health financing and agenda setting.

Global Health

The Global Health focus area targets health problems in resource-limited settings, including diseases of poverty and the tropics, and provides students with opportunities to learn first-hand about health issues of international significance. Research projects span a broad range of themes in global health, from medical sciences and clinical investigation to socio-cultural correlates of health and health care delivery. Projects in this area fulfill the practicum requirement of the Vanderbilt Institute for Global Health's Graduate Certificate in Global Health.

Several former students have recently opted to expand their global health experiences by participating in a new global health Immersion Course during their last year of medical school.

"The primary objective of the Global Health component of the Emphasis program is to nurture a growing number of students interested in global health issues, helping them to assess and understand some of the most pressing public health issues of our time in their socio-economic and culturally specific context. The Global Health focus area serves to introduce these students to the fundamental principles of service, research, planning, and management methodology in resource-limited settings. A number of students have published their work in international peer-reviewed journals or in more informal ways for general audiences. Students must plan early because overseas projects have increased complexities to obtain final approvals."

EDUCATIONAL INTERVENTION INCREASED REFERRALS TO ALLOPATHIC CARE BY TRADITIONAL HEALERS IN THREE HIGH HIV-PREVALENCE RURAL DISTRICTS IN MOZAMBIQUE

David Amsalem
Global Health

Background Problem

Delayed uptake of clinical services impedes favorable clinical outcomes in Mozambique. Care is delayed among patients who initiate care with traditional healers; patients with conditions like human immunodeficiency virus (HIV) or tuberculosis are rarely referred to the health system in a timely fashion.

Objectives

In Mozambique, both the Ministry of Health and traditional healers are enthusiastic about the creation of a formal partnership.37 To this end, the Ministério da Saúde (MISAU; Mozambican Ministry of Health), along with several formal healer organizations in Zambézia province, and the Vanderbilt University affiliated non-governmental organization Friends in Global Health (FGH) collaborated to design a formal system for documenting healer referrals to the health facility and for providing feedback to healers regarding patient diagnoses.

Materials and Methods

We conducted a pre-post educational intervention with traditional healers, assessing healer referral rates and HIV knowledge in three rural districts in Zambézia Province.

Results

The median monthly referral rate prior to the intervention was 0.25 patients (interquartile range [IQR]: 0-0.54) compared with a post-intervention rate of 0.34 patients (IQR: 0-0.71), a 35% increase ($p=0.046$). A median HIV knowledge score of 67% (IQR: 59-78) was noted 4-months pre-intervention and a median score of 81% (IQR: 74-89) was recorded 2½ months post-intervention ($p<0.001$). One hundred and eleven healers referred 127 adults, 36 pregnant women, and 188 children to health facilities. Referred patients were most likely to be diagnosed with bronchopneumonia (20% adults; 13% children) and/or malaria (15% adults; 37% children). Of 315 non-pregnant persons referred, 3.5% were tested for HIV and 2.5% were tested for tuberculosis.

Conclusions

We engaged traditional healers with some success; referral rates were low, but increased post-intervention. Once seen in the clinics, patients were rarely tested for HIV or tuberculosis, though symptoms suggested screening was indicated. We found increased referral rates through an inexpensive intervention with traditional healers, a viable, cost-effective method of directing patients to health facilities. However, quality improvement within the clinics is necessary before a substantial impact can be expected.

Mentor / Department

Carolyn Audet

A LIVESTOCK INTERVENTION FOR PEOPLE AFFECTED BY HIV/AIDS IN ZAMBÉZIA PROVINCE, MOZAMBIQUE: COMMUNITY PERSPECTIVES OF THE INTERVENTION

Kelly Bouquet
Global Health

Background Problem

Introducing a nucleus of animals into the community through a livestock lending intervention changes the physical and social environment in which people think and behave. The social cognitive theory proposes that interactions between individual perceptions or cognitions and the physical/social environment affect behavior. The aim of pairing baseline survey data from the Ovala Project with information obtained from focus groups is to understand how we are changing the physical and social environment through this intervention, and how those changes might affect an individual's wealth, overall QOL, self-esteem, self-efficacy, food security, and access to formal health care. We are also interested in determining what types of bias and stigma the intervention might introduce into the community and whether beneficiaries of the intervention perceive that the intervention will improve their health-related quality of life in tangible ways. The objective of this study is to elicit the perceptions and opinions of community members in regards to the livestock lending intervention in order to anticipate both positive and negative outcomes of the project. Treating local people as active players and decision makers by asking the right questions in a discussion-based format is a useful way to learn about a community and to understand phenomena that may be predictors for problems. These phenomena are rarely recognized or recorded by a formal survey. Indicator questions about common responses to emergencies, such as food shortages, have proven to be a means of community-based monitoring to predict behavior and risk in rural areas in Southern Mozambique^3. A similar technique using discussion and indicator questions will be employed to predict both beneficial and adverse outcomes of the Ovala livestock lending intervention. Focus groups paired with baseline demographic and QOL survey data are appropriate tools to measure quality of life^5,8,12. A study conducted in 2001 to determine the validity of the WHO Quality of Life (QOL) survey determined that the survey is an adequate cross-cultural assessment of QOL; however, discussion of culture reveals a "preliminary state of knowledge about social, economic, geographic and cultural similarities and differences in importance rating behavior" that should be further explored whenever the WHOQOL survey is employed^14. The aim of the focus groups is to explore community perceptions of quality of life and how community members anticipate that this same quality of life may or may not change as a result of the livestock lending intervention. Finally, a well-documented effect of charity and community interventions is that they often cause beneficiaries to suffer stigma in the community^6. Focus groups will provide a preliminary way of ascertaining which types of bias and stigma the Ovala livestock lending project may introduce among community members and whether beneficiaries of the intervention will be targets of that stigma.

Objectives

Aim 1: To understand the general perceptions and opinions of the community in regards to the livestock lending intervention in order to anticipate both positive and negative outcomes of the livestock lending intervention. What are the community's general opinions in regards to the livestock intervention? Specifically, we would like to elucidate participants': -plans for the goat -perceptions of how receiving the goat will change their status within the community -perceptions of how receiving the goat will change their self-esteem and self-efficacy -perceptions of how receiving the goat will change the family's financial situation -perceptions of how receiving the goat will change their daily life -perceptions of how receiving the goat will change the family's access to formal health care Objective 1: Ask focus group participants to give their own opinions and to repeat the opinions that they have heard expressed in their communities about the livestock lending intervention. Objective 2: Analyze data obtained in focus groups regarding the livestock lending intervention using interpretive phenomenology and Krueger's framework analysis to elucidate meaningful themes and ideas that could inform and shape future studies.

Materials and Methods

Focus groups will be conducted in each of the four community Associations (Ile, Gilé, Lugela, and Mopeia) to validate survey parameters, to obtain general qualitative data relevant to the livestock intervention, and to assess how the livestock intervention may be linked to measurable health outcomes in the eyes of community members. Investigators and FGH staff will recruit volunteer community members to participate in the focus groups. Focus groups will be composed of 6-10 women and will last 2-3 hours. Focus groups will be recorded on tape recorder and transcribed. Focus group transcripts will be translated (from local languages to Portuguese and from Portuguese to English) as necessary. All translations will be back-translated by a second translator and checked for accuracy. The qualitative data obtained will be analyzed by coding and by the application of both interpretative phenomenology and Krueger's framework analysis^5,8,9,12,13. Results and findings, summary of themes, and recommendations will be included in a final written report.

Conclusions

A major result of the goat project is the accumulation of non-cash assets that can help beneficiaries overcome barriers to health care such as transportation and poor diet. Beneficiaries equated goat ownership to wealth. A second finding is that beneficiaries identified significant social implications of wealth such as improved self-esteem and self-efficacy. This can help beneficiaries overcome identified barriers to health care such as poor treatment by hospital staff. High self-efficacy is also a strong predictor of improved health seeking behavior. Developing a culturally- appropriate scale to measure self-efficacy is an efficient and cost-effective way to evaluate the impact of livestock lending interventions on health behavior. Further study & interventions - Conceptualization of self-esteem & self-efficacy - Barriers to health care (that can be addressed through a microfinance project): •Transportation •Disposable income •"Padrinhos" •Poor treatment by hospital staff

References

References Available Upon Request

Acknowledgements

VUSM Emphasis Program stipend Overall Scholarship Program Friends in Global Health, Mozambique Etelvina Sousa, FGH FGH Faculty & Staff Members: Ruth Mkhwanazi, Lázaro Calvo, Moshin Sidat, Troy Moon, Márcia Souza, Lara Vaz, Deidra Parrish MOZ Provincial Health Department-Quelimane MOZ Ministry of Agriculture- Quelimane

Mentor / Department

Daphne Carlson-Bremer, DVM, MPVM, PhD Vanderbilt Institute for Global Health

FACTORS ASSOCIATED WITH LOSS TO FOLLOW UP OF PRE-ART PATIENTS IN ZAMBÉZIA, MOZAMBIQUE

Monica da Silva
Global Health

Background Problem

In the HIV care systems currently in place Mozambique, there are several opportunities for a patient to be lost even before they begin antiretroviral treatment (pre-ART). However, there has not been any formal examination of this pre-ART population in Mozambique either quantitatively or qualitatively.

Objectives

This study aimed to examine the question of pre-ART loss to follow by in the Zambezia province of Mozambique using both quantitative and qualitative approaches to examine what distinguished those lost to follow up from those who remained in care.

Materials and Methods

HIV care and treatment data for adult (18+) patients registered in the health system between January 2010 and June 2011 was obtained. Multivariable Cox regression was used to model time to LTFU censoring at the date of death, transfer, or treatment initiation among those who are not LTFU or in care at 1 year. Twenty interviews of individuals who had missed a pre-ART clinical appointment were conducted in one district (Maganja da Costa) by a group of community leaders.

Results

Of the 13,968 patients registering for care, 212 (1.8%) died/transferred, and - 2196 (15.7%) initiated ART, and 9195 (65.8%) were LTFU during the first year. Being female, older, more highly educated, and having electricity were associated with lower risk of LTFU. Referral site is strongly associated with LTFU; laboratory, medical inpatient, and prevention of mother-to-child transmission referrals had higher hazard of LTFU compared with voluntary counseling and testing. Qualitative analysis revealed that individuals did not return to the clinic because of logistics or alternative priorities. Moreover many expressed fear of being stigmatized and rejected were they to be recognized either by their familiars or their community as an individual with HIV.

Conclusions

Pre-ART LTFU in Mozambique is very high. While efforts are made to improve patient adherence to ART, it is imperative that resources are committed to retaining patients not yet assessed for eligibility or not ART-eligible.

Acknowledgements

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SPECTRUM OF DISEASES IN ADULT PATIENTS AT VISITATION CLINIC IN SOUTHWESTERN HAITI

Magdalena Dorvil
Global Health

Background Problem

Despite increasing concern about the projected impact of Non-communicable diseases (NCDs) on mortality worldwide, there is paucity of data describing the impact of NCDs on morbidity and mortality in rural Haiti. Routine patient data collected in the past five years at Visitation Clinic (VC) in the rural region of Southwest Haiti has not been systematically reviewed to determine the most prevalent diagnoses/spectrum of illness among those presenting for routine medical care to date.

Objectives

The objective of this study was to perform a retrospective analysis of clinical data to determine the most prevalent diagnoses among adult patients presenting for routine medical care at VC.

Materials and Methods

Visitation Clinic staff currently utilizes OpenMRS™, an open-source data capture system used in resource-limited settings, to record patient demographic and clinical visit information. We analyzed clinical data for all adult patients who presented for care at VC in January 1, 2011—December 31, 2011. Each patient was de-identified by assignment of a random study ID (SID) generated by REDCap.

Results

Total number of new adult patient visits in 2011 was 1621. Average number of new patients per month was 105. This was significantly higher in July—November, consistent with the hurricane season which runs June—November. In January, 33% of new patients presented with cholera, consistent with the outbreak which began in mid-October 2010. 1268 patients included (22% excluded due to incomplete data), 731 (58%) of which were female. Ages were 18-110 years with a median of 35 years and [IQR 24 – 52]. Top five most prevalent diagnoses were iron-deficiency anemia (29.7%), gastritis (22%), UTI (20%), malaria (13.3%), and arthritis (11.7%).

Conclusions

The study shows that NCDs were overall the most common diagnoses in adult patients in this region. Possible future initiatives include establishing community health outreach/workers programs to educate this population about NCDs and how to prevent them.

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Acknowledgements

C. William Wester, MD, MPH; Ely, E. Wesley, MD, MPH; Rony Jean-Francois, MD; Janet Nicotera; Riphard Serent; Mario Davidson, PhD (VU Department of Biostatistics); Yanna Song (VU Department of Biostatistics) Vanderbilt Institute for Global Health (VIGH); Douglas Heimburger, MD, MS; Marie Martin; Overall Fellowship; Visitation Clinic Administrators and Staff

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THE PREVALENCE AND MOLECULAR CHARACTERISTICS OF METHICILLIN-RESISTANT S. AUREUS IN AN EMERGENCY DEPARTMENT IN A DEVELOPING COUNTRY

Adeline Dozois
Global Health

Background Problem

Methicillin-resistant Staphylococcus aureus (MRSA) is a common pathogen worldwide, but data are limited on its prevalence in Caribbean countries. Once thought to be a strictly nosocomial pathogen, the incidence of community-associated strains (CA-MRSA) is rising.

Objectives

The objectives of this study were to (i) determine the prevalence of MRSA among S. aureus isolates from patients presenting to the emergency department (ED) of a tertiary care hospital in Georgetown, Guyana; and (ii) classify isolates as CA-MRSA or healthcare-associated based on molecular characteristics.

Materials and Methods

Subjects of all ages presenting to the ED with skin and soft tissue infections were enrolled on a convenience basis. . A sample of purulent material was collected on an Aimies liquid swab and cultured using standard methodology. Isolates were tested for anti-microbial susceptibility. S aureus isolates were evaluated for SCCmec type and presence of pvl using PCR. Strain type was determined for a sample of 12 isolates using a Diversilab chip.

Results

89 patients were considered for enrollment. 4 subjects were excluded because informed consent could not be obtained leaving 85 subjects. Of these, 48 (56%) grew S. aureus and comprised the study population. 26 (54%; 95% CI: 40-67%) of the 48 isolates were MRSA. All S. aureus isolates were SCCmec type IV and pvl positive. These genetic features are markers of CA-MRSA. The isolates tested for strain type were all USA300.

Conclusions

Understanding the prevalence of antibiotic resistance is necessary for proper empiric management of community-associated infections. Fifty-four percent of S. aureus isolates were CA-MRSA. Such strains are thought to be more virulent, and may require more aggressive treatment. The clonal strain found in this study (USA300) is the most common CAMRA strain found in North America, but different those previously isolated in Caribbean nations. The prevalence of MRSA in this study was also higher than what is reported in other Caribbean countries, but similar to that seen in South America. Further epidemiological studies could be informative in determining the origin and spread of resistant strains in this region.

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Acknowledgements

GPHC and Guyana National Reference Laboratory staff; Creech Laboratory; Dr. Nicolas Forget, Dr. Kristen Dettorre, Dr. Ashley Brown; Shanik Fernando, Rosalynne Korman, and Meaghan McArdle

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THE IMPACT OF CULTURE ON KNOWLEDGE, ATTITUDE, AND PRACTICE OF FAMILY PLANNING IN RURAL NORTH KAMAGAMBO, KENYA

Sarah Eckhardt, Jana Lauderdale
Global Health

Background Problem

Since the Lwala Community Hospital's opening in 2007 in the North Kamagambo region of Kenya, the number of patients seeking contraceptives and family planning counseling has significantly increased. However, maternal mortality remains high and women are expected to bear many children. Although this places a large burden on women's health and increases lifetime risk of maternal mortality, cultural and religious hesitance towards family planning persists. In June 2012, the Lwala Community Hospital received funding from Planned Parenthood International to implement an educational program on family planning. Female birth attendants, referred to in Lwala as Umama Salama and Maternal Child Health Workers, will be cross-trained as family planning educators. These educators will go to private homes to offer family planning education and contraceptives for interested individuals.

Objectives

The purpose of this study was to explore how culture impacts knowledge, attitude, and practice regarding family planning in order to design an effective family planning educational program tailored to the needs of Lwala and surrounding communities.

Materials and Methods

This was an exploratory, descriptive, qualitative study employing six focus groups to collect data; the purposive sample included local men, women, Umama Salama members, Maternal Child Health Workers, religious community leaders, and Lwala Hospital health staff. Data was collected through audio-recorded focus groups using an open-ended interview guide that allowed participants to share their perceptions and discuss personal beliefs, knowledge, and experiences about family planning. Additional data was collected through a short demographic questionnaire, verbatim transcripts, observations, and field notes.

Results

Analysis/Results: Content analysis was used to assist in analyzing the data along with transcribed data, field notes, and observations. The investigators communicated throughout analysis to discuss and reach consensus on codes, categories, and emerging themes. Through an iterative process the researchers developed and agreed upon the final 5 salient themes: 1) Cultural beliefs and barriers regarding family planning; 2) Preparing the ground (education); 3) Issues with the health care system and access; 4) Protecting our women and ourselves; and 5) "War" of contradictions. Within each theme, similarities and differences between focus groups were analyzed as well.

Conclusions

This study sought to identify and describe the barriers to family planning in North Kamagambo, Kenya and to understand the cultural context in which they exist. Our findings suggest the community is open to learning and engaging in family planning. Furthermore, the community will likely benefit from this education, as misconceptions of side effects and myths regarding family planning were similar across groups. However, the groups had varying opinions on how family planning education should be approached and the rights of women to seek contraceptives independently. While there is promise of the community being open to learning more, there are still many cultural and religious beliefs that must be taken into consideration when organizing education on family planning. Implications for future education include: 1) tailoring FP education based on cultural /community needs, 2) appropriate training of educators, 3) incorporating technology, and 4) respect for differing beliefs.

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FRACTIONAL EXHALED NITRIC OXIDE LEVELS IN WHEEZING PATIENTS WITH AND WITHOUT LABORATORY EVIDENCE OF LYMPHATIC FILARIASIS

Shanik Fernando, Nicolas Forget, Shamdeo Persaud, Pheona Mohamed-Rambaran, Kristen Dettorre, Shannon Langston, Seth Wright
Global Health

Background Problem
Infection with filariasis induces an immune response in humans which is primarily mediated by eosinophils. Degranulating eosinophils release nitric oxide which is believed to be host-protective. Fractional exhaled NO (FeNO) is a breath test used clinically as a marker of airway inflammation.

Objectives
The objective of this study was to determine if bronchospastic patients with laboratory evidence of filariasis had higher levels of exhaled nitric oxide as compared to those without filariasis.

Materials and Methods
This cross-sectional analysis enrolled patients presenting to the A&E department of Georgetown Public Hospital in Georgetown, Guyana during an 8-week period in May-July 2012. Eligible patients were above the age of 18 and had wheezing consistent with asthma or had a cough of over one week duration without obvious cause. Filarial ICT testing, eosinophil count, FeNO level, and demographic survey were completed. T-test was used to compare FeNO values of those with and without positive ICT testing.

Results
A total of 86 patients were approached to participate in the study and 52 were eligible and consented to participate. 11/52 (21.1percent) were positive by ICT for filariasis. The patients who tested positive and negative for filariasis had an average eosinophil level of 396 cells (SD=260) and 423 cells (SD=395) per ul of blood respectively. The mean exhaled nitric oxide value was 37 PPB for patients who tested positive for filariasis (SD=24) and 47 PPB for patients who tested negative for filariasis (SD=41).

Conclusions
The data from this pilot study indicate that subjects with lab evidence of filariasis do not have higher levels of FeNO compared to those who tested negative for filariasis (p=.237). In fact, FeNO levels were lower in those with positive filariasis testing. Testing of FeNO is useful in some diagnostic settings but does not appear to be useful in differentiating patients with and without laboratory evidence of filariasis infection.

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Acknowledgements
Meaghan McArdle, Staff at GPHC

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DIRECT COSTS OF TREATING SEVERE SEPSIS IN LUSAKA, ZAMBIA

Brian Heiniger
Global Health

Background Problem

Severe sepsis is a common and frequently fatal condition in sub-Saharan Africa. However, the actual costs of managing sepsis in sub-Saharan Africa have not been previously evaluated. We measured the variable direct hospital costs of treating patients with severe sepsis in Lusaka, Zambia, comparing an experimental Simplified Severe Sepsis Protocol (SSSP) versus usual care.

Objectives

To evaluate the cost of implementation of a simplified severe sepsis protocol in sub-Saharan Africa.

Materials and Methods

We conducted a budget impact analysis nested within a randomized controlled trial of the SSSP in patients with severe sepsis. The treatment protocol consisted of up to 4 liters of intravenous fluids in the first 6 hours of admission, and dopamine and/or blood transfusion in selected patients. Utilization of fluids in the first 72 hours, blood transfusion, and microbiology lab services, along with hospital length of stay and critical care services were directly measured in all participants. Microcost measurements were collected in 10 consecutive participants from each arm for the following: doctor and nursing time, medications and related supplies, intravenous fluids after 72 hours, laboratory and radiological investigations, and post-discharge costs. Unit costs were obtained directly from the hospital when possible or from the literature in the case of blood transfusion costs. A one-way sensitivity analysis was performed.

Results

Mean length of hospital stay was 6.30 days (SD 6.20). The average total cost of treating each patient was calculated to be $218.26. Only 2 patients were admitted to the intensive care unit and mechanically ventilated, limiting the overall costs of care.

Conclusions

Laboratory costs accounted for nearly half of the variable direct costs. Health worker personnel costs were a relatively small proportion of costs. Increased use of intravenous fluids, as suggested in the Simplified Severe Sepsis Protocol, would be unlikely to result in significant increases in total cost.

Acknowledgements

Vanderbilt Institute of Global Health (VIGH); Marie Martin, VIGH; University of Zambia School of Medicine (UNZA SOM); University Teaching Hospital in Lusaka, Zambia; Dr. Shabir Lakhi, Department Head, Internal Medicine, UNZA SOM; Dr. Levy Muchemwa, UNZA SOM; Chileshe Mabula UNZA SOM

Mentor / Department

Dr. Doug Heimburger, Vanderbilt Institute of Global Health; Dr. Ben Andrews, Vanderbilt Institute of Global Health and University Teaching Hospital Department of Internal Medicine, Lusaka, Zambia

THE PREVALENCE OF SUSPECTED UNDIAGNOSED DIABETES MELLITUS AND USE OF RANDOM BLOOD SUGAR FOR DM SCREENING AMONG ED PATIENTS AT THE GEORGETOWN PUBLIC HOSPITAL CORPORATION

Rosalynne Korman
Global Health

Background Problem

Diabetes mellitus (DM) is a chronic disease highly prevalent in the Caribbean; the emergency department (ED) has been proposed as a possible high-yield venue for its screening.

Objectives

The objective of this study was to determine the prevalence of DM among non-critical patients at the ED at the Georgetown Public Hospital Corporation (GPHC). The sensitivity and specificity of random blood sugar (RBS) in diagnosing DM was also evaluated.

Materials and Methods

Patients presenting to the ED aged 30 or older with no PMH of DM were potentially eligible for the study. Medically or psychologically unstable patients were excluded. Subjects were enrolled on a convenience basis during pre-defined time blocks. Subjects underwent point of care (POC) RBS and POC hemoglobin A1c testing, and were grouped into one of three classifications based on the American Diabetic Association criteria for DM: not suggestive of DM (RBS <130 mg/dl and A1c <5.7%); increased risk for DM (RBS 130-199 mg/dl and/or A1c 5.7-6.4%); or likely DM (RBS >199 mg/dl with symptoms of DM and/or A1c >6.4%). Subjects classified as increased risk for DM or likely DM were counseled and referred for additional testing. Results were summarized in a ROC curve; DM was defined as an A1c >6.4%.

Results

A total of 1010 subjects presented during the time blocks. 269 met the inclusion and exclusion criteria; of these 230 (85%) consented, and 222 successfully underwent testing. 17 (7.7%) had a RBS and/or A1c indicating the likely presence of DM, and 106 (48%) had results indicating an increased risk for DM. The ROC AUC was 0.94 (95% CI 0.91-0.97); a RBS >125 was 100% sensitive and 73% specific for detecting DM, while a RBS >154 was 67% sensitive and 92% specific for detecting DM.

Conclusions

44% of participants met ADA/WHO criteria for diabetes or pre-diabetes. An elevated RBS may warrant follow-up testing for DM. The high prevalence of abnormal POC RBS and A1c results among non-critical ED patients suggests that using the ED and other non-typical screening sites may lead to earlier diagnosis of DM.

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Acknowledgements

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MYCOPLASMA PNEUMONIAE AND ITS ROLE IN ACUTE ASTHMATIC EXACERBATIONS IN A POPULATION OF BUENOS AIRES MINORS

Gregory LaChaud
Global Health

Background Problem

Mycoplasma pneumoniae has been found in a significant portion of pneumonia patients and has been linked to almost a third of acute asthma exacerbations in pediatric patients. The correlation between M. pneumoniae and CARDS toxin has been established but its relation to a specific attribute of a pediatric population has yet to be determined. Additionally, although several hypotheses have been advanced to expand on virus-induced exacerbations, such as RSV and Rhinovirus, M. pneumoniae infections have not been explored. Their mechanisms and ultimate link to asthma remains unclear. Delving deeper I hope to uncover the link between M. pneumoniae qualitative or quantitative characteristics of asthma. Mycoplasma pneumoniae is a mucosal pathogen that lives in close association with the epithelial cell layers of the respiratory or urogenital tracts. Mycoplasma pneumoniae is a unique strain of bacteria lacking cell walls that is exclusively found to parasitize human hosts. As an extracellular pathogen, the interactions between the bacteria and the host epithelial layer is imperative and, in correspondence, M. pneumoniae has adapted a specialized attachment organelle and ultimately leads to the deterioration of the brush border cilia in the epithelial cells of the respiratory tract it has infected. The eventual outcome of this infection is a change in the epithelial lining both structurally and functionally. This alteration emerges as clinical manifestations of the infected patient primarily in the form of persistent cough with hacking of phlegm, sore throat, hoarseness, fever, as well as wheezing. A large fraction of the disease burden of asthma is caused by exacerbations strongly correlated with respiratory infections. It has been reported that anywhere between 40% and 90% of asthma exacerbations are underlying due to a respiratory virus infection. Additionally, by Papadopoulos et al, it was concluded that 62% to 95% of children with acute wheezing episodes test positive for at least one respiratory viral infection. While rhinoviruses are the most frequently detected virus type in asthma exacerbations of all ages, respiratory syncytial virus and metapneumoviruses prove more prevalent in infants. It has been suggested in recent data that M. pneumoniae is responsible for 20-30% of asthma exacerbations, 20-40% of all community acquired pneumonia and also causes acute and chronic respiratory infections like: tracheobronchitis and pharyngitis. While the pathway is still unclear there is evidence that suggests co-infections by multiple pathogens may increase the risk of obtaining asthma. An ADP-ribosylating and vacuolating toxin associated with M. pneumoniae infections, named Community Acquired Respiratory Distress Syndrome (CARDS) toxin, has been directly linked to the ability of specific M. pneumoniae strains to colonize, replicate, and persist, and elicit lung disease. The presence of CARDS toxin in M. pneumoniae infection has such a strong correlation that confirmation of the presence of CARDS toxin is used in molecular diagnosis of M. pneumoniae using Real Time Polymerase Chain Reaction. There is evidence that proposes that M. pneumonia may play a pivotal role in the pathogenesis of asthma more than simply acute exacerbations, but the findings about the frequency of acute asthmatic exacerbations caused by M. pneumoniae are controversial. The main problem about the disparity in the results of this is the poor sensibility and specificity of the diagnosis methods. Unfortunately detection and replication of CARDS toxin proves difficult. This fact coupled with the knowledge that some of the samples in this study have been thawed several times is to be noted. Although this molecular diagnosis is the standard, it has not been optimized to differentiate between acute and latent infection. Therefore what we want to know if Mycoplasma pneumoniae is a common cause of acute asthma exacerbations in young asthmatic children in Argentina. Our investigation is aimed at establishing whether the asthma attack quality and severity can be linked to a M. pneumoniae infection underlying the child's asthma.

Objectives

To determine the role of Mycoplasma pneumoniae in acute pediatric asthma exacerbations in minors.

Materials and Methods

Acquisition of Samples: Belonging to a collection cohort previously acquired for previous studies, I prospectively studied ninety-one samples of acute asthma exacerbations respectively from children presenting to local Argentinian hospitals. The children of the study were between the ages of five and eighteen that presented with signs and symptoms of an upper respiratory infection. The hospitals participating in the study were Asthma Clinics of Hospital Mi Pueblo located in Florencia Varela, Hospital Evita Pueblo in Berazategui, Hospital Iriarte in Quilmes, and Hospital V. Lopez y Planes in General Rodriguez in Buenos Aires, Argentina. These hospitals covered various scopes of socioeconomic statuses for the total Buenos Aires providence. Recruiting was done by pediatric pulmonologists who worked at the respective clinics. Enrollment was during the time period of March 1st and November 1st of the years 2007 and 2008. Asthmatic children with a supplementary diagnosis of an upper respiratory infection but with no wheezing were considered control subjects, while asthmatic children with an upper respiratory infection and an acute asthmatic exacerbation were categorized as case subjects. Children with oropharyngeal abnormalities and genetic malformations, neuromuscular disorders, immunocompromised patients, or chronic cardiopulmonary diseases other than asthma were excluded from participating in the study. Information of possible significant variables such as age, sex, number of siblings, hospitalizations, history of breastfeeding, home tobacco smoke exposure, allergies, use of corticosteroids, and other variables were obtained through a questionnaire administered to the parents or guardians of the study subjects. Baseline asthma status was determined by days per week and nights per month the child experienced an asthma attack. A baseline FEV1 was also acquired. The severity of the upper respiratory infection as well as the asthma exacerbation was also categorized. These classifications were based on a modified functionalized Global Initiative for Asthma (GINA) asthma exacerbation severity scheme. The samples were analyzed to identify whether they are Mycoplasma pneumoniae positive or negative children. Detection of Mycoplasma pneumoniae was accomplished by RT-PCR (Real Time Polymerase Chain Reaction). Prior to PCR, the first step was to isolate and extract DNA from nasal wash samples using QIAmp DNA mini kit, Qiagen, Catalog No. 51304. The isolated DNA was then tested for the presence of Mycoplasma pneumoniae infection by using PCR for CARDS toxin with custom made primers and probes from Applied Biosystems. The ninety six well plates were set up using duplicate samples of forty eight patients. During the process of setting up the first plate, the amount of master mix was underestimated and the mix was only adequate for eighty eight wells excluding four subjects from being run. The second plate was run with all wells loaded with forty eight patient samples. Written informed consent was obtained from the parents or guardians of all those enrolled in the study and The Institutional Review Boards of the participating hospitals approved parameters of the study. Analysis of data: The study only recruited patients with asthma due to the need for a control to establish a baseline phenotype when comparing the presence of a Mycoplasma pneumoniae infection. The patients were also asked describe the baseline severity of their asthma. The samples run under polymerase chain reaction where then compare by presence of Wheezing vs. Non-wheezing (case vs. control), Mycoplasma pneumoniae positive vs. Mycoplasma pneumoniae negative, and finally Wheezing vs. Non-wheezing within the Mycoplasma pneumoniae positive patients. These categories would be able to adequately see if indeed there is a link between a wheezing phenotype and the presence of a Mycoplasma pneumoniae infection.

Conclusions

With six of ninety two samples containing the presence of Mycoplasma pneumoniae, this supports findings that Mycoplasma pneumoniae is not abundantly prevalent in asthma exacerbations but does not reinforce Hardy's claim that 20-30% of asthma exacerbations have been linked to M. pneumoniae infection. This study could not uncover any significant difference or particular factor that leads correlates to either wheezing or non-wheezing phenotype. Delving into the type of infection and analyzing the prevalence of wheezing compared to non-wheezing frequencies could be a fruitful avenue of research. This study found a statistically significant difference in prior asthma hospitalizations in M. pneumoniae positive compared to M. pneumoniae negative patients. With such a low finding of M. pneumoniae positive individuals a larger sample size would be needed to confirm this relationship. This study did not reveal a believed correlation between severity of acute asthma exacerbations and the presence of a M. pneumoniae upper respiratory infection. Future projects could be directed toward a larger study or studying the role of co-infections with severity or wheezing of asthmatic patients. It is imperative to note that while detection of CARDS toxin and M. pneumoniae infection has gotten better in years it is still not perfect. Detection using RT-PCR is the current gold standard. In regards to detection, these samples are several years old and have been used in other studies. This introduces possible confounding factors such as the amount of thawing and refreezing of samples may be different for different samples of our database. Also note that this study was conducted with samples collected from patients from Buenos Aires, one localized area with an exclusive and constant climate. All these factors plus other unforeseen ones may have all contributed to the decreased detection and the thus decreased prevalence of M. pneumoniae in this study.

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Acknowledgements

Fernando Polack, MD Mauricio Caballero, MD Patricio Acosta Maria Gallego

Mentor / Department

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ROLE OF INTERFERON-A LEVELS IN SEVERITY OF RESPIRATORY DISEASE IN PRETERM INFANTS

Benjamin James McCormick
Global Health

Background Problem

Viral respiratory infections are the leading cause of hospitalizations in infants and children worldwide. Very low birth weight babies are at increased risk for presenting with severe viral lung infections, especially those in developing countries where there is often a lack of prophylaxis against respiratory syncytial virus and low vaccine rates for seasonal influenza virus (Klein et al, 2007). For this population, hospitalization rates can exceed 25% during the first year of life (Bauer et al, 2005). Epidemiologically speaking, respiratory syncytial virus (RSV) is extremely important, and is the main viral cause of hospitalization in infants in the United States and in the world. Fifty percent of infants are infected with RSV during their first winter and more than 95% of children have been infected before two years of age.

Objectives

The objective of this study was to determine whether the level of type-I interferon-α in respiratory secretions associated to severity of respiratory illness in very low birth weight infants in Buenos Aires, Argentina.

Materials and Methods

Between June 2003 and May 2005, families of very low birth weight (VLBW) infants leaving the neonatal intensive care units at Juan P. Garrahan Children's High Risk Clinic and Maternidad Sarda Pediatric High Risk Clinic in Buenos Aires, Argentina, were asked to participate in a prospective study of respiratory disease in VLBW infants. Written informed consent was obtained from all parents or guardians. Children participated in the study until they reached the age of 2 years. Interferon-αlevels were obtained using the Human IFN-α Module Set ELISA kit from Bender MedSystems GmbH (Vienna, Austria). Interferon-α levels were obtained for 240 nasal wash samples. Analysis was performed using Microsoft Excel. Severity score was determined by physicians at their respective hospitals and categorized into either mild or severe distress according to baseline respiratory function.

Results

Of the 240 samples analyzed for interferon-α level, 55 could be used to define the association between IFN-α levels and severity of disease. To determine the relationship between IFN-α levels and severity we accorded the IFN-α level to its respective episode and graphed the severity. For those patients we found with mild respiratory distress (n=47), we found the median interferon-α level 78.5 pg/ml, mean 117.8pg/ml. Patients with severe respiratory distress (N=8) exhibited a median interferon level of 67.0 pg/ml, mean 178.1 pg/ml.

Conclusions

In this study we examined the relationship between interferon-α levels in nasal wash samples of the Buenos Aires VLBW cohort and severity of subsequent episodes of respiratory illness to help further understand the relationship between cytokines and exacerbation of respiratory distress. Our results do not yield conclusive evidence to support the existence of a relationship between interferon-α and severity of respiratory illness in this population. Though admittedly this is not a giant breakthrough in the field of pediatrics, it rules out one more factor and is one more step in finding out what factors cause severe disease in some and not in others. Finding these factors would be an important discovery and would allow for the targeting of target populations for proper vaccine use, prophylaxis, and more careful observation.

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Mentor / Department

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A DOCTOR OF MY OWN: A DOCUMENTARY FILM ON MEDICAL EDUCATION IN SUB-SAHARAN AFRICA

Trisha S. Pasricha
Global Health

Background Problem

According to the WHO, Sub-Saharan Africa carries 24% of the world's burden of disease, but only 3% of the world's healthcare workforce. Capacitating new medical schools in these countries as a sustainable part of the solution has gained increasing attention in recent years. By some estimates, 100 medical schools are slated to open within the next decade. This documentary film comes at a pertinent time as lessons learned in Namibia can assist in the development of other emerging schools.

Objectives

Healthcare problems in developing countries, particularly in Sub-Saharan Africa, have been the subject of intense scrutiny, and supportive efforts include financial aid and consultative endeavors to change the paradigm. However, a critical and relatively neglected element has been the role of media in shaping opinion and in the education of stakeholders. With the emphasis of enabling schools to confront specific challenges of the local community, we undertook an experiment to produce a documentary to provide a novel and provocative visual examination of empowering Sub-Saharan Africa through medical education.

Materials and Methods

A film graduate and second-year medical student traveled to Namibia to capture first-hand accounts and field experiences of the day-to-day challenges of healthcare delivery and medical education in the country. The skeletal crew immersed themselves for 8 weeks conducting interviews of leadership, students, and allied health workers in the field. We documented the successes and hurdles of an effective development process. The documentary was shot entirely on a Nikon D800 and edited in Final Cut Pro.

Results

The film portrayed three themes of relevance to current medical education in Africa, traveling with students and faculty from the Namibian capital, Windhoek, to village clinics in the rural North. The first are innovations in teaching doctors within resource-limited settings, including a unique "community excursion program" that the documentary explores as part of the student's third year. Designed to inform students of the needs of poorly-funded rural healthcare in their own country, the immersion program provides a singular, and as the film reveals, challenging hands-on approach to student learning. The second theme is the importance of developing context-specific medical competency training and curricula that reflect the local community. Because of the immense shortage of available healthcare workers, the film furthermore highlighted inter-professional learning as a valuable teaching aid. Additionally, the film investigated incentives aimed to stem the "brain drain" out of Sub-Saharan Africa. Interviews of healthcare workers and students in village clinics expressed that adequate lifestyle factors and availability of medical resources—more than monetary compensation—were a greater incentive to remain working in the villages. The documentary also examined the admission policy's "regional quota system" in an effort to recruit and retain more students from the communities that the school eventually wants its doctors to serve.

Conclusions

Despite the difficulties of funding, a sparse faculty, and limited post-graduate training programs, there remains a strong political will motivating the establishment of new schools. We have documented several limitations and strategies that must be addressed in supporting and planning medical schools in resource-limited regions. Our efforts culminated in a documentary film to effectively inform stakeholders of the role of medical education in Sub-Saharan Africa. We believe that in a small way the lessons we have learned will instruct and inform other individuals seeking to educate future doctors across the globe.

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Acknowledgements

University of Namibia School of Medicine, Sara's Wish Foundation, Nichols Humanitarian Fund, VIGH Overall Fellowship, Dr. Doug Heimburger, Marie Martin

Mentor / Department

Dr. Quentin Eichbaum, Vanderbilt University School of Medicine

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Dr. Kripalani has expertise in the performance of observational research studies (surveys, qualitative research, and secondary data analysis), as well as intervention studies (quality improvement interventions and randomized controlled trials) to inform and improve patient care. His research in health literacy and hospital medicine has been recognized nationally, and he enjoys mentoring medical students and post-doctoral trainees.

Melissa McPheeters, PhD, MPH, Assistant Professor of Obstetrics and Gynecology and Medicine and Public Health, is Co-Director of the Vanderbilt EPC, Deputy Director for Women's Health Research at Vanderbilt, and Co-Director of the Vanderbilt CTSA Database core. In addition to her research as a healthcare epidemiologist, Dr. McPheeters has more than 16 years of experience in the translation of research to practical and useful products. Dr. McPheeters' PhD, completed in 2003, was in healthcare and reproductive epidemiology, with an emphasis on the use of epidemiologic analytic methods in large databases – she has continued this work over the past eight years, focusing on expanding approaches to analyses in administrative data, such as hospitalization data, as well as large-scale weighted surveys. Dr. McPheeters is an expert in comparative effectiveness reviews and on epidemiologic study design and analysis, with content expertise in maternal and child health. She has worked at the CDC and at state government in addition to her academic career and brings a strong public health perspective to her work.

Healthcare & Public Health Research

The student experience in the area of Healthcare and Public Health Research and Management is designed around a research track or management track. Students in the research track complete a hypothesis driven investigation in a field of healthcare research, such as health behavior and education, epidemiology, or outcomes research. Common research methods in this area include chart review, patient surveys, database analysis, qualitative research, systematic review, and clinical trials. The management track involves a healthcare management internship and quality improvement project, in which the student works as part of an interdisciplinary team to improve an aspect of patient care.

NEUROLOGIC FUNCTIONAL AND QUALITY OF LIFE OUTCOMES AFTER TBI: CLINIC ATTENDEES VERSUS NON-ATTENDEES

Jana Bregman
Healthcare and Public Health Research and Management

Background Problem

Little is known about factors related to attendance to a dedicated clinic for traumatic brain injury (TBI) patients. We compare demographic differences, neurologic functional and quality of life outcomes after TBI among clinic attendees and non-attendees.

Objectives

To assess functional and quality of life outcomes in a TBI population and to compare these outcomes among TBI patients who attended the MTBIC and those who did not. In addition, to further describe the population that the MTBIC is attracting.

Materials and Methods

This IRB-approved retrospective cohort study includes TBI patients >=18y with identified intracranial hemorrhage admitted to a level I trauma center from 7/2010-5/2012 who were offered a 3-month no charge clinic appointment and were phone-accessible. Predictors of quality of life and functional outcome were determined by the Quality of Life after Brain Injury (QOLIBRI) and Extended Glasgow Coma Scale (GOSE) utilizing a regression model with clinic attendance, insurance status, post-injury cognitive therapy and baseline injury severity (GCS, Injury Severity Score or ISS).

Results

Of 232 phone-accessible patients, 64(27.59%) attended the clinic. Stratified by clinic attendance, univariate analysis difference was workers' compensation carried more among attendees (14% vs. 3%,Chi2(3)=11,p<.05). In the multivariable model, compared to carriers of private insurance, those without insurance and those with workers' compensation had lower QOLIBRI scores by 16.6points(95%CI:7.2-25.9) and 25.8points(95%CI:11.9-39.9), respectively, and higher probability of poor GOSE(OR=3.0,95%:1.5-5.9 and OR=9.09,95%:2.9-33.3). Patients receiving post-injury cognitive therapy had higher QOLIBRI scores by 11.6points (95%CI:4.0-19.2).

Conclusions

Attendees were more likely to be receiving workers' compensation, which was independently predictive of lower quality of life and neurologic function as compared to those with private insurance. Cognitive therapy improved quality of life after TBI. TBI clinic attendance was not associated with quality of life or disability status.

References

References Available Upon Request

Acknowledgements

Laura D. Wilson MS; Mayur B. Patel MD, MPH, FACS; Yanna Song MS; Mario A. Davidson PhD; Stephen S. Humble BS; Michael R. de Riesthal PhD

Mentor / Department

Oscar Guillamondegui MD, MPH, FACS; Division of Surgery/Critical Care

PATIENT EXPECTATIONS AND COMPLIANCE IN ROTATOR CUFF TREATMENT

Brian Cash
Healthcare and Public Health Research and Management

Background Problem

Studies in several medical fields have indicated that patient expectations are predictive of health outcomes. Evidence has recently accumulated implicating this relationship in rotator cuff surgery as well. No mechanism has yet been identified to explain how expectations predict outcomes. We hypothesize that patient expectations regarding success of a rotator cuff physical therapy program are associated with compliance, and suggest this relationship as the link between expectations and outcomes.

Objectives

1. Perform a systematic review to summarize the existing literature regarding the role of patient expectations in predicting outcomes of rotator cuff interventions. 2. Determine the variables correlated with patient compliance to a physical therapy program for treatment of atraumatic full-thickness rotator cuff tears.

Materials and Methods

A systematic review of the MEDLINE database was performed. Relevant studies were evaluated independently by two authors and qualitatively summarized. A cohort of patients assigned to a physical therapy program for treatment of atraumatic full-thickness rotator cuff tears was retrospectively analyzed by multivariate analysis to identify factors associated with compliance.

Results

Sixteen full-text manuscripts were identified and assessed. Four of these studies met the criteria for this review. All four were prospective and included 525 patients requiring rotator cuff surgery. Expectations were measured with the MODEMS questionnaire, while outcomes were evaluated by a variety of patient reports and physician assessments. The results of the review indicated that higher preoperative expectations predict better outcomes. In our retrospective cohort study, male sex was significantly associated with compliance ($p<0.01$), but patient expectations was not ($p=0.12$).

Conclusions

Higher patient expectations for rotator cuff surgeries predict better outcomes. Expectations were not shown to associate with compliance. It is likely that mechanism by which expectations predict outcomes is complex and involves several variables. Nonetheless, physicians may improve outcomes by appropriately managing their patients' expectations in rotator cuff treatment.

References

References Available Upon Request

Acknowledgements

MOON Shoulder Group

Mentor / Department

Dr. John Kuhn, Orthopaedic Surgery Dr. Warren Dunn, Orthopaedic Surgery

EFFECT OF NEUTROPENIA ON SERIAL C-REACTIVE PROTEIN LEVELS IN BACTEREMIC NEONATES

Sarah Coggins
Healthcare and Public Health Research and Management

Background Problem

Sepsis is a leading cause of neonatal mortality. Several laboratory markers are used in neonatal intensive care units (NICUs) to diagnose sepsis, including complete blood counts with differential and C-reactive protein (CRP) values. Cases have been reported of blood culture-positive sepsis in which CRP levels did not rise in the setting of neutropenia.

Objectives

To evaluate for evidence of a relationship between CRP and absolute neutrophil counts (ANCs) among the typical NICU population. To evaluate serial CRP measurements and ANCs in bacteremic NICU infants.

Materials and Methods

In a retrospective chart review, we collected ANC and CRP values from all bacteremic patients admitted to Vanderbilt's NICU between 2006 and June 2012. We analyzed ANC and CRP data from the time of phlebotomy for blood culture and for 7 subsequent days. We also included ANC and CRP values from 1,000 randomly selected NICU patients (regardless of diagnosis) to test correlation.

Results

We identified 362 independent instances of bacteremia. CRP was negative (<10mg/L) at initial evaluation in 199/362 (55%) cases, 68 of which were deemed as confirmed infections. CRP failed to rise in subsequent measurements in 38 cases of confirmed bacteremia. Eleven cases of negative serial CRP were associated with neutropenia (ANC<3,500). Six of those 11 had bacteremia with coagulase-negative Staphylococcus (CoNS), a possible contaminant. Detailed review of the remaining 5 cases revealed either mixed infection or clinical signs inconsistent with sepsis. For comparison, we reviewed 27 instances of negative serial CRP in bacteremic NICU patients with ANC>3,500, finding 3 non-CoNS cases with clinically-confirmed sepsis. We studied 3,113 time-correlated CRP and ANC sets from 1,000 random NICU patients, finding a positive correlation between ANC and CRP ($R=0.25$, $p<0.001$).

Conclusions

Clinically-confirmed non-CoNS sepsis is rare among bacteremic infants with confirmed infections and serially negative CRP results (3/68, 4.4%). Despite a weak positive correlation between ANC and CRP, falsely-negative serial CRP occurs independently of neutropenia.

Acknowledgements

Dr. James L. Wynn, MD and Melissa L. Hill (Neonatology) and Dr. James C. Slaughter, PhD (Biostatistics) also contributed to this study. Funding provided by the Vanderbilt School of Medicine Emphasis Program and a 2012 Darlene Batey Hoffman Summer Scholarship.

Mentor / Department

Dr. Joern-Hendrik Weitkamp, MD (Neonatology)

IMPACT OF OCCUPATIONAL INJURY AMONG ORTHOPEDIC SURGEONS

William T. Davis
Healthcare and Public Health Research and Management

Background Problem

Orthopaedic surgery is a physically demanding profession which requires many hours per week in positions known to contribute to musculoskeletal injury and pain. Injuries to surgeons can affect the delivery of care and impose costs on the health care system and providers.

Objectives

The aim of this study was to determine the prevalence and types of injuries sustained at the workplace during the career of an orthopaedic surgeon as well as impact of such injuries on practicing surgeons.

Materials and Methods

A survey was developed to assess occupational injury among surgeons. Electronic surveys were distributed via email to all orthopaedic surgeons in Tennessee. Data were analyzed to determine statistical associations of demographic and workplace factors with rate of injury.

Results

140 of 495 surveys (28%) were returned with representation from all orthopaedic subspecialties. 61 (44%) respondents reported sustaining one or more injuries at the workplace. A statistically significant association was found between years performing surgery and prevalence of injury ($p=.03$), with surgeons working between 21-30 years reporting the most injuries. By the area injured, surgeons reported the following numbers of injuries: 35 (25%) hand, 27 (19%) lower back, 14 (10%) neck, 10 (7%) shoulder, and 9 (6%) other. Among injured surgeons, 23% missed work due to injury, with 8% missing at least three weeks. 37% of injured respondents reported that no institutional resources were available to support recovery for their injuries.

Conclusions

Our study demonstrates that many orthopaedic surgeons sustain occupational injuries during their careers. The volume of work missed suggests that occupational injury has economic implications for the health care system and providers. The number of injured respondents reporting no institutional support suggests that better attention should be paid to this issue.

References

References Available Upon Request

Acknowledgements

Vasanth Sathiyakumar

Mentor / Department

Manish K. Sethi, MD Department of Orthopaedic Trauma

TUMOR SIZE INCREASE FOLLOWING PREOPERATIVE RADIATION OF SOFT TISSUE SARCOMAS DOES NOT AFFECT PROGNOSIS

Gadini O. Delisca
Healthcare and Public Health Research and Management

Background Problem

Administration of preoperative radiotherapy for extremity soft tissue sarcoma improves local control, while allowing for a more conservative surgical resection. During radiation treatment tumor size typically remains constant. In a subset of patients, however, a size increase in the tumor occurs. While this may lead to a change in surgical plans the effect on overall outcome is unknown.

Objectives

Our goal was to investigate the prognosis of patients who had a size increase of at least 20% over the course of preoperative radiotherapy versus those who did not.

Materials and Methods

This retrospective study evaluated 70 patients treated for localized primary STS of the extremities between January 2000 and December 2008. Kaplan-Meier curves for disease-specific and metastasis-free survival were calculated for both groups.

Results

Sixty-one patients had stable or decrease local tumor size following preoperative radiotherapy and 9 patients had an increase of at least 20% in tumor size. There were no statistically significant differences found in disease-specific survival and metastasis-free survival (Gray's test, $p = 0.93$ and $p = 0.68$, respectively) among the two groups.

Conclusions

Our results indicate that a 20% increase in tumor size following preoperative radiotherapy did not result in a worse outcome for patients when compared to those who had stable or decrease local tumor size following preoperative radiotherapy.

References

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Acknowledgements

Vignesh Alamanda BS, Yanna Song MS, Kristin Archer PhD, DPT, Herbert Schwartz MD, Ginger Holt MD

Mentor / Department

Department of Orthopaedics and Rehabilitation Mentor: Dr. Ginger Holt

IDENTIFYING HIGH FREQUENCY USERS OF VUH EMERGENCY DEPARTMENT SERVICES

Stephen C. Dorner
Healthcare and Public Health Research and Management

Background Problem

Over the past 20 years, emergency department (ED) utilization rates have grown at nearly double that of the U.S. population. This trend has fueled speculation that uninsured patients, acutely ill Medicaid patients, and patients without primary care providers (PCPs) seek care from EDs at disproportionate rates, driving the rise in healthcare costs. As such, frequent ED patients are commonly categorized as "super users." However, previous studies analyzing this heterogeneous population rely on highly variable, arbitrary criteria to define 'super use'.

Objectives

To establish data-driven thresholds for high ED resource utilization of the Vanderbilt University Hospital (VUH) Adult ED.

Materials and Methods

Data between 30 April 2011 and 01 May 2012 were abstracted from the VUH ED electronic medical record system for analysis. We used tabular and graphical methods to describe the data in terms of ED visits, hospital admissions, and yearly charges. Our goal was to assess the relationships between these three facets of the data and determine how the data clustered into patterns of ED use.

Results

There were 44,832 patients who utilized the ED in the last year representing 63,412 visits. We found an inverse relationship between ED-only visits and admissions, suggesting that these are two distinct patient populations frequently using the ED. Among patients not admitted to the ICU, those with total charges in excess of the 90th percentile had at least 3 admissions. Among those 6,600 patients, 28% had commercial insurance, 29% had Medicare, 19% had Medicaid, and 20% were uninsured.

Conclusions

Our findings suggest that patients with two or fewer admissions do not drive total charges below the 90th percentile. This suggests that three admissions may serve as a viable threshold for high resource utilization. Additionally, we found that the majority of patients with total charges above the 90th percentile is insured, and by a provider other than Medicaid.

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Acknowledgements

Cathy Jenkins, MS Stephan Russ, MD, MPH Dandan Liu, PhD Karen Miller, RN, MPA

Mentor / Department

Ben Heavrin, MD, MBA Department of Emergency Medicine

INVESTIGATING THE FACTORS THAT INFLUENCE PATIENT PREFERENCE FOR TREATMENT WITH NOVEL AGENTS FOR CANCER THERAPY

Hillary Drexler
Healthcare and Public Health Research and Management

Background Problem

A study completed at Vanderbilt University reviewed the records of all patients seen by the thoracic medical oncology team from November 2005 to November 2008 and found that 43% of patients who were eligible to enroll in an available clinical trial declined. Through discussions with patients, it was determined that the frequency and duration of drug administration and potential adverse events may be large contributing factors. However, the level at which each factor contributes to one's willingness to participate is still unknown. How frequent is too frequent? Exactly which side effects is one willing versus unwilling to tolerate, and for how long? It is important to elucidate these factors because therapies are advancing and including more targeted approaches to treatment. Yet, these treatments cannot be approved without scientifically and ethically sound clinical trials. If we can gain a better understanding of the factors that patients consider when enrolling in clinical trials, then we stand a better chance at creating meaningful conversations between the patient and the physicians in addressing any questions and concerns. As a result of improved communication, physicians may better serve the needs of their patients, which may allow for higher patient enrollment. Ultimately, this would allow for more targeted therapies to be approved and become available to the general population.

Objectives

The protocol was written with three specific aims: "The goals of this study are to explore the theoretical impact that frequency of drug administration and grade one or two toxicities of targeted agents may have on cancer patient's potential compliance and willingness to undergo treatment. Specific Aim 1: To determine if there is a difference in patients' willingness to comply with treatment based on different frequencies of drug administration by disease type. Specific Aim 2: To determine if there is a difference in patients' willingness to comply with treatment based on toxicities by disease type. Specific Aim 3: To determine if there is a difference in patients' willingness to comply with treatment based on the magnitude of benefit by disease type."

Materials and Methods

A total of 200 patients (100 breast cancer patients and 100 lung cancer patients) will be enrolled in this study. All patients ages 18-85 with a diagnosis of breast or lung cancer who speak English and are seen as the Vanderbilt Ingram Cancer Center and One Hundred Oaks are eligible to participate. Patients are approached by a medical student, nurse, or physician if they are willing to complete a one-time questionnaire. Each person who undergoes the consent process and signs the consent has the option of taking the survey on their own on paper or taking it with the medical student as he/she reads the question allowed. If taken on one's own, the survey takes approximately 20 minutes. The questionnaire is de-identified using a study number, and it includes three sections: demographics, questions related to potential treatments with regards to frequency and duration of drug administration, and questions related to potential treatment with regards to toxicities. All questions are phrased related to a length of benefit that was projected from the treatment. Once the survey is completed, the first 50 patients (approximately) were given a $20 gift card to Target, and the rest were and still are handed a $10 gift card to Target. The survey is then entered into REDCap by a medical student. Results will then be analyzed using an uncorrected chi-squared statistical test.

Conclusions

Differences may exist in patient willingness to comply with treatment based on frequency and duration of drug administration, toxicities, and magnitude of benefit. Understanding these differences holds a promising future for improving communication between physicians and patients and ultimately increasing patient enrollment in clinical trials.

References

References Available Upon Request

Acknowledgements

Apart from my two mentors (Dr. Leora Horn and Dr. Emily Castellanos), I would also like to thank the nurses and staff in the Ingram Cancer Center who helped collect surveys and distribute gift cards. In addition, I would like to thank Dr. Julie Means-Powell, Dr. Ingrid Mayer, and Dr. Vandana Abramson who allowed me to speak with and survey their breast cancer patients. Finally, I would like to thank Pamela Horowitz who helped me call, conset, and survey patients throughout the fall and winter when Dr. Horn was on maternity leave.

Mentor / Department

Dr. Leora Horn (Principal Investigator), Department of Hematology-Oncology Dr. Emily Castellanos, Chief Resident, Department of Internal Medicine

COMMON OUTPATIENT SURGERIES: WHAT PREDICTS UNPLANNED ADMISSIONS?

Stephen Gadomski
Healthcare and Public Health Research and Management

Background Problem
Although breast reduction surgery is a common, outpatient procedure, few studies are available that examine factors that predict conversion from an ambulatory procedure to an unplanned admission.

Objectives
See Methods.

Materials and Methods
All patients who underwent an ambulatory reduction mammoplasty, CPT code 19318, between January 2005 and December 2011 at an academic medical center were identified. Unplanned admission, the primary outcome of the study, is defined as the presence of an unintended hospital stay (both immediately and within 30 days post-operative) or an ED visit within 30 days of the procedure. Chi-squared/Fisher's exact test and simple logistic regression were utilized to determine the presence of any significant correlations between the primary outcome and either perioperative risk factors or operative variables. Additional relationships amongst the predictor variables will be explored utilizing more sophisticated statistical methods, particularly to adjust for covariance.

Results
Initially, there were 1,038 patients identified as having underwent a reduction mammoplasty within the study time frame. After excluding those patients scheduled for an inpatient procedure (7) and those patients under 18 at the time of the procedure (70), there were 961 records analyzed. Of these, there was an unplanned admission rate of 5.72% (55/961). Common complications that resulted in admissions include surgical site infection (n=15, 5.72%), hematoma formation (n=6, 0.62%), and wound dehiscence (n=6, 0.62%). Of note, there was only one pulmonary embolus that occurred 2 weeks after surgery and was identified during an ED visit. BMI ($p = 0.012$), positive history of smoking (OR 2.96, $p=0.003$), anesthesia duration ($p<0.001$), surgical duration ($p<0.001$), surgical start time later than 1500 (OR 8.51, $p=0.042$), surgical end time later than 1800 (OR 4.32, $p=0.006$), surgical end time ($p=0.032$), EBL ($p=0.017$), and the presence of multiple concomitant procedures (OR 1.97,$p=0.044$) all were significantly correlated with an unplanned admission. Further analysis is needed to clarify these relationships.

Conclusions
N/A at this time.

References
References Available Upon Request

Acknowledgements
Jesse Ehrenfeld, MD, MPH, Associate Professor of Anesthesiology, Director of Perioperative Data Systems Research John Bradford Hill, MD, NYU Langone Medical Center

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Oscar Guillamondegui, MD, MPH, Assistant Professor of Surgery

BACTEREMIA IN NON-NEUTROPENIC PEDIATRIC ONCOLOGY PATIENTS

Kelly Garcia
Healthcare and Public Health Research and Management

Background Problem

Currently children with cancer have a high risk of bacteremia due to immunosuppression and indwelling central venous catheters used during treatment. However there is little published evidence to help determine the risk of bacteremia in febrile non-neutropenic patients (absolute neutrophil count >500 cells/μg). A risk prediction model would help determine a patient's risk of bacteremia so that therapy could be tailored to the individual.

Objectives

This study was designed to evaluate a model that effectively predicts bacteremia in pediatric oncology patients with non-neutropenic fever.

Materials and Methods

This retrospective cohort study identified patients from Monroe Carell Jr. Children's Hospital at Vanderbilt diagnosed with cancer between 2007-2009, who underwent treatment from 2007-2010 with chemotherapy using a central venous line. Clinical data for each non-neutropenic fever episodes (defined as temperature >38.0°C for at least an hour or any temperature >38.3°C, and ANC >500 cells/μg) was abstracted from the electronic medical record. Information was de-identified and evaluated by statisticians who applied multivariate logistic regression modeling, and internally validated using bootstrapping technique.

Results

Highest odds ratios for risk factors of bacteremia were: having a Hickman line-14.38, having a PICC line-7.55, and the presence of hypotension-2.0 (systolic or diastolic blood pressure <5th percentile within 2 hours of initial blood culture). There were also protective factors. Two preliminary risk prediction models were developed from calculated odds ratios. The risk prediction models have receiver operating characteristic curves with the C-statistics of >0.9.

Conclusions

There are many risk factors for bacteremia in pediatric oncology patients as well as protective factors. Risk factors identified include having an increasing temperature, a Hickman line, a PICC line, or the presence of hypotension. Significant protective factors include a diagnosis of acute lymphoblastic leukemia, and the presence of URI symptoms when controlled for all other factors. The risk prediction models will have substantial clinical utility.

References

References Available Upon Request

Acknowledgements

Debra Friedman, MD (1,2), Kathleen Weber, MPH (1), Jennifer Esbenshade, MD, MPH (3), Zhiguo (Alex) Zhao, MS (4), and Ayumi Shintani, PhD, MPH (4), Cecilia Di Pentima, MD, MPH (3), Robert Lindell, MD (1), Ato Wallace (1), Monique Simpson (1), Haerin Lee (1), Adam Esbenshade, MD, MSCI (1). (1) Department of Pediatrics, Division of Hematology/Oncology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN. (2) Vanderbilt-Ingram Cancer Center Cancer, Vanderbilt University Medical Center, Nashville, TN. (3) Department of Pediatrics, Division of Infectious Disease, Vanderbilt University Medical Center, Nashville, TN. (4) Department of Department of Biostatistics, Vanderbilt Center for Quantitative Sciences, Vanderbilt University School of Medicine, Nashville, TN

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VALIDATION OF SPOT SCREENING DEVICE FOR AMBLYOPIA RISK FACTORS IN A PEDIATRIC OPHTHALMOLOGY CLINIC SETTING

Glynnis Garry
Healthcare and Public Health Research and Management

Background Problem

Early detection of amblyopia is critical to preventing permanent visual impairment in children. The Spot Vision Screener is a handheld digital screening device that evaluates children for the presence of amblyopia risk factors (ARFs).

Objectives

We validated this screening device in a controlled pediatric ophthalmology clinic setting.

Materials and Methods

During a 3-month period, 215 children (ages 2 to 9 years) were screened using Spot in a pediatric ophthalmology clinic before receiving a comprehensive gold standard eye exam. Gold standard examinations were evaluated using the new AAPOS Vision Screening Committee guidelines and compared with results from the Spot Vision Screener. Results from Spot were evaluated using two different manufacturer referral criteria; v1.0.3 and v1.1.51. The specificity and sensitivity for each set of referral criteria to detect ARFs was calculated.

Results

215 children were screened by Spot (n=80 had amblyopia, n=150 had ARFs); 156 children were referred, and 59 passed. Using the original criteria (v1.0.3), the device had a sensitivity of 91% and a specificity of 71% to detect ARFs. The updated referral criteria (v1.1.51) were applied to 156 patient records in a masked manner, and the specificity (77%) improved substantially within the masked population while the sensitivity (83%) was minimally affected.

Conclusions

Spot v1.0.3 had a high sensitivity to detect all types of ARFs but over-referred for suspected myopia and strabismus. Spot v1.1.51 maintained sensitivity of the device while improving its specificity, yet additional refinement of the criteria is warranted to further increase specificity. Increasing the criteria threshold for myopia, astigmatism, and anisometropia, while decreasing the threshold for hypermetropia are recommendations from this study for the optimization of specificity for the Spot Vision Screener.

References

References Available Upon Request

Acknowledgements

The Authors wish to thank Sina Omran for his assistance with data analysis, as wel as the Vanderbilt Emphasis Research Program and the Vanderbilt Eye Institute for providing the funding and support for this research opportunity.

Mentor / Department

Sean Donahue, M.D., Ph.D. Pediatric Ophthalmology

SYNTHROID V. GENERIC LEVOTHYROXINE FOR TREATING CONGENITAL HYPOTHYROIDISM IN YOUNG CHILDREN

Fayrisa I. Greenwald, Lulu Wang
Healthcare and Public Health Research and Management

Background Problem

The Food and Drug Administration (FDA) asserts that most generic and brand-name levothyroxine (synthetic thyroid hormone) preparations are interchangeable. However, the FDA does not evaluate the effects of the preparations on the most sensitive marker of thyroid function: thyroid stimulating hormone (TSH). Many clinicians prefer using brand-name levothyroxine for patients because they do not have confidence in the FDA's methods.

Objectives

We were interested in assessing if brand-name Synthroid or generic levothyroxine would be better for controlling the variation in TSH and free T4 for young children with congenital hypothyroidism.

Materials and Methods

An electronic medical records database was searched to identify all patients seen for congenital hypothyroidism from April 2006 to April 2011. We identified patients who had been treated either exclusively with Synthroid or generic preparations of levothyroxine from birth through 36 months. We recorded the initial TSH on newborn screen; all subsequent TSH and free T4 measurements; the total number of TSH checks for each patient; the number of months that the patient was followed; and the total number of dosing adjustments that the patient received since the TSH was under 5 microunits/ml. The primary outcome was the variation in TSH between the two treatment groups; the secondary outcomes were number of dose changes, and the free T4 variation between the groups.

Results

The Wilcoxon Rank Sum Test demonstrated no difference in the standard deviation (SD) for TSH between the two treatment groups, and the linear mixed model showed a lower TSH standard error (SE) for patients taking generic. There was no difference in dosing adjustments. The Wilcoxon Rank Sum Test showed similar free T4 variability between the groups; the Linear Mixed model demonstrated that the generic group had a lower free T4 SE.

Conclusions

Our data suggests that generic levothyroxine is therapeutically interchangeable with Synthroid in young children with congenital hypothyroidism.

References

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Acknowledgements

I would like to thank Dr. Jefferson P. Lomenick for serving as a fantastic mentor, Ms. Lulu Wang for helping to gather data, Mr. Steve B. Ampah and Dr. Benjamin R. Saville for their help with the statistical analyses of the data, and Drs. Ashley Shoemaker and Daniel Moore for conducting a peer review of our project.

Mentor / Department

Dr. Jefferson P. Lomenick, Assistant Professor of Pediatrics, Division of Endocrinology, Vanderbilt University School of Medicine

DO LEVEL 1 TRAUMA CENTERS ADDRESS THE PSYCHOLOGICAL RESPONSES ASSOCIATED WITH TRAUMA?

Katherine E. Guess
Healthcare and Public Health Research and Management

Background Problem

Of the thousands of trauma patients treated annually at Level 1 trauma centers in the United States, 10-25% develop Acute Stress Disorder (ASD) and 10-40% develop Post Traumatic Stress Disorder (PTSD) in the wake of their hospitalization. No previous study has addressed the presence or absence of assessment and/or educational programs for ASD/PTSD provided to trauma patients and caregivers at these institutions.

Objectives

The purpose of this study was to determine whether Level 1 trauma centers provide ASD and PTSD assessment and educational programs to trauma patients and their caregivers, to identify the health professionals who conduct these programs, and to ascertain whether an association exists between the assessment and educational programs provided and individual hospital characteristics.

Materials and Methods

This study represents the results of an electronic survey conducted to determine ASD and PTSD assessment and education in August 2012. Participant hospitals were selected based on American College of Surgeons (ACS) or state Level 1 designation. 207 institutions met criteria and formulated the basis of this study. The survey addressed the following: populations assessed or educated for ASD and PTSD, timing of assessment or education programs, and specific assessment or educational tools utilized. Data collected included institutional characteristics and survey responses. Hospital characteristics examined included the date of trauma center establishment, total number of hospital beds, total number of trauma-specific beds, and ACS vs. state designation. Analysis was conducted to inventory the responses and determine the presence of an association between the assessment and educational programs for ASD and PTSD and hospital characteristics. Nonparametric tests of proportions were used to determine statistical significance.

Results

131 centers either partially or completely responded to the survey (68.6%). 6% of responders reported formal assessment of all patients, regardless of symptoms, for ASD; 3% assess all patients for PTSD. 0% formally assess all caregivers for ASD/PTSD. Education regarding ASD/PTSD was reported in 7% of centers for all patients and 9% for all caregivers. Of institutions that provide assessment and/or education for ASD/PTSD, psychiatrists primarily conduct the assessment and education. No association was found between the presence of an assessment or educational program and the date of trauma center establishment, total number of hospital beds, total number of trauma-specific beds, and ACS vs. state designation. ($p>0.1$ for all analyses)

Conclusions

An overwhelming minority of U.S. Level 1 trauma centers offers formal assessment or educational protocols for ASD and PTSD to all trauma patients and caregivers. The personal repercussions and societal costs continue to escalate unchecked. The psychological burden of trauma on survivors and caregivers remains unquantified and represents a silent epidemic in this vulnerable population.

References

References Available Upon Request

Mentor / Department

Raeanna C. Adams MD, Trauma

HOMERUN-HOSPITAL MEDICINE REENGINEERING NETWORK: IMPROVING TRANSITIONS OF CARE

Catherine Higham
Healthcare and Public Health Research and Management

Background Problem

An increasing number of patients are readmitted to the hospital within 30 days of a previous discharge. This is reflects negatively on the quality of care of the index admission and results in increasing—and potentially unnecessary—costs. There is currently a lack of comprehensive data regarding potential quality indicators and/or predictors of readmission.

Objectives

This study seeks to use data from in-person patient interviews, physician surveys, and patient medical records to identify and gain a better understanding of measures that are associated with and/or predict readmission within 30 days. We have collected data on available social supports, discharge planning, communication between providers, time until outpatient follow-up, adequacy of discharge documentation, and adequacy of medication reconciliation. Additionally, we want to determine the percentage of potentially preventable readmissions.

Materials and Methods

This study is a multi-center investigation; Vanderbilt is one of 12 medical centers across the country participating. The study consists of a readmitted patient cohort and a control cohort of randomly selected discharged patients, regardless of readmission status. Each cohort consists of 100 patients from General Internal Medicine, Hospital Medicine, or Geriatrics services. For each patient, we have collected the following data: an in-person patient perspectives interview, physician surveys of the patient's primary care provider, discharging physician, and readmitting physician, a discharge audit chart abstraction, and an adjudication review.

Results

We are still in the process of data collecting and therefore do not yet have the final data or analysis. Preliminary data analysis suggests that up to 1/3 of the readmissions were potentially preventable. Some potential ways to prevent readmission cited by adjudication reviews include improved communication of information, improved coordination between providers, and improved discharge planning.

Conclusions

N/A

Acknowledgements

Sunil Kripalani, MD, MSc Eduard Vasilevskis, MD Dan Markley, DO Anna Fahy, VMS IV Mary Lou Jacobsen, research coordinator

Mentor / Department

Sunil Kripalani

DEVELOPMENT OF ALGORITHMS FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION

Deepa Joshi
Healthcare and Public Health Research and Management

Background Problem

Immunizations are essential to public health, representing cost effective means to reduce global disease burdens. As with any medical intervention, certain risks are associated with immunization. The Brighton Collaboration is a non-profit, international research network that provides standardized, validated and objective methods for monitoring vaccine safety. The organization created standardized case definitions to assess adverse events following immunization (AEFI). Each case definition outlines criteria needed to define AEFIs according to one of three levels of diagnostic certainty. Universally accepted case definitions allow for greater international comparability of patients with AEFIs, may increase reporting rates of AEFIs and promotes vaccine safety reassessment. While the case definitions have the potential for enhanced data collection, the current format is not user friendly since the case definition is buried within a 10-12 page journal article.

Objectives

The goal of this project was to improve the usability of the case definitions by converting them into algorithms.

Materials and Methods

We first reviewed Brighton's case definitions and abstracted key diagnostic criteria. Using SmartDraw Software, these critical criteria were transposed into a stepwise flowchart that guides users to a level of diagnostic certainty or another appropriate conclusion. 23 algorithms were created and each was reviewed independently by a fellow investigator who applied sample cases to the algorithms.

Results

We are currently in the process of validating the algorithms. We submitted our project for IRB approval and VICTR funding to have allergy and vaccine experts compare the algorithms to the original case definitions. We will then conduct a prospective randomized trial to compare the accuracy of the algorithms versus the original case definitions in obtaining the appropriate level of diagnostic certainty for sample cases.

Conclusions

The long-term goal is that these algorithms will serve as a tool for global communication for AEFIs in developing countries that will allow for enhanced data comparability.

References

References Available Upon Request

Acknowledgements

Dr. Kathryn Edwards Dr. Elizabeth Williams Molly Sullivan VSAN Staff Vanderbilt Vaccine Research Program

Mentor / Department

Dr. Kathryn Edwards, Dr. Elizabeth Williams; Vanderbilt Vaccine Research Program

PEDIATRIC ATV INJURY PATTERN AND SEVERITY

Rebecca A. Kasl
Healthcare and Public Health Research and Management

Background Problem

All-terrain vehicles (ATVs) and obesity pose pediatric health risks. Overweight children frequently present to a Pediatric Emergency Department (PED) after an ATV crash. Few reports describe crash-associated injury patterns and severity.

Objectives

Determine if overweight children in ATV crashes are associated with higher hospital costs and more severe injury patterns.

Materials and Methods

A single reviewer retrospective chart review was performed on patients presenting to the Vanderbilt PED from 2003 to 2011. Subjects were identified from StarPanel and TRACS based on chief complaint and ICD-9 code. Injury pattern severity was measured by the Automated Injury Scale (AIS).

Results

280 subjects ages 2-15 with mean 11.2 ± 3.6 years were identified. 69% were male; 97% were Caucasian; and 73% were drivers. Helmet use was seen in 33% and absent or undocumented in the remainder of cases. 67% had injuries in multiple body segments with thoracic, long bone, and cranial damage being most common. The median hospitalization costs were $23785 (LQ $13880, UQ $39754). Higher costs are associated with a change in weight percentile from 80% to 95% (SE 0.31; 0.02-0.59). No evidence associates weight percentile with any AIS score. Factors affecting injury profile include helmet-use, gender, and history of ADHD. Non-helmeted subjects are associated with more severe AIS head/neck (OR 1.75; 1.17-2.59) and face injury (3.07; 1.7-5.53), yet less severe AIS extremity injury (0.56; 0.38-0.81). Males are likely to have more severe AIS chest (1.92; 1.18-3.14) and abdomen injury (2.02; 1.12-3.67) than females. Subjects without a diagnosis of ADHD are likely to have less severe AIS face injury (0.47; 0.22-0.99).

Conclusions

Overweight children can have higher hospital costs. Despite the higher cost of care, they have similar injury severity. Mechanism of injury in this population merits further study. Patient gender, helmet-use, and history of a disruptive behavior disorder appear to influence injury pattern and severity.

Acknowledgements

Julie Phillips MD, Cristina Estrada MD, Kristen Crossman MD, Purnima Unni MPH, Mario Davidson PhD, Yanna Song MS

Mentor / Department

Thomas Abramo, MD; Department of Pediatric Emergency Medicine

PERIOPERATIVE EXPOSURES ASSOCIATED WITH INCREASED LENGTH OF STAY AFTER PULMONARY RESECTION

Patrick Kelly
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Background Problem

Surgical resection for early stage lung cancer remains the standard of care. Length of stay (LOS) is a surrogate variable for morbidity and mortality. Previous large database work established nine variables associated with prolonged LOS in patients undergoing lobectomy.

Objectives

The current study applies a similar model to patients undergoing several types of lung resection surgery and seeks to identify additional perioperative exposures associated with increased LOS measured in days.

Materials and Methods

We analyzed our prospectively collected surgical database containing all patients undergoing lung resection for known or suspected lung cancer at VUMC 2004 to 2010. Additional perioperative variables were added by retrospective chart review. Patients missing information on LOS were excluded. We included the 9 variables previously found to be associated with prolonged LOS for lobectomies. The additional intra-operative exposures included thoracoscopic approach (VATS, y/n), total surgery time (minutes), urine output (mL), estimated blood loss (mL), and intraoperative intravenous input (crystalloid, colloid, and transfusion volume, mL). The outcome of interest was post-operative LOS (days). Missing values were multiply imputed before analysis. A multivariable regression for LOS was performed using the 12 variables at a predetermined significance level of $\alpha=0.05$.

Results

We identified 483 pulmonary resections including 240 lobectomies, 139 single-wedge resections, and 104 multiple-wedge resections. The median LOS for all patients was 5 days. We replicated previously identified clinical variables associated with increased LOS, i.e. Zubrod score, preoperative CRI, and FEV1. Of the additional exposures considered, estimated blood loss was associated with increased LOS.

Conclusions

Zubrod score, preoperative CRI, and FEV1 are important preoperative variables in patients undergoing wedge resection in addition to lobectomy. There is a strong association between estimated blood loss and LOS even when controlling for multiple intraoperative confounders. Blood loss should be included in models for predicting LOS, and efforts to reduce intraoperative blood loss may improve patient outcomes.

References

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Mentor / Department

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COMPARATIVE EFFECTIVENESS OF ANTERIOR AND POSTERIOR SURGICAL TREATMENT OF THORACOLUMBAR BURST FRACTURES

Bharat Kilaru
Healthcare and Public Health Research and Management

Background Problem

Thoracolumbar burst fractures characterize severe vertebral compression from extreme trauma and result in unstable anterior and middle column compromise. Surgical treatment includes anterior decompression with our without stabilization and posterior decompression with or without fusion. The optimal surgical approach remains debated. Anterior corpectomy and fusion allows shorter segment fusion but requires an invasive approach through the chest and diaphragm. Posterior approaches avoid chest wall invasion but often require longer fusion constructs with chronic loss of mobility in more spinal motion segments.

Objectives

Through cost effectiveness-driven patient reported outcomes analysis, we endeavor to compare anterior and posterior surgical approaches in stable thoracolumbar burst fracture patients without neurologic deficit. We performed a comparative effectiveness analysis to determine the differences in the morbidity and outcomes of these two surgical approaches in real-world care.

Materials and Methods

We employed a one-year review to evaluate one-year patient reported outcomes, total back-related medical resource utilization, missed work, and health state values. All patients presented with thoracolumbar burst fractures (T10-L2) without neurological deficit. Outcomes data including numeric pain rating scale (NRS-Back, NRS-Leg), ODI, SF-12 PCS, SF-12 MCS and EQ-5D; MRI, CT and X-ray imaging; return to work status, narcotic use, disease specific healthcare resource utilization, patient-reported one-year medical utility consumption, and patient satisfaction was collected retrospectively. Patient reported outcomes were assessed via telephone interview and compared between the two treatment groups.

Results

The outcomes scores between anterior and posterior approaches to thoracolumbar burst fracture patients without neurologic deficit are statistically similar in a selection 43 patients. 28 patients were treated with a posterior approach (multilevel pedicle screw fixation) and 15 underwent a thoraco-abdominal approach for an anterior corpectomy and reconstruction (cage and anterior screw plate construct). All patients were Grade E (neurologically intact) at presentation based on ASIA Impairment Scale. Baseline radiographic and clinical characteristics and pre-injury functional status were statistically similar between the two treatment groups. There was no significant difference in length of surgery, length of hospital stay, 90-day morbidity or one-year post-operative pain, disability, or quality of life between the two groups: NRS-BP($p=0.25$), NRS-LP ($p=0.71$), ODI% (0.74), SF-12 PCS ($p=0.14$), SF-12 MCS ($p=0.26$), EQ-5D ($p=0.35$) and Zung Depression ($p=0.26$).

Conclusions

The comparative effectiveness analysis reported no significant difference in one-year outcomes between anterior and posterior surgical approaches for thoracolumbar burst fractures without neurological deficit. Both are validated, safe treatment options. In the context of comparable patient reported outcomes, specific surgical approaches can be evaluated on cost-effectiveness of selection.

References

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Acknowledgements

Saniya S. Godil, MD; Akshitkumar M. Mistry, BS; Scott L. Parker, MD; Matthew J. McGirt, MD

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RAPID RESPONSE TEAM UTILIZATION FOR EVALUATION AND MANAGEMENT OF ACUTE CLINICAL DETERIORATION IN UROLOGIC SURGERY PATIENTS

Chirag Kulahalli
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Background Problem

Hospitals have implemented rapid response teams (RRT) in order to prevent adverse events in clinically deteriorating patients. Typical RRTs consist of critical care physicians, nurses, or respiratory therapists and respond to patients with acute changes in vital signs; they are charged with evaluating, providing treatment, and triaging such patients.

Objectives

We aimed to examine characteristics and outcomes of RRT activation for urologic surgery patients at a tertiary care center.

Materials and Methods

We identified all patients admitted between January 2009 and December 2011 who had RRT activations on the adult urology service. Associated characteristics and outcomes were collected through chart review. We then compared characteristics of patients who died or required further intervention (transfer to a higher level of care or a second RRT activation) with those who did not.

Results

Of 4403 admissions, 61 (1.4%) urology patients had RRT activations. Most RRT activations were called for cardiac and/or respiratory decompensation. Of the 61 initial RRT activations, 22 (36.1%) resulted in no further intervention, 22 (36.1%) in transfers to ICU, 11 (18.0%) in transfers to step-down care and 6 (9.8%) in a second RRT activation. Fifty-seven (93.4%) patients were eventually discharged while 4 (6.7%) died. Patients who required further intervention were more likely to have had a respiratory cause for RRT activation than those who did not (56% vs. 18%, $p<0.01$).

Conclusions

RRTs provide a means to triage and stabilize patients with clinical deterioration in order to prevent morbidity and mortality. Our study shows that one third of patients required no further intervention after RRT activation, two thirds were transferred to higher care or had a second RRT activation, and overall 93.4% were discharged alive. Further research will address predictors of RRT utilization, appropriate utilization and the impact of RRTs on preventable outcomes.

Acknowledgements

David F Penson MD, MPH, April N Kapu ACNP, Chaochen You MD, Liza Weavind MD, and Roger Dmochowski MD

Mentor / Department

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CHANGES IN ADJUVANT ENDOCRINE THERAPY OVER ONE YEAR AMONG POST-MENOPAUSAL WOMEN WITH EARLY STAGE BREAST CANCER INITIATING AROMATASE INHIBITORS

Danielle LaMorte
Healthcare and Public Health Research and Management

Background Problem

Aromatase inhibitors (AIs) are standard of care for adjuvant endocrine therapy (AET) to prevent recurrence of early stage breast cancer in postmenopausal women. Previous AET adherence research has focused on the 25-96% adherence observed with tamoxifen, but more information is needed about AI adherence, especially regarding the role of arthralgia (joint pain or stiffness) in AET changes.

Objectives

Our objective was to understand AET changes within a year of AI initiation.

Materials and Methods

We examined AET switching (either to another AI or to tamoxifen), overall changes in AET (including switching and temporary or permanent discontinuation), and physician- and patient-reported arthralgia, using data abstracted from medical records and self-administered surveys among 93 patients initiating AI. We conducted Chi-square and Wilcoxon univariate analyses.

Results

Anastrazole was initially prescribed to 64 patients (69%), letrozole to 28 patients (30%), and exemestane to 1 patient. A year after AI initiation, 64 patients (69%) had no change in AET. Among the 29 patients (31%) who had an AET change, 14 switched to at least one other AI, 11 switched to tamoxifen, 9 temporarily discontinued AET, and 7 entirely discontinued AET (categories not mutually exclusive). Average time to first AET switch was 182.7 days. Average number of AET switches was 1.4. Arthralgia was the most common reason for AET changes, noted in the records of 19 patients (66% of those who changed AET). Patients who changed AET reported more severe arthralgia (median pain from 0-10 among 8 joint groups =1.4, interquartile range [IQR]=0.3-2.6) at week 12 than those who did not (median=0.3, IQR=0-1.1), p=0.03. A higher proportion (46%) of the 28 patients who initiated with letrozole changed AET due to arthralgia, compared with 20% of the 64 patients who initiated with anastrazole (p=0.01).

Conclusions

A substantial proportion of women initiating AI change AET over one year. Arthralgia appears to play a key role in AET changes, particularly for letrozole as compared with anastrazole. More longitudinal patient-reported arthralgia data are needed to guide clinical decision making about AI initiation and AET changes.

Acknowledgements

KE Hartmann, V Abramson, I Mayer, N Peacock, DF Cella

Mentor / Department

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INCIDENCE AND RISK FACTORS FOR RECURRENT UVEITIS AFTER LONG-TERM TREATMENT

Margot Lazow
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Background Problem

Uveitis, inflammation of the uvea, accounts for >10% of severe vision loss in developed countries, and can be autoimmune, infectious, or due to trauma or malignancy. Autoimmune uveitis is often treated with immunosuppression, and if inactive for at least 12 months on immunosuppressants, treatment is stopped, but uveitis recurs in some patients.

Objectives

The purpose was to determine the incidence and associated risk factors for recurrent uveitis in patients with autoimmune chronic uveitis with at least 12 months of inactive disease on immunosuppression followed by elective cessation of treatment.

Materials and Methods

This was a retrospective cohort study. Records of 1,901 patients with ICD-9 codes for uveitis were reviewed, and 42 eyes of 23 patients met inclusion criteria. Patients were included in the study if they had non-infectious, autoimmune chronic uveitis diagnosed by a fellowship-trained uveitis specialist, and were inactive for at least 12 months on immunosuppression before cessation of treatment, with at least 6 months of follow-up. Subject characteristics, lab data, and documented clinic visits were reviewed and recorded. The Fisher exact test was used to compare categorical values between remission and recurrence eyes.

Results

Uveitis recurred in 15 of 42 eyes (35.7%). Eyes with anterior uveitis were more likely to be in remission than eyes with intermediate, pan, or posterior uveitis ($p< 0.05$). The recurrence group was more likely to have stopped immunosuppression at a younger age (<25y/o) ($p<0.05$); average age of immunosuppression cessation was 29.1+/-19.1 for the recurrence eyes, vs. 42.2+/-21.4 for the remission eyes. In addition, we noted two trends: females seemed more likely to recur than males ($p =0.11$), and eyes with <20months of inactive disease on immunosuppression before stopping seemed more likely to recur ($p=0.1$).

Conclusions

Uveitis recurred in approximately 1 of 3 eyes. Having anterior uveitis, and stopping immunosuppression at an older age and after at least 20months of inactive disease seem to decrease risk of recurrence.

Mentor / Department

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CLINICAL AND PATHOLOGIC CHARACTERISTICS OF BREAST CANCER IN PATIENTS WITH PI3K MUTATIONS

M. Cooper Lloyd
Healthcare and Public Health Research and Management

Background Problem

PI3K mutations are common in breast cancer and represent a clinically useful therapeutic target. As more PI3K pathway inhibitors enter the clinical arena, it is important to understand the characteristics of patients harboring mutations.

Objectives

This study seeks to identify the clinical and pathologic characteristics of breast cancer in patients at Vanderbilt University Medical Center (VUMC) with PI3K mutations.

Materials and Methods

Electronic medical records of all breast cancer patients seen at VUMC, and whose tumors underwent SNaPShot testing from September 2010 to January 2013, were reviewed. PI3K mutation rates, tumor grade, receptor status (ER/PR/HER2), pathology, number of positive lymph nodes, recurrence rates and recurrence-free survival were tabulated for all patients and by PI3K mutation status.

Results

300 eligible patients were identified, with PI3K mutations detected in 83 (28%). Patients with PI3K mutations were more likely to be ER/PR positive (73% vs. 48%; $p<0.001$) or ER/PR/HER2 positive (12% vs. 3.6%; $p=0.035$), while patients without PI3K mutations were more likely to be ER/PR/HER2 negative (25% vs. 7.2%; $p=0.001$) or HER2 positive only (9.2% vs 2.4%; $p=0.043$). Tumors with PI3K mutations were more likely to be of the invasive lobular type ($p=0.045$). More patients with PI3K mutations had intermediate grade tumors compared to those without mutations (49% vs. 34%; $p=0.015$), while those without mutations were more likely to have high grade tumors ($p=0.0001$). No significant differences were found in number of positive regional lymph nodes between the groups. Average recurrence-free survival was longer for those with PI3K mutations (68 vs. 50 months; $p=0.05$).

Conclusions

Tumors with PI3K mutations were more likely to be ER/PR positive, of intermediate grade and invasive lobular type, and associated with longer recurrence-free survival. These data and the potential eligibility of patients harboring mutations for clinical trials support the prognostic and clinical utility of SNaPShot testing for all breast cancer patients at a tertiary care center.

References

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Acknowledgements

Thank you to Dr. Abramson and the Emphasis Program at VUSM for supporting this project.

Mentor / Department

Dr. Vandana Abramson, Department of Medicine

PREDICTORS AND OUTCOMES OF TRACHEOSTOMY AFTER TRAUMATIC BRAIN INJURY

John W. McKenna
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Background Problem

Often, critically ill traumatic brain injury (TBI) patients need prolonged mechanical ventilation and tracheostomy placement. Numerous studies have investigated patient outcomes among early and late tracheostomy groups, however, no study has compared outcomes for those who received a tracheostomy to those that did not.

Objectives

Our goal was to describe the short-term outcomes and define the risk factors for predicting those severe TBI patients who will receive a tracheostomy.

Materials and Methods

This is an IRB-approved retrospective cohort study of Level 1 trauma center patients age>=18y admitted to the ICU between 2000-2011 with admission Glasgow Coma Scale(GCS)<=8, Head-Abbreviated Injury Scale(AIS)>=3, and with CT evidence of intracranial hemorrhage. Patients experiencing confounding events<96h (mortality,extubation,tracheostomy,discharge) were excluded. To predict tracheostomy, a logistic regression model utilized covariates of age, gender, race, GCS, AIS(Head,Face,Chest), injury severity score(ISS), and insurance status. Multivariable models assessed the influence of tracheostomy on ventilator days, ICU-length of stay (LOS), hospital-LOS, and mortality at 1, 3, and 12-months.

Results

Of 2,929 TBI patients meeting inclusion criteria, 2,346 met exclusion parameters. Among our cohort of 583 patients, 350 (60%) underwent tracheostomy. Compared to a 65 year-old patient, there is an increased probability of tracheostomy placement in a 35 year-old patient(OR=1.72[95%CI:1.13-2.62]). AIS, ISS, GCS, race, and gender were not risk factors for tracheostomy placement. Uninsured patients had a decreased probability of receiving a tracheostomy, compared to privately insured patients (OR=0.54[95%CI:0.31-0.93]). Without a tracheostomy, the probability of mortality was increased at all time intervals (1-month-OR=9.63[95%CI:5.83-15.92], 3-month-OR=8.27[95%CI:5.12-13.38], and 12-month-OR=5.84[95%CI:3.73-9.12]). With a tracheostomy, ventilator days increased by 4.35 days[95%CI:3.67-5.03], ICU-LOS increased by 4.47 days[95%CI:3.56-5.37], and hospital-LOS increased by 10.2 days[95%CI:8.41-12.0].

Conclusions

Age and insurance status are independent predictors for tracheostomy placement after TBI. Tracheostomy placement is associated with prolonged mechanical ventilation and longer LOS but also increased long-term survival.

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Acknowledgements

Laura D. Wilson MS; Yanna Song MS; Mario A. Davidson PhD; Stephen S. Humble BS; Jesse M. Ehrenfeld MD, MPH; Oscar D. Guillamondegui MD, MPH, FACS; Pratik P. Pandharipande MD, MSCI; Mayur B. Patel MD, MPH, FACS

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CLINIMETRIC ASSESSMENT OF PATIENT EXPERIENCE WITH UNILATERAL VOCAL FOLD PARALYSIS

Monique McKiever
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Background Problem

Unilateral vocal fold paralysis (UVFP) occurs from iatrogenic, traumatic, compressive, or idiopathic injury to recurrent laryngeal nerve. A thorough understanding of UVFP patient experience related to voice, swallowing, and breathing dysfunction is lacking.

Objectives

The aim of this study is to¬ measure frequency of voice, swallowing, and breathing symptoms due to UVFP and to qualitatively assess how UVFP affects quality of life.

Materials and Methods

Patients with UVFP were interviewed from May-August 2012. In total, 50 patients underwent semi-structured interviews to describe their UVFP symptoms and changes to their quality of life. Specific domains that were assessed included voice, swallowing, and breathing and how these affected their personal and professional lives.

Results

Of 50 patients interviewed, greater than 90% of paralyses resulted after neck or cardiothoracic surgery. The most immediate complaint after surgery was loss of voice (dysphonia). Patient reported dysphonia included “hoarse,” “squeaky,” and “raspy” speech. In all, 70% of patients complained of difficulty breathing after onset of UVFP. Breathing difficulties include “shortness of breath” during speech (74%), new difficulties in “bearing down” limiting bowel movements and ability to lift objects (30%), and difficulty breathing during physical activities. Respiratory difficulties significantly affected patient endurance during physical activity. Moreover, 70% of patients described symptoms of dysphagia, which started after paralysis. 40% of patients reported liquids as being most difficult to swallow, 30% reported solids, 10% had difficulty with all consistencies, and 10% specified “dry food” as eliciting most of their symptoms.

Conclusions

Many UVFP symptoms elicited are conspicuously absent in the current literature. Patients participating in this study described a myriad of symptoms involving voice, swallowing, and breathing. By delving more into the patient UVFP experience and attempting to better understand the diversity of UVFP presentations, we can better personalize medical, behavioral, and surgical interventions to optimize their quality of life.

Acknowledgements

Dr. David O. Francis, Vanderbilt Voice Center

Mentor / Department

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QUALITY OF CARE AMONG SOUTHERN LOW-INCOME RACIALLY DIVERSE NSCLC PATIENTS

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Background Problem
Timely diagnosis and treatment of non-small cell lung cancer (NSCLC) is necessary for improved outcomes. Patients who have delays in their diagnosis may present with advanced disease and limit the curative options such as surgical resection.

Objectives
We conducted an initial assessment of patient reported quality and timeliness of care in a southern, low-income and primarily African American (AA) population.

Materials and Methods
The Southern Community Cohort Study (SCCS) is a prospective cohort study conducted across a 12-state area of the Southeast among adults age 40-79 primarily recruited from community health centers. A total of 85,806 participants were enrolled from March 2002 to September 2009 with 2/3rds self-reporting as AA. During 2010-2012, we administered a cancer navigation questionnaire to SCCS study participants who reported during a routine follow-up interview that they had been diagnosed with NSCLC.

Results
The survey was administered to 39 surviving lung cancer patients in the SCCS diagnosed with NSCLC. The mean time between diagnosis and interview was 34 months (range, 6 – 81 months). Respondents were 44% (17/39) AA and 56% (22/39) Caucasian, and 51% had a household income of less than $15,000 per year. In symptomatic patients, 47% (8/17) reported that they waited more than a month before seeing their physician. Diagnosis of lung cancer occurred within two months after the initial clinic visit for 95% (37/39) of patients. An initial treatment was received within six weeks after making their treatment decision for 97% (35/36) of patients responding to the questionnaire. Patients who were non-respondents due to death may have experienced delays that were not reported.

Conclusions
Nearly half of symptomatic NSCLC study participants were delayed in the initial evaluation for over a month. Barriers to access to care in this low income and racially diverse population are not known and are under investigation.

References
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Acknowledgements
Eric Grogan, Steve Deppen, William Blot, J. Bill Putnam, NIH NRSA 5T35HL090555 grant, Vanderbilt Emphasis Progam

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BLOOD PRESSURE MONITORING FOR OUTPATIENT DERMATOLOGIC SURGERY: A SURVEY OF MOHS SURGEONS

Tejaswi Mudigonda
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Background Problem

There has been significant interest in the lay press and medical literature recently regarding the number and types of complications associated with the use of office based surgery, such as Mohs micrographic surgery (MMS). Mohs surgery is widely regarded as a safe and efficacious procedure for the treatment of multiple cutaneous malignancies but patient complications do occur. In general, postoperative MMS complications can be divided into two categories: localized (wound dehiscence, localized bleeding, superficial wound infections, flap or graft necrosis) and systemic, which involves compromise of a bodily function or organ. The incidence of post-operative localized complications is as low as 1.6%. The incidence of systemic complications has not been accurately determined in the literature due to the extreme rarity of these complications. Blood pressure (BP) monitoring for Mohs surgical patients and subsequent risk management has received little attention in the literature. Studies in other surgical fields, including ophthalmology and dentistry, have shown BP monitoring may not be useful for stratifying patients and assessing risk of complications

Objectives

The purpose of this survey study was to evaluate the current practice of obtaining pre-, peri-, and postoperative blood pressure (BP) measurements on patients undergoing Mohs Micrographic Surgery (MMS). A secondary aim was to determine how Mohs surgeons were utilizing this information.

Materials and Methods

A one-time e-mail questionnaire, using surveymonkey.com, was sent to all available members of the American College of MMS (ACMS) to evaluate their use of BP monitoring preop-, intraop-, and postoperatively. The survey was sent in April of 2012 and all responses were collected after a study period of 30 days. A reminder email was sent out to those who did not respond approximately two weeks after the initial email. There were a total of 14 questions, most requiring a simple yes/no answer, and one open-ended question. All survey responses were kept anonymous. The survey included demographic questions on the Mohs surgeons' age, experience, and academic title (faculty member or director) if applicable. All members whose e-mail addresses were available through the ACMS were surveyed. The total number of surveyed surgeons was 850 and 260 responses were obtained, yielding a 30.6% response rate.

Results

74% (191/258) of Mohs surgeons surveyed reported checking preoperative BP and 32.7% (81/248) obtained postoperative measurements. Only 7.4% (19/258) of Mohs surgeons reported monitoring BP intraoperatively. 83.5% (157/188) of Mohs surgeons reported obtaining BP measurements due to a perceived increased risk of cardiovascular complications. 33.9% (64/189) of Mohs surgeons reported encountering complications in hypertensive patients, while 66.1% did not. The most commonly reported complication was increased intra- and postoperative bleeding with or without hematoma formation. Systolic and diastolic BP levels used by surgeons to delay surgery or provide antihypertensive medications also varied widely. Of the 190 respondents, 173 clinicians postpone surgery in patients with systolic BPs over 160 mmHg, with the highest proportion (71/173) postponing surgery at the 200-209 mmHg range. 188 respondents reported postponing cases based on elevated diastolic BP. Of these respondents, the majority (102/163), used somewhere between 100-109 mmHg diastolic as a cut-off for postponing surgery. Of the 58/260 Mohs clinicians who replied to the survey question, the most commonly used class (39/58) were benzodiazepines (i.e. diazepam, lorazepam, and midazolam).

Conclusions

While 33.9% of respondents reported experiencing complications in hypertensive patients, ranging from increased bleeding to stroke, controlled studies are lacking regarding what risk, if any, elevated BPs play in the Mohs outpatient surgery setting. The limitations of this study include a response rate of only 30%and recall bias. Additionally, our survey only included Mohs fellowship trained surgeons, and may not be reflective of the practice of non-fellowship trained Mohs surgeons. Further studies are needed to determine the prognostic value, if any, of obtaining pre-, intra-, and postoperative BP monitoring during MMS in the outpatient setting

References

References Available Upon Request

Acknowledgements

Dr. Daniel Christensen, Dr. Thomas Stasko, Dr. Wilfred Lumbang

Mentor / Department

Currently, Dr. Wilfred Lumbang (originally Dr. Thomas Stasko)

ANALAYSIS OF BIPAP THERAPY IN CHILDREN BASED ON WEIGHT

Bushra Samaiya Mushtaq
Healthcare and Public Health Research and Management

Background Problem

Obesity and asthma as comorbidities pose a challenge when treating children presenting the PED in status asthmaticus. Bilevel positive airway pressure (BiPAP) is an accepted treatment modality for children in status asthmaticus. Our purpose was to determine if weight had any influence on length of BiPAP time, BiPAP settings, overall hospital lengths of stay and PICU admissions for status asthmaticus children presenting to the PED.

Objectives

Our purpose was to determine if weight had any influence on length of BiPAP time, BiPAP settings, overall hospital lengths of stay and PICU admissions for status asthmaticus children presenting to the PED.

Materials and Methods

Patients placed on BiPAP in the PED for status asthmaticus from 1/1/10 – 8/31/12 were included in the analysis. Subjects were divided into the following weight subgroups based on the growth curve: <90%ile, 90-97%ile and >97%ile. These groups were further subdivided into moderate and severe asthma exacerbations. Subjects received standard asthma therapies in addition to BiPAP. Data was obtained at bedside by respiratory therapist or collected retrospectively by study investigators. Data was stored and analyzed using a RedCap database.

Results

Three hundred fifty-nine (n=359) subjects were analyzed. Figure 1 shows time on BiPAP per visit. Children whose weight was >97%ile revealed trends towards longer treatment times on BiPAP compared to the other two groups. The moderate subjects who weighed >97%ile had statistically significant longer treatment periods ($p<0.006$) when compared to the <90%ile moderate group. Initial BiPAP settings are listed in Figure 2. When controlling for age, higher BiPAP settings correlated with increasing weight.

Conclusions

Subjects who weighed more trended greater mean time on BiPAP and initial BiPAP settings. Weight did not affect PICU admissions or overall length of hospital stay. Further prospective investigation of the weight effect on status asthmaticus subjects receiving BiPAP is warranted.

Mentor / Department

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HYPOALBUMINEMIA IS ASSOCIATED WITH INCREASED CREATININE LEVEL DURING VANCOMYCIN THERAPY

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Healthcare and Public Health Research and Management

Background Problem

Vancomycin is a glycopeptide antibiotic that inhibits cell wall synthesis by binding to the D-Ala-D-Ala terminus of nascent peptidoglycan pentapeptide. Vancomycin is used exclusively against gram-positive bacteria and important clinical indications include bloodstream infections and endocarditis caused by methicillin-resistant Staphylococcus aureus. However, the risk for toxicity has increased due to the emergence of resistant organisms requiring higher vancomycin doses, specifically for dose-related toxicities such as nephrotoxicity. Vancomycin associated nephrotoxicity is associated with age, creatinine clearance, vancomycin dose dosing interval, and concomitant nephrotoxic medications. Given the frequency and potential clinical impact of renal toxicity, we sought to identify other clinical factors associated with elevated creatinine during vancomycin therapy. In a retrospective cohort of patients treated with vancomycin, we used linear regression modeling to determine significant associations with the outcome of peak creatinine level during the first two weeks of vancomycin therapy from among our pre-specified covariates of patient demographics, vancomycin dosing, laboratory values, and concomitant medications.

Objectives

We sought to determine the contribution of other host characteristics on creatinine during vancomycin therapy. In this retrospective cohort study, data for hospitalized patients > 18 years of age were extracted from the Synthetic Derivative, a data repository containing de-identified electronic medical records data from this institution.

Materials and Methods

In this retrospective cohort study, data for 415 (primary cohort) and 485 (validation cohort) adult hospitalized patients who received vancomycin were extracted from the data repository and analyzed using linear regression. The patient cohorts for this study were derived from the SD, an institutional databank containing de-identified electronic medical records data for over 1.7 million unique individuals. The primary cohort included all individuals over 18 years of age in the SD with documentation of a vancomycin trough level, documentation of the associated dose and dosing interval, and measurement of serum creatinine and is part of a larger study investigating genetic determinants of vancomycin pharmacodynamics; as the primary study included genetic interrogation, availability of a DNA sample in BioVU, the Vanderbilt DNA repository, was also required. Exclusion criteria included: vancomycin trough obtained prior to the third dose (and therefore not reflecting steady state); dialysis therapy, extracorporeal membrane oxygenation (ECMO), heart transplantation prior to or during vancomycin course, identified by current procedural terminology (CPT) codes and manual review; and documentation of multiple dosing regimens of vancomycin prior to trough which were unable to be resolved by manual review. All data were extracted from the SD using automated strategies. After data extraction, charts were manually reviewed to confirm data accuracy. Analyses of both the primary and validation cohort were completed using R v 2.15.0. Linear regression was used to model the outcome, peak creatinine, as a function of the variables listed. Non-linear terms were initially considered via splines for the predictor variables age, height, weight, body surface area, creatinine, albumin, and vancomycin trough, but were reduced to linear terms for easier interpretation after observing no evidence of non-linearity. The outcome variable (peak creatinine) was log transformed to satisfy normality assumptions of the linear model. Parameter estimates were exponentiated to obtain estimated ratios of geometric means as a measure of effect size for each predictor, with corresponding confidence intervals and p-values. Because many patients in the primary cohort had at least one missing value for one of the predictors in the model, multiple imputation strategies on the predictors were used to obtain parameter estimates. This allowed all observed data to be used in the regression model. Individuals with missing data were not included in the validation cohort, so no data imputation was required.

Results

Using linear regression, we found significant associations of higher peak creatinine to longer vancomycin dosing interval ($p<0.008$), higher vancomycin trough ($p<0.001$), higher baseline creatinine ($p\leq0.0005$) and low serum albumin ($p\leq0.002$). For albumin, each 1 mg/dL decrease in serum albumin predicted an ~8% increase in peak serum creatinine (95% confidence interval 3-14%). Therefore, vancomycin dosing interval, vancomycin trough, baseline creatinine, and hypoalbuminemia predicted elevated serum creatinine in adult patients on vancomycin. Close monitoring of serum creatinine and vancomycin levels is recommended in patients with hypoalbuminemia.

Conclusions

In this study, we confirm prior associations of elevated trough levels to higher peak creatinine values while on vancomycin therapy. We also observe that indicators of poor renal function, including elevated baseline creatinine and long vancomycin dosing intervals, are associated with higher creatinine values, as expected. We also demonstrate a novel inverse relationship between serum albumin values and the peak serum creatinine. The validity of this new association is supported by the statistical significance of the association as well as the consistency of this finding in a second validation cohort.

Mentor / Department

Buddy Creech Infectious Diseases, Pediatric

LIFE AFTER LAPAROTOMY: A DATABASE TO DETERMINE LONG-TERM OUTCOMES OF POST-TRAUMA LAPAROTOMY PATIENTS

Chelsea R. Samson
Healthcare and Public Health Research and Management

Background Problem

Patients with abdominal trauma may require a laparotomy, thus hindering further organ damage, but also predisposing them to enduring morbidities. Due to frequent loss of follow-up, long-term complications are not known and are often underestimated when data from only a single institution is considered.

Objectives

This project strives to create a database of information on adult patients admitted to Vanderbilt University's Trauma Department between 1995 and 2006 requiring laparotomies. The scope of the database is intended to be large in size, time, and geographic distribution to provide a greater perspective on long-term outcomes and care for laparotomy patients.

Materials and Methods

119 eligible patients identified via the Trauma Registry of the American College of Surgeons (TRACS) had records that could be linked to the Tennessee Hospital Association (THA) archives. While TRACS provided demographic and perioperative information for the initial admission, THA queries detailed admissions to any Tennessee hospital following the laparotomy (excluding community health systems), between 2005 and 2011. Elixhauser and Charlson comorbidity scores and details of Vanderbilt University Medical Center visits were collected through retrospective review of electronic medical records. Mortality status was obtained through the Social Security Death Index.

Results

Preliminary analysis shows that 86% (n=102) of the patients were readmitted to a Tennessee hospital between 2005 and 2011. Emergent digestive system ailments were the most common reasons for readmission. The mortality rate is 11%, to date, with an average of 4 years between the initial laparotomy and death. Though injury severity scores were not significantly different between the living and deceased, average ages were (35 versus 45 years, respectively).

Conclusions

Abdominal complications in trauma patients are common for many years after a laparotomy, with pre-traumatic physiologic reserve playing an important role in long-term wellbeing. More work is underway to characterize patients who require frequent readmissions in order to encourage preemptive interventions by physicians.

References

References Available Upon Request

Acknowledgements

Thank you to Dr. Oscar Guillamondegui, Dr. Jesse Ehrenfeld, Dr. Mario Davidson, and Dr. Richard Miller for their invaluable support.

Mentor / Department

Dr. Oscar Guillamondegui, Associate Professor of Surgery and MD Director of the Vanderbilt University Trauma ICU

INCREASED EXPOSURE TO PHENOBARBITAL IS ASSOCIATED WITH POORER NEURODEVELOPMENT THAN EXPOSURE TO LEVETIRACETAM IN INFANTS WITH NEONATAL SEIZURES

Ciaran Smolinsky
Healthcare and Public Health Research and Management

Background Problem

Anti-epileptic drugs (AEDs) such as levetiracetam (LEV) and phenobarbital (PB) are used to treat neonatal seizures but their long-term effects on neurodevelopment are unknown. AED exposure in older children is associated with cognitive decline, making their use concerning in neonates.

Objectives

We hypothesized that neurodevelopmental outcomes after LEV are more favorable than PB after accounting for differences in seizure severity, etiology, and brain immaturity at seizure onset.

Materials and Methods

We performed a retrospective study of all infants who received AEDs for neonatal seizures in the Vanderbilt Neonatal Intensive Care Unit (01/07-12/10). We collected clinical and cumulative AED exposure data from medical and pharmacy records from birth to hospital discharge. Outcomes were death, cerebral palsy (CP), and corrected age scores on the Developmental Assessment of Young Children (DAYC) at 12 months and Bayley Scales of Infant Development 3rd ed. (BSID) at 24 months. Analyses were adjusted for number of electrographic seizures (proxy for severity) and gestational age (GA). Overall tests of significance ($p<0.05$) were followed by 2 step-down analyses ($p=0.025$ each) testing AED vs. none and exposure-response.

Results

Among 280 patients, 106 received PB only, 33 LEV only, and 141 received both. In the 69 patients who died, there were no associations with either AED exposure. DAYC scores were available for 133 patients, BSID scores for 69. Associations between AEDs and scores at 12 months were identical to 24 month results. PB had a strong negative dose-effect on BSID cognitive and motor scores, with 8.1 and 9 point decreases for every additional 100 mg/kg ($p=0.01$). Associations between LEV and cognitive and motor scores were also significant ($p=0.01$) but less clinically meaningful, with decreases of 2.2 and 2.6 points per 300 mg/kg. No association between LEV and CP was found. However, the probability of CP by 2 years rose from 16% to 68% from the lowest doses to highest dose of PB ($p=0.01$).

Conclusions

Independent of eitiology and after controlling for the number of electrographic seizures and GA, increased exposure to PB and LEV in neonates is associated with worse cognitive and motor outcomes, particularly for high dose PB exposure. These results underline the need for prospective randomized controlled trials with long-term follow-up and dose-effectiveness studies of new AEDs for neonatal seizure disorders.

Acknowledgements

Nathalie Maitre, James C. Slaughter, Matthew Marshall

Mentor / Department

Nathalie Maitre, neonatology

DEVELOPING A MODEL TO ASSESS RISK OF BACTEREMIA IN PEDIATRIC CANCER PATIENTS WITH NEUTROPENIC FEVER

Kathleen Weber
Healthcare and Public Health Research and Management

Background Problem

Pediatric cancer patients receiving immunosuppressive drugs are at an elevated risk of systemic infections that require prompt treatment to avoid serious complications or death. Despite the fact that most febrile neutropenic patients do not have bacteremia, all are treated empirically while awaiting blood culture results. Currently there are no widely accepted evidence-based criteria upon which to determine the risk of bacteremia and identify those patients who need the most aggressive therapy. Having the ability to assess risk upon presentation would allow physicians to make informed decisions regarding the initial management of these patients.

Objectives

To develop a validated scoring system for bacteremia risk assessment in pediatric patients with neutropenic fever using information available at the time of presentation.

Materials and Methods

This retrospective cohort study used Vanderbilt's electronic medical records system to extract patient information from 388 episodes of neutropenic fever. The study population consisted of all patients diagnosed with malignancy between 2007 and 2009 who were under 23 years of age at the time of diagnosis and treated at the Vanderbilt Children's Hospital. An event was defined as a documented episode of fever (≥38°C orally) while neutropenic (ANC<500 cells/µl) and with a central line in place. Multivariate logistic regression will be used for risk-prediction modeling of bacteremia. An ROC curve will be used to evaluate the model. The findings will be internally validated using bootstrapping and an additional cohort of patients diagnosed in 2010 with events from 2010-2012 will be used for independent external validation.

Results

This study is currently in the data cleaning and verification phase.

Conclusions

We hope to create a model that accurately assesses the risk of bacteremia using relevant patient characteristics. We intend to validate this model with an additional cohort from Vanderbilt Children's Hospital and through other patient populations. Reliable risk assessment will allow physicians to better manage patients with neutropenic fever.

References

References Available Upon Request

Acknowledgements

Adam Esbenshade, MD MSCI Kelly Garcia, BA

Mentor / Department

Dr. Adam Esbenshade, Pediatric Hematology/Oncology

RISK FACTORS AND MORTALITY ASSOCIATED WITH ACUTE KIDNEY INJURY IN CHILDREN FOLLOWING CONGENITAL CARDIAC SURGERY

Kelly Williamson
Healthcare and Public Health Research and Management

Background Problem

Children undergoing congenital cardiac surgery (CCS) are at risk for acute kidney injury (AKI). This risk is often attributed to hypoperfusion, inflammation and exposure to nephrotoxic medications. Known risk factors for AKI in this population include younger age, pre-existing kidney injury, cyanosis, complex surgical procedures, prolonged cardiopulmonary bypass, intraoperative hypotension, sepsis and low cardiac output states.

Objectives

Here we report our experience on the medium and long term outcomes of AKI in CCS. We describe the perioperative risks for development of AKI, as measured by the pRIFLE score, in children following CCS, and report the associated intermediate and long-term mortality associated with AKI in this population.

Materials and Methods

Our Study population included all patients that underwent cardiac surgery at our institution from 2004 through 2006. The primary definition of acute renal failure was based on pRIFLE using estimated creatinine clearance (pRIFLE eCCL). To evaluate the independence of associated factors, we performed an ordinal logistic regression using the variables as potential risk factors for pRIFLE. To measure the magnitude of associated factors with respect to mortality, we performed a survival analysis using a proportional hazard model.

Results

We found duration of cardiopulmonary bypass (CPB) and age as the only variables independently and significantly associated with pRIFLE. As patient age increases from 0.30 years to 3.5 years, the odds of having a pRIFLE score greater than zero are 75% less likely. Age, single ventricle status, and a pRIFLE score of 3 were independently and significantly associated with mortality.

Conclusions

Patients undergoing congenital cardiac surgery at an earlier age and those requiring prolonged cardio-pulmonary bypass are at increased risk for the development of AKI as defined by pRIFLE. Mortality risk following CCS is increased in younger patients, those requiring prolonged cardiopulmonary bypass and those experiencing post operative renal failure as defined by pRIFLE.

References

References Available Upon Request

Acknowledgements

I would like to thank Dr. Scott Watkins, Dr. Brian Donahue, and Mario Davidson PhD.

Mentor / Departent

Dr. Scott Watkins with the Division of Pediatric Cardiac Anesthesiology at Vanderbilt Children's Hospital

SELF-REPORTED DRIVING BEHAVIORS IN ICU SURVIVORS: A SURVEY AND ANALYSIS

Denise Ye
Healthcare and Public Health Research and Management

Background Problem

Specific functional outcomes following critical illness have not been well-described. Driving is an important daily activity that has been unstudied in the ICU population; adverse changes related to driving have negative implications for both public safety and individual independence and well-being.

Objectives

This study seeks to: 1) determine the prevalence of driving difficulties in ICU survivors at remote time-points after critical illness 2) evaluate whether ICU survivors perceive significant changes in their driving behavior and performance since their critical illness, and 3) analyze potential associations between duration of delirium in the ICU and self-reported changes in driving ability.

Materials and Methods

This was a cross-sectional study conducted in a convenience sample of patients who were enrolled in the BRAIN-ICU study. Subjects were 151 adult medical and surgical ICU survivors and current drivers. At 4 to 6 years post-discharge following their index hospitalization, subjects were assessed via telephone using the 45-item BRAIN-ICU Driving Questionnaire (BIDQ).

Results

Patients had a mean age of 57 (SD=7); 25% were over 65. Patients had a mean ICU LOS of 7.4 (SD=7.7), and a mean hospital LOS of 12.4 (SD=8.4). Patients reported driving significantly fewer distances post-ICU compared to pre-ICU, with an average decrease of 115 miles ($p<0.0001$). Self-reported driving skill and safety orientation decreased significantly ($p=0.00011$) upon initial return to driving; in patients over the age of 65, there was little recovery of this initial decrease over time. Delirium duration was not a predictor of driving restriction ($p=0.71$) or driving ability/behavior ($p=0.45$).

Conclusions

ICU survivors experience significantly limited driving mobility following critical illness and often fail to return to pre-ICU levels with respect to driving ability. Future research needs to objectively evaluate driving ability after critical illness, and critical care teams may need to engage issues pertaining to driving with their patients.

References

References Available Upon Request

Acknowledgements

Timo Lajunen, Yanna Song, Mario Davidson, Natasha Adamson, Wes Ely, James Jackson

Mentor / Department

Dr. Wes Ely, Dr. James Jackson

Michael Laposata is the Edward and Nancy Fody Professor of Pathology and Medicine at Vanderbilt University School of Medicine. He is the pathologist-in-chief at Vanderbilt University Hospital and director of clinical laboratories and the Executive Vice-Chair of Pathology, Microbiology and Immunology. He received his M.D. and Ph.D. from Johns Hopkins University School of Medicine and completed a postdoctoral research fellowship and residency in Laboratory Medicine (Clinical Pathology) at Washington University School of Medicine in St. Louis. He took his first faculty position at the University Of Pennsylvania School Of Medicine in Philadelphia in 1985, where he was an Assistant Professor and director of the hospital's coagulation laboratory. In 1989, he became Director of Clinical Laboratories at the Massachusetts General Hospital and was appointed to faculty in pathology at Harvard Medical School. In 2005, he was recognized by the Institute of Quality in Laboratory Medicine of the Centers for Disease Control and Prevention for this innovation. Dr. Laposata is the recipient of 14 major teaching prizes at Harvard, the Massachusetts General Hospital, and the University Of Pennsylvania School Of Medicine. His recognitions include the 1989 Lindback award, a teaching prize with competition across the entire University of Pennsylvania system; the 1998 A. Clifford Barger mentorship award from Harvard Medical School; election to the Harvard Academy of Scholars in 2002, and was the recipient of the highest award by vote of the graduating class for teaching in years 1 and 2 at Harvard Medical School in 1999, 2000, and 2005. In 2009, he was inducted into membership of Vanderbilt's Academy for Excellence in Teaching.

Lillian Nanney, Ph.D., is a Professor of Plastic Surgery, Cell & Developmental Biology, Medical Education and Administration. Throughout her long career at Vanderbilt she has served as the Director of Plastic Surgery Research and in former years she has served as the Co-Director of the Skin Disease Research Center, and the Founder and Director of Vanderbilt's Institutional Immunohistochemistry Core Laboratory. Her primary research efforts have centered around the study of a broad spectrum of conditions ranging from poor or delayed skin repair (burns, chronic wounds, mouse models of injury) to undesirable hyper proliferative growth conditions that include malignancy. . Dr. Nanney's contributions extend to the national level where she recently served as the national president of the Wound Healing Society She has taught Gross Anatomy throughout her career and she serves as a founding director of the Academy for Excellence in Teaching and in 2005 was the recipient of Vanderbilt's institutional teaching award forbest teaching in a small group setting Dr. Nanney has served as the area head for Lab-Based Research since the inception of the emphasis Program.

Laboratory-Based Research

Experiences in the Laboratory Based Biomedical Research Area of the Emphasis Program are focused on hypothesis driven investigation primarily based within a laboratory environment. Each student becomes an active participant in a research program and completes a clearly defined project. During the first year, the lab-based explorer becomes acclimated with new protocols, becomes an integral member of the team and becomes well versed in the foundational literature in his/her chosen field of focus. By summer the student is ready for full-time research making ever-evolving modifications to the research plan while attending occasional relevant seminars with the cohort of students in the lab-based research area. Guiding students as they move through the project selection phase with its wealth of potential mentors and research areas toward their transformation into skillful and meticulous contributors at the bench is rewarding and fascinating for Co-Directors Lillian Nanney, Ph.D. and Michael Laposata, MD, Ph.D. Some students select projects based on collection of human samples and subsequent analysis at the lab bench. Others select in vivo work with unique animal models. Still others conduct in vitro analysis using sophisticated molecular tools. As students immerse themselves in experiential learning, each begins to take ownership and pride in expected and unexpected accomplishments. By the end of second year most students are making plans for national poster presentations and several polish off portions of manuscripts. A select number of students develop a real affinity for lab-based investigation and quickly seek and find new mentors and projects and maintain a sustain research experience throughout medical school. A few become fully committed and plan for a Medical Scholars year or enter the MSTP program. Every student hones his/her abilities to critically evaluate journal articles. Each has an opportunity to improve their interpersonal skills while experiencing the synergistic power of collaborative research. All students come to realize that the thrill of success in lab research is balanced with formidable challenges. Each student develops a much richer appreciation for the behind-the-scenes effort and serendipity that fuels discoveries that shape the future of medicine.

HUMAN NEUTRALIZING MONOCLONAL ANTIBODIES THAT RECOGNIZE RESPIRATORY DROPLET TRANSMISSIBLE H5N1 INFLUENZA VIRUSES

Shyam Deshpande
Laboratory-Based Biomedical Research

Background Problem

Recent studies suggest that mutations in H5 hemagglutinin (HA) proteins of H5N1 influenza viruses confer respiratory droplet transmission in mammalian models in ferrets. These findings indicate that such changes may also allow the highly pathogenic H5N1 strains to transmit via respiratory droplets in humans. Currently, there are no specific vaccines protective against respiratory droplet transmissible (rdt) H5N1 influenza.

Objectives

Do individuals vaccinated against wild-type (wt) H5N1 generate antibodies protective against rdt-H5N1 influenza?

Materials and Methods

Neutralizing human monoclonal antibodies (mAbs) to wt-H5N1 were obtained from previous studies involving the vaccination of volunteers against wt-H5N1. Rdt-H5 HAs were generated via gene synthesis or site-directed mutagenesis of wt-H5 sequences with subsequent protein production. Binding affinity of human mAbs to rdt-H5 HA was examined, and head versus stem antibody binding epitopes were determined.

Results

Human neutralizing mAbs isolated from wt-H5N1 vaccine recipients are capable of recognizing the head region of both wt-H5 and rdt-H5 HAs.

Conclusions

Human mAbs capable of binding rdt-H5 HA offer the potential for rational vaccine design to H5N1 influenza. With further elucidation, these HA epitopes could be incorporated as immunogens in vaccines to confer protection against rdt-H5N1 influenza in addition to wt-H5N1 influenza.

Acknowledgements

I would like to thank Dr. James Crowe and Dr. Natalie Thornburg for their guidance and support as well as the VUSM Emphasis Program and VVC for funding and resources.

Mentor / Department

James Crowe, MD, Vanderbilt Vaccine Center

THE REQUIREMENT OF VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IN THE PALATE

Lucy Boyce Kennedy
Laboratory-Based Biomedical Research

Background Problem
Cleft lip and cleft palate (CL/CP) are the most common human craniofacial defects with an incidence of up to 1/500 infants. The pathogenesis of CL/CP is not well understood. Vascular endothelial growth factor (VEGF) plays a role in the early development of vascular networks in the palate. Previous studies in mice have shown that VEGF deficiency is associated with CL/CP.

Objectives
We studied the requirement of VEGF during palate development using mice with a conditional deletion of VEGF in (1) cranial neural crest cells (CNC) using Wnt1cre (VEGF Wnt1cre CKO mice) and (2) palate mesenchyme using Osr2cre (VEGF Osr2cre CKO mice).

Materials and Methods
Immunostaining; qRT-PCR

Results
Immunohistochemistry (IHC) staining of embryonic palates with the endothelial marker PECAM indicates that vascularity is reduced in VEGF Osr2cre CKO mice compared to controls at embryonic day 14.5 (e14.5). Further, qPCR analysis of vascular markers found significant downregulation of markers including smooth muscle actin (smA) and PECAM in VEGF Wnt1cre CKO mice at e14.5 compared to controls. Osteoblast differentiation markers alkaline phosphatase, osteocalcin, runx2, and osterix were significantly downregulated in VEGF Wnt1cre CKO mice at e16.5 compared to controls, which indicates diminished bone development. This finding correlates with an abnormal palate phenotype in the VEGF Wnt1cre CKO mice; the normal palate fuses at e15.5. Finally, qPCR analysis of markers in the Notch and transforming growth factor β (TGFβ) signaling pathways, which have been shown to be involved in palate development, revealed dysregulation of markers including Hes1, Hey1, bone morphogenetic protein 2 (BMP2), alk5, TBR3, and TGFβ2 in the VEGF Wnt1cre CKO mice at e16.5.

Conclusions
These results indicate that VEGF expression in the palate is necessary for normal vascular and bone development. Further, the contribution of VEGF to palate development may involve the Notch and TGFβ signaling pathways.

References
References Available Upon Request

Acknowledgements
Thanks to Cyndi Hill and Yan Zhao. Funding was provided by the T-35 Heart, Lung, and Vascular program.

Mentor / Department
Steven Goudy, MD, Otolaryngology

CXCL21-CXCR4 SIGNALING IN CEREBRAL VASOSPASM

Travis Ladner
Laboratory-Based Biomedical Research

Background Problem

Cerebral vasospasm is a significant contributor to the morbidity and mortality of aneurysmal subarachnoid hemorrhage (SAH). There are no definitive biochemical predictors for which patients will experience vasospasm. The CXCL12-CXCR4 axis mediates vasospasm in the coronary microvasculature and is also associated with atherosclerosis and restenosis. Given that CXCL12 and CXCR4 are expressed in the native brain, and in particular overexpressed in malignant glioma, we investigated the role of this axis in cerebral vasospasm.

Objectives

1. Test the hypothesis that the CXCL12-CXCR4 signaling pathway is activated in aneurysmal SAH. 2. Test the hypothesis that the inhibition of the CXCL12-CXCR4 signaling pathway with AMD3100, a CXCR4 antagonist, diminishes the incidence and degree of cerebral vasospasm in aneurysmal SAH.

Materials and Methods

36 rats were divided into 4 groups: SAH + AMD3100, SAH + vehicle, SAH alone, normal saline injection alone. In the SAH groups, blood was withdrawn from the ventral tail artery and injected into the cisterna magna; in the normal saline group, saline was injected into the cisterna magna instead. Cerebrospinal fluid (CSF) and serum were collected for analysis with ELISA for expression of CXCL12. This process was repeated 48 hours later. 5 days later, CSF and serum were collected, the animal was sacrificed, and the brain harvested. In the interval, animals received either 3mg/kg AMD3100 or 1mL saline vehicle every 12 hours. The basilar artery and surrounding parenchyma were analyzed for CXCR4 expression with immunohistochemistry and degree of vasospasm with morphometric analysis.

Results

36 rats have been successfully included in the study so far: 10 received SAH + serial AMD3100, 11 received SAH + serial normal saline, and 9 received neither. 6 rats were injected with normal saline into the cisterna magna. Preliminarily, the CSF concentration of CXCL12 was determined for 13 consecutive rats: 3 SAH + AMD3100, 7 SAH alone, and 3 normal saline injection alone. Upon ANOVA, there was no significant relationship across groups. However, there was a non-significant trend for SAH AMD3100 day 0 vs. day 7 (0.35 vs. 0.49 ng/mL, t-Test, p=0.2246) and SAH AMD3100 day 7 vs. saline day 7 (0.34 vs. 0.49 ng/mL, t-Test, p=0.1177). Data for CSF expression of CXCL12, vessel expression of CXC4, and vessel dimensions are pending.

Conclusions

Cisterna magna puncture is a reliable method for producing subarachnoid hemorrhage. The CXCL12-CXCR4 axis is currently an untested pathway in cerebral vasospasm and represents a potential therapeutic target with AMD3100. However, we observed no significant relationship between SAH and CSF CXCL12 concentration. Given the small sample size of our preliminary analysis, this study was underpowered to observe such a difference, and any interpretation is premature. The non-significant trend observed may indicate that CXCL12 is upregulated in SAH. Future analysis on a greater number of samples must be performed in order to better understand this relationship. Additional work will address the relationship between CXCR4 signaling and degree and incidence of vasospasm.

References

References Available Upon Request

Acknowledgements

I'd like to thank Young Lee, Imad Khan, and Komron McLean for their support and friendship throughout this project. I'd also like to thank members of the McLaughlin lab for their technical assistance in data analysis. Finally, I'd like to thank Dr. Singer for his exemplary mentorship and guidance throughout this process.

Mentor / Department

Robert J. Singer, Department of Neurosurgery

THE ROLE OF AMD3100 IN PREVENTING CXCR4 MEDIATED CEREBRAL VASOSPASM AFTER SUBARACHNOID HEMORRHAGE IN A RAT MODEL

Young Min Lee
Laboratory-Based Biomedical Research

Background Problem

The leading cause of death and disability after aneurysmal subarachnoid hemorrhage (SAH) is cerebral vasospasm which occurs in 20 to 30 percent of cases. Cerebral vasospasm was first described in 1951, and since then, has been recognized as the leading event causing increased morbidity and mortality after successful treatment of initial SAH. Stromal-derived factor-1α (SDF-1α) is a cytokine expressed and secreted from organs and tissues in response to ischemia. Its sole receptor, CXCR4, is a membrane receptor highly expressed on vascular endothelial cells. Myocardial protein expression of SDF-1α was increased after cardioplegia induced ischemia, and SDF-1α was localized to vascular endothelial cells. It was shown that SDF-1α induced coronary microvessel contraction, which was inhibited by AMD3100, a CXCR4 antagonist.

Objectives

We hypothesize that similar mechanisms may be present in cerebral microvasculature, and that AMD3100 may be a candidate intervention targeted at decreasing cerebral microvessel contraction.

Materials and Methods

SAH was induced in twenty rats using the double hemorrhage model, of which 10 received AMD3100 treatment and 10 received sham treatment with saline. Fresh non-heparinized autologous blood from the tail artery (0.2 mL) was injected into the cisterna magna on days 1 and 3. After the second hemorrhage ten rats in the treatment group received 3 mg/kg/day of AMD-3100 administered via intraperitoneal injection every 12 hours until sacrifice on the 7th day. SAH control rats were given equivalent volumes of saline via intraperitoneal injection instead at these same time-points. Another ten rats were null SAH, and received normal saline into the cisterna magna instead of blood at days 1 and 3. All rats were sacrificed at day 7, and levels of CXCR4 receptor and SDF-1α were compared using ELISA. Serial sections of brain tissue were taken at 50, 200, and 500 micrometers deep to the brain surface. On these sections, the internal luminal diameter and wall thickness of parenchymal arterioles were obtained.

Results

A total of 10 rats in the SAH treatment, 11 rats in the SAH control, and 7 rats in the null SAH successfully underwent all procedures and were sacrificed at day 7. ELISA was performed for SDF-1α levels in the cerebrospinal fluid. Preliminary CSF concentrations of SDF-1α (in ng/mL) for 3 SAH treatment, 6 SAH control, and 3 null SAH were 0.35 (SD=0.11), 0.36 (SD=0.31), and 0.51 (SD=0.31), respectively, on day 1. On day 3, the concentrations were 0.35 (SD=n/a), 0.39 (SD=0.20), and 0.49 (SD=0.29), respectively. At time of sacrifice (day 7), these concentrations were 0.49 (SD=0.03), 0.37 (SD=0.20), and 0.34 (SD=0.09). There were no significant differences in any of the SDF-1α concentrations in blood within treatment group and within treatment day by 2-way ANOVA with Bonferroni post hoc correction.

Conclusions

There were no significant differences in the CSF concentrations of SDF-1α between the treatment groups on days 1, 3 and 7. Likewise, there were no significant differences in the concentrations of SDF-1α between days 1, 3, and 7 for each of the treatment groups. However, these data were based on preliminary analysis of just 12 of 28 rats and may were likely severely underpowered. Once analysis has been completed on the rest of the samples and brain sectioning and staining complete, results will be reanalyzed and a more up-to-date conclusion may be obtained.

References

References Available Upon Request

Mentor / Department

Robert J. Singer, M.D. J. B. Marshall Laboratory for Neurovascular Therapeutics Vanderbilt Department of Neurosurgery

OPTIMIZATION OF A MURINE MODEL OF THE HUMAN PHENOMONON OF CAPSAICIN-INDUCED SECONDARY HYPERALGESIA

Clinton D. Morgan
Laboratory-Based Biomedical Research

Background Problem

Administration of intradermal capsaicin in humans has long been known to produce a biphasic response: namely, an initial hypoalgesia, due to TRPV1 desensitization in the area of application and a subsequent, intense, broader centrally-mediated mechanical allodynia lasting hours (Torebjork 1992) due to persistent activation of SC Lamina I neurons (Janig 2011). In the era of transgenic mouse lines, there is an urgent need for reliable murine pain models of this human biphasic response.

Objectives

Identification of proper vehicle, injection site, and time-course for a murine model of capsaicin-induced secondary hyperalgesia.

Materials and Methods

Capsaicin (Sigma M2028) was diluted in 100% ethanol, then to 1% EtOH in saline or 7.5% Tween-80/1% ethanol in saline. For dorsal hindpaw injections, 5uL was injected intradermally, followed by 10s evacuation. For gastrocnemius injections, 10uL was injected subcutaneously. C57/B6 male mice were tested in isolated rooms at RT with white noise present after 2h acclimation period on an elevated wire mesh floor; injections were administered at T0 and von Frey filaments (.008g to 2.56g, North Coast Medical) were applied through the mesh to the plantar hindpaw. Filaments were pressed until bent, held for 2s, and then removed. Withdrawal within 2s was a positive response.The “up-down” method of von Frey testing was utilized (Yaksh 1994) to calculate median withdrawal threshold (g).

Results

Although previous reports utilize Tween-80 in rat models (Lin 1997, 2003, 2007; Li 2008) of capsaicin-induced hyperalgesia, even low (7.5%) concentrations of Tween-80 on its own, induces allodynia. 1% ethanol in saline seems to induce less plantar allodynia as a vehicle, especially applied proximally away from plantar testing surface. 2mM capsaicin generates profound long-lasting secondary hyperalgesia (n=5/condition).

Conclusions

10uL of 2mM capsaicin in 1% ethanol subcutaneously administered near the gastrocnemius muscle produces long-lasting (up to 2h) plantar secondary hyperalgesia in mice. To confirm trend, addition of mice are needed.

References

References Available Upon Request

Acknowledgements

Daniel O’Brien, B.S., P. Jeffrey Conn, Ph.D for Mentorship, Sherri Vogt for logistical support with mice.

Mentor / Department

Dr. Robert Gereau IV, Ph.D. Chief, Washington University Pain Center Washington University in St. Louis School of Medicine

SIX2 EFFECTS ON WILMS TUMOR BEHAVIOR

David Neblett
Laboratory-Based Biomedical Research

Background Problem

Wilms Tumor (WT) is the most common pediatric kidney cancer and is thought to arise through aberrant mesenchymal-to-epithelial transition of multipotent nephron progenitors. SIX2, a transcription factor normally expressed in self-renewing metanephric mesenchymes, is repressed once kidney maturation completes. However, WTs retain SIX2 expression for unclear purposes. We postulate WTs utilize SIX2 for self-renewal of its cancer stem cell.

Objectives

This study was designed to characterize the effect of SIX2 overexpression on behavior of the human WT cell line WiT49. We hypothesize that SIX2 overexpression will cause an increase in WT proliferation rate and anchorage-independent growth.

Materials and Methods

We engineered a novel expression vector containing green fluorescent protein (GFP) for tracking SIX2 and the 2A cleavage peptide to liberate SIX2 from this epitope (GFP-2A-SIX2). This transgene was subcloned into the pcDNA3.1 plasmid, containing a neomycin cassette for pressure selection. pcDNA3.1-GFP-2A-SIX2 and a pcDNA3.1-GFP control were transfected by electroporation into wild-type WiT49 cells. Transgene expression was confirmed by fluorescent microscopy (GFP) and Western blotting (SIX2). Behavioral effects were characterized with anchorage-independent growth assays, proliferation assays, and gene-expression profiles.

Results

SIX2 expression has been validated in vitro and by Western blot. For proliferation, SIX2 cells had increased average absorbance versus wild-type WiT49 cells at 24 hours (0.3465 v. 0.2188), 48 hours (0.4135 v. 0.2701), and 72 hours (0.4476 v. 0.3522). For anchorage-independent growth, average colony diameter was 89.05 micrometers for SIX2 and 90.57 micrometers for WiT49. Average number of colonies per well was 337.78 for SIX2 and 531.89 for WiT49.

Conclusions

Relative to wild-type WiT49 cells, SIX2-overexpressing cells show enhanced proliferative response, consistent with its embryonic self-renewal promotion, but did not increase tumorigenicity. Currently, the pcDNA3.1-GFP control cell line is being transfected and stabilized. All assays will be repeated for comparison with this more ideal control. Future plans include in vivo studies in a heterotransplant mouse model.

Acknowledgements

I would like to thank Dr. Bo Lovvorn for the opportunity to work on this project. I am grateful to Dr. Lovvorn, Janene Pierce, and Andrew Murphy for sharing all of their knowledge and expertise and for the patience they showed to me in the process. I am forever appreciative for the contributions they have made to my education and future. I would also like to thank Bryan Cawthon in the lab of Dr. Kevin Ess for sharing his time, resources, and expertise in the technique of electroporation.

Mentor / Department

Dr. Harold N. Lovvorn, Department of Pediatric Surgery

EXPRESSION OF MICRORNAS IN MERKEL CELL CARCINOMA

Matthew S. Ning
Laboratory-Based Biomedical Research

Background Problem

Merkel cell carcinoma (MCC) is a primary neuroendocrine carcinoma of the skin. Although not as prevalent as other skin cancers, MCC is more aggressive than melanoma and has a higher mortality rate, with reviews citing an overall five-year survival of sixty percent. Unfortunately, while the incidence of MCC increases, our knowledge of these tumors remains limited.

Objectives

In an attempt to expand our understanding, we focus our attention on microRNAs, small single-stranded RNA molecules that participate in the negative regulation of gene expression. MicroRNAs have been implicated in the pathogenesis of various skin cancers, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). Through their unique role in posttranscriptional regulation, they can function as important regulators of tumor growth and metastasis; however, the differential expression of microRNAs and their role in pathogenesis have yet to be explored in MCC.

Materials and Methods

To identify microRNAs specific to MCC (MCC-miRs), high-throughput sequencing (HTS) of small RNA libraries was performed on several tissue samples: MCC, melanoma, SCC, BCC, normal skin, and normal lymph node. Comparison of the sequencing profiles identified several microRNAs upregulated (>2.5-fold) and downregulated (>2-fold) in MCC versus other tissues. To validate some of these candidates, their expression was measured via qRT-PCR in a larger group of MCC samples (n=20) and in a comparison group (n=23) composed of other cutaneous tumors (melanoma, SCC, BCC) and normal skin.

Results

Out of those evaluated, eight microRNAs were confirmed to be upregulated (>2.5-fold) in MCC: miR-502-3p, miR-9, miR-7, miR-340, miR-182, miR-190b, miR-873, and miR-183. In addition, three microRNAs were confirmed to be downregulated (>2-fold) in MCC: miR-3170, miR-125b, and miR-374c.

Conclusions

Several of these microRNAs have been implicated in the pathogenesis of other cancers and may play a role in the development, progression, and metastasis of MCC. Thus, the MCC-miRs serve as attractive targets for further investigation.

References

References Available Upon Request

Acknowledgements

I am indebted to Dr. Ann Richmond and the VICC/Meharry/TSU Cancer Partnership for funding through the U54 Summer Cancer Research Program Grant (NIH/NCI 5U54 CA91405-10). I would also like to thank Dr. Annette Kim for providing us with several of the MCC tissue samples used in this study.

Mentor / Department

Dr. Thomas Andl, Ph.D; Division of Dermatology, Department of Medicine

MMP-9 INHIBITION AFTER ACUTE ISCHEMIC CEREBRAL INFARCTION: A NOVEL NEUROTHERAPEUTIC FOR BLOOD–BRAIN BARRIER MODULATION

Mitchell J. Odom
Laboratory-Based Biomedical Research

Background Problem

Ischemic stroke is defined by a lack of blood, and therefore oxygen and nutrients, to the brain. During ischemia, metalloproteinase (MMP) activity is upregulated, and these molecules begin to target structural proteins in the basal lamina of cells. The breakdown of these proteins can lead to the disruption of the blood-brain-barrier (BBB), a protective anatomical lining created by endothelial tight junctions preventing the entrance of exogenous molecules into the brain. Breakdown of the BBB is always associated with worse outcomes, even if reperfusion after ischemia is achieved.

Objectives

We endeavored to assess the effects of an intra-arterially administered MMP inhibitor on BBB integrity following an acute ischemic cerebral infarction.

Materials and Methods

0 adult (12 weeks old) male rats bred to be spontaneously hypertensive undergo a middle cerebral artery occlusion (MCAO) for 90 minutes. This is achieved by inserting a removable silicon-tipped filament into the internal carotid artery until it fully occludes the middle cerebral artery. The filament is removed after 90 minutes, allowing for reperfusion and the intra-arterial administration of either Norcantharidin (an MMP inhibitor), or DMSO (vehicle). Multiple testing modalities will be conducted to assess the degree of BBB disruption, the size of the infarct, and the degree of behavioral/motor deficit that is present post-stroke.

Results

Initial dose-finding tests have been completed, resulting in consistent outcomes during a seven-day recovery. Preliminary results show a non-significant decrease in stroke volume between the treatment and control populations ($p > 0.05$). Significant differences were found when assessing neurological and motor scores, with the treatment groups showing consistently higher scores.

Conclusions

Using this MCAO model, we will be able to assess the efficacy of Norcantharidin on BBB integrity after an ischemic stroke. With greater power, we anticipate seeing the continued improvement of the treated vs control groups.

References

References Available Upon Request

Acknowledgements

Imad Khan Moneeb Ehtesham NIH T35 grant in Heart, Lung, and Vascular Biology

Mentor / Department

Robert J. Singer, Neurosurgery

EVALUATING CELLULAR DYNAMICS OF MELANOMA CELLS (BRAF V600E) IN RESPONSE TO BRAF INHIBITORS

Chengwei Peng
Laboratory-Based Biomedical Research

Background Problem

Metastatic melanoma is the most deadly form of skin cancer. It is normally unresponsive to traditional chemotherapy treatments. In roughly 60% of these tumors, there is mutation of the protein kinase B-RAF at the V600E position. This finding led to the development of targeted BRAF inhibitors that have led to significantly better outcomes in comparison to traditional chemotherapy. However, the initial reduction in tumor burden is not sustained throughout the course of the treatment and relapses occur.

Objectives

Evaluating the dynamics of melanoma cells during treatment with the BRAF inhibitor can give a better understanding of possible reasons for tumor relapse.

Materials and Methods

To examine the dynamics of the cellular response that underlies this, melanoma cells A375 and SKMEL-5, both harboring the BRAF V600E were fluorescently labeled with a nuclear marker, H2B, and a marker of the G1-S transition, FUCCI. Cells were imaged at the single cell level during treatment with PLX 4720 and intermitotic times were determined.

Results

In A375 cells, there emerged three population of cells, a population that died, a slow dividing population, and a fast dividing population. Although there was cell death present, it made up a very small fraction of the population. The majority of the population belonged to either the fast dividing or the slow dividing cells. In contrast, SKMEL-5 cells exhibited an initial death burst with the population stabilizing as the treatment continued.

Conclusions

Melanoma A375 and SKMEL-5 cells exhibit heterogeneous behavior under treatment with BRAF inhibitors. Furthermore, A375 consists of a large fraction of the population that are slowly dividing and may represent a source of cells for tumor relapse. SKMEL-5 cells contain an initial death burst, but is not sustained over time.

Acknowledgements

Entire Quaranta lab: Keisha Hardeman, Bishal Patel, Darren Tyson, Jing Hao, Peter Frick, and Akshata Udyavar

Mentor / Department

Vito Quaranta Department of Cancer Biology

IDENTIFYING AND CHARACTERIZING THE JNK3 BINDING SITE ON SCAFFOLD PROTEIN ARRESTIN-3

Alejandro Perez
Laboratory-Based Biomedical Research

Background Problem

Arrestins bind to active phosphorylated G-protein-coupled receptors (GPCRs) thereby blocking further signaling, targeting receptors for internalization, and initiating alternative signaling. Among four subtypes in mammals, two ubiquitously expressed non-visual arrestins, arrestin-2 and -3, are multi-functional adaptors, interacting with dozens of non-receptor partners, including MAP kinases. Arrestin-3 promotes the activation of JNK3 through scaffolding highly conservative ASK1-MKK4(MKK7)-JNK3 signaling pathways. Previous studies have demonstrated that arrestin-3 assembles these signaling pathways by directly binding each kinase. As a multi-functional adaptor, non-visual arrestins directly associate with dozens of partners; however, the binding sites on arrestins for each partner remain largely unknown. Defining the regions (or domains) in arrestin-3 responsible for high-level JNK3 activation would provide insight into the mechanism by which arrestin-3 enhances the activity of this signaling pathway.

Objectives

(1) Identification of the binding sites of JNK3 on scaffold protein arrestin-3. (2) Development of tag-fusion arrestin-3 peptides that are suitable for defining the binding sites of arrestin-3 with dozens of other partners. (3) Characterizing the JNK3 binding regions of arrestin-3.

Materials and Methods

(1) Constructing and purifying MBP-arrestin-3 fusion peptides: Ten MBP-arrestin 3 fusion peptides (including all of the fragments from the non-receptor binding side of arrestin-3) were created by subcloning the corresponding arrestin-3 cDNA fragments to pMal P2T plasmids. These fusion peptides were purified using amylose beads. JNK3 was purified as previously described. (2) MBP-Pulldown and His-Pulldown: Assessment of the binding of the MBP-arrestin 3 fragment fusion proteins to JNK3 was carried out via a pull down assay using the fusion proteins as the bait protein and JNK-3 as the prey protein. An anti-JNK-3 antibody was used for visualization of the western blots. In order to confirm the results, the reverse pull-down assay was carried out, using His-tagged JNK3 as the bait protein and the MBP-arrestin 3 fragment fusion proteins as the prey proteins. An anti-MBP antibody was used for visualization of the western blots. Three MBP-fusion peptides have been identified as JNK3 binding regions. To further confirm these fragments are responsible for JNK3 binding in wild-type arrestin-3, we performed a competition assay to determine whether these fragments are able to inhibit the association between arrestin-3 and JNK3. (3) JNK3 activation assay: The binding peptides are expected to compete with wild-type arrestin-3; therefore, the arrestin-3-mediated JNK3 activation should be inhibited by these peptide fragments. The effects of each peptide on JNK3 activation will be tested both in vitro and in intact cells.

Results

The most prominent binding to JNK3 was demonstrated by MBP-T1A. MBP-T3 and MBP-T6 also show binding to JNK3, but with lower affinity.

Conclusions

This suggests that MBP-T1A region is where binding to JNK3 occurs in the N domain of arrestin-3. MBP-T3 and MBP-T6 are likely involved in the binding of JNK3 to the C domain of arrestin-3. Future experiments using cell-based assays will examine whether expression of these arrestin-3 fragments capable of binding JNK3 can inhibit activation of JNK3 in a dose-dependent fashion by competing with endogenous arrestin-3.

Acknowledgements

Xuanzhi Zhan, Ph.D.

Mentor / Department

Vsevolod Gurevich, Ph.D., Department of Pharmacology

ROLE OF SINGLE-STRANDED DNA-BINDING PROTEINS IN HEAD AND NECK CANCER STEM CELL FUNCTION

Daniel Pipilas
Laboratory-Based Biomedical Research

Background Problem

Single-stranded DNA-binding proteins (SSBPs) are up-regulated in locally invasive and metastatic head and neck tumors. Many scientists believe that invasiveness is positively correlated with "stemness," (i.e. the relative number and/or function of cancer stem cells in a tumor population).

Objectives

The objectives of this project were to develop an assay that measures spheroid-forming ability as a surrogate for stemness and to quantify the frequency of stem cells within head and neck squamous cell carcinoma cell lines with different levels of SSBP expression. This assay has been previously used to quantify sphere-forming ability of neuronal cell lines and of other squamous cell carcinomas, but has not typically been performed using stringent limiting dilution approaches.

Materials and Methods

Six different human head and cancer cell lines were assessed using a sphere-forming assay under experimental conditions that induce quiescent stem cells to proliferate and form macroscopic spheroid structures. A known number of cells were plated in non-adherent wells at concentrations in which only one or fewer spheres would grow per well. Growth factors were given to the cells at regular intervals for 2 to 3 weeks. The results were analyzed using L-calc software. This software calculated the frequency of sphere-forming cells through limiting dilution analysis. Finally, stem cell frequency for each cell line was related to SSBP expression. Certain cell lines were also transfected to up-regulate SSBP2 expression and compared with the parental line.

Results

A comparison of stemness to SSBP2 and SSBP3 expression suggested that cells with a higher expression of these oncoproteins generally had a higher frequency of stem cells. Cells that had low basal expression of SSBP2/3 in general had lower sphere-forming ability. The results were somewhat variable; however, SSBP expression correlated with the frequency of stem cells in culture.

Conclusions

The sphere-forming assay serves as a good surrogate for measuring stem cell frequency when carried out using a stringent limiting dilution technique. This project successfully surveyed head and neck SCC lines to correlate the level of SSBPs with the underlying number and/or activity of malignant stem cells in individual human tumor cell lines.

Mentor / Department

Stephen Brandt, Division of Hematology-Oncology, Department of Medicine

THE ROLE OF CB2 ENDOCANNABINOID RECEPTOR AND MTORC1 IN NEUROPROGENITOR CELL PROLIFERATION IN TUBEROUS SCLEROSIS

Daniel J. Pomerantz
Laboratory-Based Biomedical Research

Background Problem

Tuberous Sclerosis (TSC) is a genetic disorder involving abnormal control of mTOR kinase activity of the brain, kidney, skin and heart. Neurological dysfunction in TSC can manifest in autism spectrum disorder and epilepsy syndromes with associated benign brain lesions including subependymal giant cell astrocytomas (SEGAs) and cortical tubers. As Tuberous Sclerosis is both a genetic disorder of skin and brain, TSC may be an ideal model disease for study using induced pluripotent stem cells (iPSCs) to create a more accessible pool of patient-derived neural progenitors and neurons for in vitro experimentation. Recent research has suggested a prominent role of endocannabinoids in neural progenitor cell (NPC) proliferation, migration and differentiation. Cannabinoid receptor expression of CB1, CB2 and TRPV1 in epileptogenic developmental disorders, including TSC, appears to be modulated in both mouse and human brain tissue. NPC proliferation may also be mediated by CB2 regulation of mTORC1 signaling cascade, a major pathway which is disturbed in TSC.

Objectives

To isolate the potential molecular and cellular mechanisms of CB2 mediated mTORC1 signaling in iPSCs and NPCs in TSC.

Materials and Methods

Skin cells from two control and two TSC patients were biopsied and reprogrammed into IPSCs through plasmid induction. Four cell colonies from each patient line were picked at random and grown in mTESR- pluripotency media. IPSCs were grown in embryoid body (EB) media for six days for EB formation and neural induction media dual-SMAD inhibitors for seven days for neuroprogenitor (NP) cultures. Immunohistochemisty were performed to isolate iPSC pluripotency and spontaneous differentiation into neurons, EB formation and NP cultures. IPSCs and NPs were treated with Rapamycin, HU-308 and SR144,528 for mTORC1 and CB2 receptor modulation.

Results

Immunostaining experiments confirmed that 14 control and TSC patient iPSC colonies were positive for pluripotency markers AP and OCT4. IPSCs from patient lines spontaneously formed Rapamycin sensitive glutamergic and GABAergic neurons. EBs and PAX6+ NPs were formed in all patient lines. NP experiments evaluating CB2 modulation in control lines suggest enhanced PAX-6 positivity in the presence of a CB2 agonist, while experiments in TSC patient lines are inconclusive to date.

Conclusions

IPSCs can be generated from TSC patient tissue and can undergo directed differentiation into a variety of cell types including neural progenitors. Disrupted mTORC1 signaling in iPSCs from TSC patients can lead to spontaneous differentiation into both glutamergic and GABAergic neurons. CB2 agonist enhances PAX-6+ neuroprogenitor production. Continuing experiments will evaluate the role of CB2 receptor modulation in TSC.

References

References Available Upon Request

Acknowledgements

I would like to thank my mentor Dr. Kevin Ess for being such a kind and accessible mentor throughout this year and ultimately allowing me to pursue my own independent ideas. I would like to thank Bryan Cawthon for exceptional technical assistance, without which this project would have been significantly less possible. I would also like to thank the following people for their advice and support throughout this Emphasis: Eric Armour, Laura Armstrong, Dr. Inan Olmez, Dr. Robert Carson, Dr. Cary Fu, Kevin Kumar, Dr. Aaron Bowman, and the Vanderbilt Department of Neurology.

Mentor / Department

Kevin C. Ess, Ph.D., M.D. Departments of Neurology, Pediatrics, and Cell and Developmental Biology

BLOCKING THE P2X7 RECEPTOR IN A RAT NERVE-INJURY MODEL IMPROVES LONG TERM FUNCTIONAL OUTCOMES

Charles Rodriguez-Feo
Laboratory-Based Biomedical Research

Background Problem

Activation of the P2X7 Receptor on nerve cells causes the formation of pannexin pores, which allows the influx of calcium across the cell membrane. Polyethylene glycol (PEG) and methylene blue (MB) have previously been shown to delay Wallerian degeneration if applied during microsuture repair of the severed nerve. Our hypothesis is that by modulating calcium influx via the P2X7 receptor pathway, we could improve PEG based axonal repair. The P2X7 receptor can be stimulated or inhibited using bzATP or Brilliant Blue (FCF), respectively.

Objectives

Improve the current PEG based nerve fusion protocol by using compounds that augment the P2X7 pathway.

Materials and Methods

A single incision rat sciatic nerve injury model was used. The defect was repaired using a previously described PEG, MB fusion protocol. Experimental animals were treated with 100 µL of 100 mM FCF solution (n=8) or 100 µL of a 30 mM bzATP solution (n=6). Control animals received neither FCF, bzATP, nor PEG. Compound Action Potentials (CAPs) were recorded prior to transection (baseline), immediately after repair, and 21 days post operatively. Animals underwent behavioral testing 3,7, 14, and 21 days post operatively. After sacrifice, nerves were fixed, sectioned, and immunostained to allow for counting of total axons.

Results

Rats treated with FCF showed an improvement as compared to control at all time points (n=8) ($p = .047$, .044, .014, and .0059 respectively). A statistical difference was also shown between FCF and bzATP at Day 7 ($p = .008$), but not shown with days 3, 14, and 21. ($p=.60$, .0733, and .1724, respectively).

Conclusions

Blocking the P2X7 receptor improves functional outcomes after PEG mediated axonal fusion.

Acknowledgements

K. Sexton, R. B. Boyer, A. O. Pollins, N. L. Cardwell, L. B. Nanney, B. Shack, W. P. Thayer

Mentor / Department

Dr. Wesley Thayer, Vanderbilt University Department of Plastic Surgery

FORCES AND TRAUMA ASSOCIATED WITH MINIMALLY-INVASIVE, IMAGE-GUIDED COCHLEAR IMPLANTATION

Pooyan Rohani
Laboratory-Based Biomedical Research

Background Problem

Minimally-invasive, image-guided cochlear implantation (CI) utilizes a patient-customized microstereotactic frame to access the cochlea via a single drill-pass. The proposed benefits of this approach include a potential reduction in operative trauma and time. Additional investigation is necessary to assess the safety of this approach to CI.

Objectives

Previous studies have examined the amount of force applied during electrode insertion in the setting of traditional CI. In this series of experiments, we investigated the average force and trauma associated with the minimally-invasive approach.

Materials and Methods

Microstereotactic frames for six fresh cadaveric temporal bones were built using CT scans to determine an optimal drill path following which drilling was performed. A tympanomeatal flap was raised, the round window (RW) overhang taken down, and the RW membrane reflected posteriorly. CI electrodes were inserted using surgical forceps to manually advance the CI electrode array, via the drilled tunnel, into the cochlea. Forces were recorded using a six-axis load sensor placed under the temporal bone during insertion of lateral wall electrode arrays (2 each of Nucleus CI422, MED-EL standard, and MED-EL standard with stiffeners). Tissue histology was performed by removing the lateral wall of the cochlea allowing photo-documentation of electrode position and microscopic assessment of intracochlear tissue.

Results

After drilling, CT scanning demonstrated successful access to cochleae in all six bones. Average insertion forces were 0.0088-0.0780N. Peak forces were 0.0564-0.4688N. Tissue histology showed complete scala tympani insertion in all specimens with depth of insertion ranging from 360-600 degrees. No intracochlear trauma was identified.

Conclusions

In this cadaver model with a minimally-invasive, image-guided CI approach, the use of lateral wall electrodes was associated with insertion forces comparable to traditional CI surgery. Deep insertions were obtained without identifiable trauma.

Acknowledgements

Robert Labadie, MD, PhD; Jason Pile, MS; C. Gary Wright, PhD (The University of Texas Southwestern Medical Center); Lueder Kahrs, PhD; Ramya Balachandran, PhD; Gregoire Blachon; Nabil Simaan, PhD; Funding from Vanderbilt Institute for Clinical and Translational Research (VICTR); Funding from National Institute on Deafness and Other Communication Disorders (NIDCD)

Mentor / Department

Robert Labadie, MD, PhD; Department of Otolaryngolgoy-Head and Neck Surgery

A STUDY OF CORTICAL CONNECTIONS OF FUNCTIONAL ZONES IN POSTERIOR PARIETAL CORTEX AND MOTOR CORTEX ON NEW WORLD PRIMATES

Tulsi Roy
Laboratory-Based Biomedical Research

Background Problem

Posterior parietal areas of the cortex (PPC) use visual, somatosensory, and auditory signals to encode planned movements, then relayed to areas of the premotor cortex and motor cortex. Micro-stimulation studies on anesthetized galago monkeys show that electrical stimulation via micro-electrodes of the rostral PPC produce different movement patterns, and moreover, that long-train stimulation of motor areas coextensive with motor and premotor areas evoke ethologically relevant behavior (reach-and-grasp, defensive gestures, hand-to-mouth, among others). The evidence suggests that the posterior parietal region interacts with parts of the frontal cortex to produce these biologically relevant behaviors.

Objectives

This research is intended to study neural circuitry underlying specific motor behaviors related to the motor, premotor, and posterior parietal cortex and their respective thalamic counterparts by creating a functional map of significant subdivisions of frontal and posterior parietal cortices. In so doing, we may be able to determine distinct zones in rostral PPC and frontal motor cortex where different classes of complex movement are evoked. Because the striatum receives inputs from the motor and somatosensory cortex, we will use various tracers to visualize cortical projections to the putamen and caudate. Of note, unlike previous studies using “flattened” cortices, this study aims to preserve the anatomic architecture to get a more accurate representation of the spatial relationships and extent of segregation/overlap between the different frontal-parietal networks.

Materials and Methods

Micro-stimulation was performed on one squirrel monkey. Electrical stimulation of cortical neurons with short and long (50-500 ms) trains of electrical pulses using microelectrodes was used to identify areas of interest for injections of neurohistologic tracers (BDA, Fluoro Ruby, and Dextran Alexa 488). After one week, the animal was sacrificed and the brain was then sectioned and histochemically processed. Cells that took up the tracers of interest were then plotted using light and fluorescent microsopy and computer program, Igor-Pro. Individual images were then visualized, aligned, and overlapped using the software program, Canvas. Images could then be compiled into a functional map.

Results

This case is fully plotted. Images will be overlapped and compared to architecture of Nissl/Ach-stained sections to identify cortical layers and other structures. This way we can really understand the full results of the study and evaluate spatial relationships between PPC, M1 (motor), PMV (premotor) and their respective projections into the putamen.

Conclusions

While this study will need to be replicated with other subjects, images do demonstrate projections from PPC, M1, and PMV (premotor cortex). Further comparison will subsequent cases and Nissl/Ach architecture will allow a better understanding into the exact nature of these spatial relationships.

Mentor / Department

Iwona Stepniewska and Jon Kaas, Department of Psychology

VALIDATION OF A UNIQUE METHODOLOGY FOR RECELLULARIZING PORCINE AORTIC VALVES

Richard Samade
Laboratory-Based Biomedical Research

Background Problem

Congenital valvular malformations affect one in every 100 live births in the United States and may cause numerous and serious sequelae during infancy and adulthood. Mechanical and bioprosthetic prostheses are routinely indicated for severely damaged aortic valves. However, these prostheses are prone to complications and cannot accommodate for overall growth in pediatric recipients. A preferable alternative would utilize a valve seeded with the recipients's cells and that can sufficiently recapitulate normal physiological function.

Objectives

This investigation aims to (1) refine a two-step decellularization protocol of adult porcine aortic valve leaflets, (2) recellularize the leaflets with aortic valve interstitial and endothelial cells, and (3) characterize gross and histological changes in the valves due to various hydrostatic pressures and strains.

Materials and Methods

Aortic valve leaflets were harvested post-mortem from adult porcine subjects in a local abattoir. These tissue samples were incubated for two days in a detergent-based solution, followed by one day of treatment with nucleases. Various stains and light and fluorescent microscopy were used to study histological features of the valves. A number of lipid-based transfection reagents were compared and subsequently used to introduce fluorescent reporter constructs into target aortic valvular cells. A bioreactor chamber was constructed for the study of hydraulic performance of native, decellularized, and recellularized aortic valve conduits.

Results

The decellularization protocol removed nuclei and cell membranes, but did not significantly disrupt the characteristic strata of extracellular matrix (ECM) proteins in prepared sections. Elastin was less abundant in the ventricularis layer following decellularization. Lipid based transfection was successful in introducing the desired constructs into target cells.

Conclusions

Collectively, these results demonstrate the possibility of preparing an acellular scaffold with preserved ECM strata. This scaffold can be amenable to subsequent recellularization and permit studies of mechanical strains and pressures correlating with normal and pathological states.

Acknowledgements

I would like to recognize first and foremost my Emphasis mentor, Dr. H. Scott Baldwin, for his overall guidance and feedback on the direction of my project and helping to provide a more tangible clinical context for it. Dr. Christopher Brown has also helped me tremendously on many occasions by providing me needed materials, arranging for appropriate technical training in needed laboratory techniques, and providing detailed critiques on the outcomes of experiments at various stages. Dr. Paige DeBenedittis has also be immensely helpful in providing me training for experimental techniques when the situation called for it. Kevin Thompkins and Leshana Saint Jean of the Baldwin Laboratory also provided me sage advice from time to time as well. I must also thank Dr. W. David Merryman and his laboratory's members (particular Steven Boronyak) for their assistance in providing bioengineering advice on the latter stages of my projects and offering to perform mechanical measurements on my decellularized and recellularized valvular constructs.

Mentor / Department

H. Scott Baldwin, M.D. of the Department of Pediatrics, Division of Cardiology

INDUCED PLURIPOTENT STEM CELL PLATFORM FOR HUMAN CARDIAC DISEASE MODELING & DRUG DISCOVERY

Calvin C. Sheng
Laboratory-Based Biomedical Research

Background Problem

Despite rapid advancements in medicine, cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, accounting for approximately 1 in every 3 deaths. For instance, ischemic events cause irreversible damage to the myocardium, and congenital heart diseases lead to dysregulation of contractions. Our wide array of molecular techniques has allowed us to narrow etiologies of specific CVDs down to single nucleotide polymorphisms. However, one of the major challenges in reducing cardiovascular-related mortality has been establishing an ex vivo model of human cardiomyocytes for generating autologous cardiac tissue and studying the underlying pathogenesis.

Objectives

The purpose of this study is to evaluate whether human induced pluripotent stem cell (iPSC) technology holds the potential to be that cardinal platform for human cardiac disease modeling & drug discovery.

Materials and Methods

We reprogrammed healthy and diseased patient fibroblast samples into iPSCs and directed differentiation of these cells into confluent beating monolayers of cardiomyocytes, utilizing a modified Matrix sandwich method. The cell lineages and sub-clones include: n=9; SM5, CD2, CD3, CC2, &CE6 = controls; LViP1, LViP3, LCL4, & LCL8 = disease lines. The iPSC-cardiomyocytes were evaluated via immunostaining, calcium imaging, electron microscopy, patch clamp electrophysiology studies, pharmacological evaluations using FDA-approved drugs such as dofetilide, and a proteomics study.

Results

Nine unique cell lines were made into cardiomyocytes (iPSC-CMs) with 100% success rate. Immunostains show strong expression of cardiac markers troponin-T and alpha-actinin. Initial calcium imaging studies of iPSC-CMs showed a chain reaction of calcium-induced calcium release across a beating monolayer syncytium. Electron microscopy of diseased iPSC-CMs illustrated severe cellular abnormalities such as disarray of myofilaments, excess of ribosomes, and a lack of mitochondria. Through patch clamps, we have identified presence of atrial, ventricular, and nodal-like cells with resting membrane potentials in the physiologic -70mV to -80mV range. Preliminary drug assays using FDA-approved drugs in both healthy and diseased patient-derived cardiomyocytes elicited a number of physiologic phenomena, including tachycardia, brachycardia, and early after depolarization. Notably, diseased LViP cells were ~2.5x more sensitive to drugs than control SM5 cells. Proteomics expression profiles of control CC2 and diseased LViP showed 99.7% similarity, though the latter lacked significant mitochondrial proteins.

Conclusions

All of these characteristics provide the groundwork for our robust, universal, and efficient cardiac induction system as a viable platform for disease modeling and drug discovery.

Acknowledgements

I'd like to thank everyone in the Hong lab for their support, our collaborators in Dr. Al George's and Dr. Dan Roden's labs, the Vanderbilt Cell Imaging Shared Resource Core, Dr. James Atkinson for EM's, and the NIH T-35 Training Grant.

Mentor / Department

Charles C. Hong, Department of Cardiovascular Medicine

THE REGULATION OF MIRNA EXPRESSION BY E-CADHERIN AND TGF-BRII IN ESOPHAGEAL SCC

Kenneth Taubenslag
Laboratory-Based Biomedical Research

Background Problem
E-cadherin is a gatekeeper of the epithelial phenotype. Coordinated loss of E-cadherin and the growth factor receptor TGF-βRII is conducive to increased invasion in esophageal SCC. We hypothesize that Activin A, a TGF-β-family ligand, may play a role in tumorigenesis in the absence of TGF-β receptor signaling.

Objectives
n/a

Materials and Methods
To identify miRNAs involved in ESCC, we examined miRNA expression by qPCR in human esophageal cells, comparing cells constitutively expressing E-cadherin to cells with dominant-negative mutant E-cadherin as well as double-mutant dominant negative E-cadherin and TGF-βRII: E, EC and ECdnT respectively. Additionally we compared miRNA expression and E-cadherin status in various tumor cell lines.

Results
miR-31 and miR-106b showed upregulation in EC and ECdnT cells grown on plastic. Conversely, miR-21 was downregulated with loss of E-cadherin and in the double mutant cells. miR-200a and miR-19a were induced with Activin A treatment only in the ECdnTs, while let-7f was downregulated in the absence of E-cadherin and TGF-βRII signaling. In the tumor cells lines we found upregulation of miR-31, miR-21, miR-106b, and miR-200 family members correlating to high E-cadherin expression. miR-92 and miR-129, on the other hand, were only upregulated in TE8 cell lines, which do not express E-cadherin.

Conclusions
miR-31 is upregulated in a lung, gastric, and esophageal cancers as well as melanoma. This supports the role of miR31 as an onco-miR in our cell system. miR-106 is oncogenic in breast and prostate cancers validating our finding that this miRNA is upregulated downstream of E-cadherin and TGFβ-RII. We identified three potential targets of Activin signaling: miR-200a, miR-19a, and let-7f. We also identified two novel markers of epithelial-mesenchymal transition (EMT): miR-92 and miR-129, which are upregulated in the mesenchymal TE-8 esophageal SCC cell line. Future studies will focus on identifying downstream targets via microarray as well as functional assays after knockdown or up-regulation of select microRNAs.

Acknowledgements
Rainelli Koumangoye, Claudia Andl, U54 Meharry/VICC/TSU Cancer Disparities Grant

Mentor / Department
Dr. Claudia Andl, Assistant Professor of Surgery, Assistant Professor of Cancer Biology

DIET AFFECTS WASTING AND DEVELOPMENT OF OSTEOPOROSIS, BUT NOT FRACTURE HEALING, IN PLASMINOGEN DEFICIENT MICE

Matthew Taussig
Laboratory-Based Biomedical Research

Background Problem

Extravascular fibrin accumulation has recently been identified as an etiologic factor in multiple chronic diseases as a result of its ability to stimulate inflammatory responses. Consequently, mice deficient of plasminogen (Plg-/- mice), the precursor of plasmin – the primary fibrinolytic, are known to waste within a few weeks of maturity. In addition, we have determined that these mice have aberrant fracture healing and develop premature osteoporosis in association with elevated inflammation (IL-6) all of which are abolished by imposing a concomitant fibrinogen deficiency.

Objectives

While evaluating how diet affects the development of osteoporosis in Plg-/- mice, we serendipitously discovered that high-fat and low-fat synthetic diets ameliorates wasting and osteoporosis. Given this observation, we hypothesized that a change in diet from standard to a synthetic diet would also rescue fracture healing in these mice.

Materials and Methods

Plg-/- and wild type (WT) mice weaned (3wks) onto a synthetic diet were monitored for growth, weight, and body composition. Simple fractures were induced in the left femur using an open-fracture model (8wks) monitored with serial Xrays. Histological, serological, and μCT analysis was performed at 20 weeks.

Results

Synthetic-diet-fed Plg-/- mice have normal weight, skeletal growth, bone fractional volume, and IL-6 levels (compared to WT). Synthetic-diet-fed Plg-/- mice, however, display a leaner body composition and fail to heal their fractures.

Conclusions

Although wasting and skeletal degeneration were rescued by altering diet in Plg-/- mice, surprisingly fracture healing was still impaired. Because the inflammatory profile of the Plg-/- mice was increased on standard diet and was normal on synthetic, it is likely that wasting and degeneration is mediated by aberrant inflammation. In contrast, our results suggest that impaired fracture healing is likely caused by local accumulation of fibrin as these pathologies develop in synthetic-fed Plg-/- but not in the Plg-/-/Fib-/- mice. This demonstrates that the pathophysiology of wasting and healing resulting from an accumulation of fibrin occurs through different mechanisms and has important implications in fracture healing as well as for chronic diseases such as arthritis and osteoporosis.

References

References Available Upon Request

Acknowledgements

Heather A. Cole, Lynda O'Rear, Nicholas Mignemi, Tetsuro Oba, Masato Yuasa

Mentor / Department

Jonathan Schoenecker Assistant Professor of Orthopaedics and Rehabilitation, Pharmacology and Pediatrics

INDUCED OVEREXPRESSION OF VEGF AMELIORATES GLOMERULOSCLEROSIS PROGRESSION IN MICE

Anne Wilson
Laboratory-Based Biomedical Research

Background Problem
Vascular endothelial growth factor (VEGF) is a pro-angiogenic factor produced by the podocyte in glomeruli. In healthy mice, overexpression of VEGF leads to proteinuria. However, in the setting of chronic renal disease, podocyte loss reduces VEGF in glomeruli, which may contribute to glomerulosclerosis progression.

Objectives
We investigated whether induced overexpression of VEGF after glomerulosclerosis could decrease progression.

Materials and Methods
VEGF loxp (V) mice were mated with TetO-podocin-Cre (R) mice to create double transgenic mice (RV) that permit inducible overexpression of VEGF, or single transgenic mice (R), which will not induce VEGF. All mice underwent 5/6 nephrectomy (Nx). At 8 weeks after 5/6 Nx, overexpression of VEGF was induced by administration of 2 mg/mL doxycycline in the drinking water. Mice were sacrificed at week 12, or earlier in severely ill mice. Systolic blood pressure and proteinuria were measured at week 0, week 8, and the time of sacrifice, and glomerulosclerosis assessed.

Results
RV mice did not have proteinuria at baseline (ACR 72.2 ± 8.2 µg/mg). At week 8, both RV and R mice had developed proteinuria (RV: 8835.6 ± 2996 µg/mg; R: 7760.6 ± 1791 µg/mg). Systolic BP increased significantly in both groups from week 0 to week 8 (RV: 116.4 ± 4.96 week 0 to 140.9 ± 9.1 mmHg at week 8; R: 117.7 ± 2.4 week 0 to 139 ± 5.7 mmHg at week 8, $p<0.05$). After administering doxycycline at week 8, RV mice survived longer than R mice (17.3 days vs. 15.2 days). Systolic BP did not change significantly from week 8 to sacrifice in RV or R mice. In R mice, there was a 3.5 fold increase in proteinuria (measured by ACR) on average from week 8 to sacrifice, while in RV mice, ACR remained steady over this time period. However, despite longer survival times, there was less glomerulosclerosis in RV mice (sclerosis index 1.05 ± 0.18, 0-4 scale) than in R mice (1.31 ± 0.16).

Conclusions
Our data indicate induced overexpression of VEGF slows the progression of existing glomerulosclerosis and prevents increased proteinuria by local mechanisms, not through systemic blood pressure effects.

Acknowledgements
Haichun Yang, Agnes B. Fogo

Mentor / Department
Agnes B. Fogo, M.D., Dept. of Pathology, Microbiology and Immunology

EFFECT OF MTG8 MUTANT ON SW620 APOPTOSIS AND PROLIFERATION

Lilly Zhu
Laboratory-Based Biomedical Research

Background Problem

Myeloid Translocation Gene 8 (MTG8) is a member of the Myeloid Translocation Gene family of transcriptional co-repressors. MTG8 serves as a scaffolding protein that binds transcription factors with a complex of transcription co-repressors including histone deacetylases. Hypermethylation of MTG8 has been implicated in ovarian tumors. Similarly, decreased MTG8 expression was observed in metastatic pancreatic tumors rather than primary pancreatic tumor. MTG8 knockout mice showed developmental gut defects. Six mutations clustering in the evolutionarily conserved nervy domains in MTG8 or MTG16 were found in a colon and breast tumor screen. We hypothesized that these mutations may affect tertiary structure, binding to transcription co-repressors, and ultimately MTG8 function.

Objectives

We wanted to determine how MTG8 mutations altered cell apoptosis and proliferation programming.

Materials and Methods

Human colorectal cancer cell line SW620 cells were transiently transfected with GAL4-tagged vectors: double mutant (E472K, A474S), triple mutant (R386W, R395W, E472K), wild type MTG8, or empty pCMV5 as control. To detect differences in apoptosis, protein was collected 3 days post-transfection and immunoblotting for cleaved Caspase-3 was performed. Cell proliferation was measured by WST1 assay and color intensity was quantified by a plate reader at 440nm.

Results

Apoptosis: Control, WT MTG8, double mutant, and triple mutant had similar levels of whole Caspase 3 and cleaved Caspase 3. Proliferation: Three days after seeding, CTL cells had absorbance of .638±.27 units, WT MTG8 .088±.02, double mutant .306±.07, and triple mutant .093±.05. By one-way ANOVA analysis with Newman-Keuls post-test, absorbance was significantly reduced in WT MTG8 compared to CTL for all three days ($p<.05$). Double mutants had significantly higher absorbance than WT MTG8 at day 2.

Conclusions

Wild Type MTG8 and mutants did not have enhanced Caspase-3 cleavage or Caspase-3 expression suggesting that the mutants do not affect apoptosis. WT MTG8 greatly decreased the proliferation of SW620 cells, which was partially reversed by MTG8 double mutant, suggesting that MTG8 double mutant impairs MTG8 function.

References

References Available Upon Request

Acknowledgements

Dr. Williams, Wei Ning, Shenika Poindexter, Bobak Parang, Caitlyn Barrett, Amber Bradley Emphasis Program T35 Summer Research Program

Mentor / Department

Dr. Christopher Williams, Gastroenterology Division

Don Moore, Ph.D. is a Professor of Medical Education and Administration, Director, Division of Continuing Medical Education at Vanderbilt University School of Medicine. Director of Program Evaluation for Curriculum 2.0. He has devoted a considerable amount of his professional career examining, writing and speaking about continuing medical education and a number of other related areas such as: practice-based CME, planning and assessing CME, and how Physicians learn. His research interests also include the role of CME in physician change, office systems for CME, and the impact of CME on health care outcomes. He was recently inducted into Vanderbilt's Academy for Excellence in Teaching.

Medical Education

This educational experience is designed to introduce students to theory and practice in the learning and teaching of medical students, residents, practicing physicians and patients as well as provide an opportunity to develop a project in an area of interest. Students will be provided with opportunities to examine the practice of education in a wide variety of health care settings. Students will have opportunities to examine

- How learning occurs in medical school, residency, and practice
- How students can develop reflection and self assessment skills to develop an approach to lifelong learning that can be used throughout their medical careers
- What teaching strategies help medical students, residents, practicing physicians, and patients learn
- Assessing the progress of student, resident, or patient learning
- Curriculum development in specific content areas

The student experience will introduce them to the community of scholars at Vanderbilt and elsewhere who study and work in the field of medical education. Each student will work with a mentor who will provide direction to the student as he or she determines an area of focus, develop a project proposal, implement the project proposal, present findings, and prepare findings for publication. In addition, students in the Medical Education area will be expected to participate in ongoing educational activities such as Medical Education Grand Rounds andMedical Education Journal Club.

"Working with students in the Emphasis Program has been one of the highlights of my work at Vanderbilt. It has been an honor and a privilege for me to share their excitement and satisfaction as they worked through and accomplished their projects.."

LET'S TALK ABOUT SEX: A GENERATIONAL COMPARISON OF SEXUAL KNOWLEDGE AND ATTITUDES IN THE OLDER POPULATION

Vanessa Buie
Medical Education

Summary
Increasing rates of AIDS and STDS in the older population supports the notion that sexual interest and activity play a huge role in people's lives as they age. With this necessitates a need for more aging sexual education for everyone involved with the older population. The aim of his study is to identify gaps in knowledge and differences in attitudes between populations to facilitate an educational dialogue between younger physicians and older patients. The study methodology compares attitudes and knowledge of an older population (>55 y/o) attending Fifty-Forward events, 4th year, and 1st year medical students using the validated Aging Sexual Knowledge and Attitudes Survey of Charles White, National Institute of Mental Health. Our hypothesis is that there is a correlation between increased sexual knowledge and age with more permissive attitudes in elderly followed by 4th year then 1st year medical students. Vanderbilt University medical students (VMS) were surveyed using REDCap through an online interface and email system. Members of Fifty Forward were invited to a lecture followed by a paper survey. An analysis of variance and descriptive statistics were performed with N= 123 (51 VMS1, 33 VMS4, and 40 Fifty Forward members). A difference in sexual knowledge between groups was found with VMS4 having greater knowledge than Fifty Forward members followed by VMS1 ($p=0.0016$). No difference was found between groups' sexual attitudes, a key difference compared to past literature, suggesting that attitudes toward sexuality in aging is becoming more socially acceptable.

Brief Description
This project provides a comparison of first year and, fourth year medical students and community dwelling seniors documenting both differences in knowledge and similarities in attitudes about sexuality in aging. These outcomes provide insight for physicians and the seniors they care for.

References
References Available Upon Request

Acknowledgements
Yanna Song, MS; Mario Davidosn, PhD; Fifty Forward of Middle Tennessee

Mentor(s) and Department
Dr. James Powers, MD Associate Professor of Medicine Department of Geriatrics

A SURVEY OF LGBT NEEDS AT VANDERBILT UNIVERSITY HOSPITAL

Sean Chester
Medical Education

Summary
Lesbian, gay, bisexual, and transgender (LGBT) individuals face disparities when accessing and receiving healthcare. The medical system contributes to these disparities, including an institutional climate and culture that fails to comprehensively address the needs of LGBT individuals that may perpetuate ignorance and discrimination. The purpose of this study was to characterize the climate and culture experienced by LGBT individuals at the Vanderbilt University Medical Center (VUMC) with the aim of identifying opportunities for climate improvement to enhance the healthcare for LGBT patients. An anonymous, online institutional climate survey, adapted from previously validated instruments, was used to assess the attitudes, experiences, and perceptions of LGBT and non-LGBT medical students, residents, physicians, non-physician clinical staff, and other employees at a large academic medical center. Results revealed that LGBT individuals experienced significant disparities, with LGBT individuals more likely to conceal SO/GI to avoid intimidation and harassment ($p < 0.001$), avoid disclosing SO/GI to a colleague or superior ($p < 0.001$), and fear for their physical safety ($p < 0.001$). LGBT respondents further were less likely to believe that clinical staff is aware of LGBT health concerns ($p = 0.046$). LGBT students and employees disproportionately perceive and experience bias, harassment, and discrimination, which likely reflect the experiences of LGBT patients. The results of this institutional climate survey suggest that comprehensive training, inclusive policies and practices, and the development of mechanisms to address LGBT-specific harassment and discrimination are necessary to improving climate at academic medical centers.

Brief Description
My study examined the institutional climate for LGBT students and employees at the Vanderbilt University Medical Center.

References
References Available Upon Request

Mentor(s) and Department
Dr. Jesse Ehrenfeld, Department of Anesthesiology

Keith G. Meador, MD, ThM, MPH, is Professor and Vice-Chair for Faculty Affairs in Psychiatry and Professor of Preventive Medicine at Vanderbilt University. He is the Director of the Center for Biomedical Ethics and Society and on the Associate Faculty of the Graduate Department of Religion at Vanderbilt. Also, he is the Director of Mental Health and Chaplaincy through the VISN 6 MIRECC as part of a national initiative to foster integration of chaplaincy services into mental health care within the Department of Veterans Affairs. He joined the faculty at Vanderbilt in July of 2010 and previously served as Professor of Psychiatry and Behavioral Sciences at Duke University where he gave direction to centers in the Medical Center and Divinity School focused on the intersections of religion, theology, and health. He is a physician and board certified psychiatrist with training in geriatric psychiatry, theology, and public health. Dr. Meador is a Phi Beta Kappa graduate of Vanderbilt University and received his medical degree from the University of Louisville. He completed his residency in psychiatry and fellowship in geriatric psychiatry at Duke University. His theological education leading to the ThM was at Duke Divinity School and he received his MPH in Epidemiology from the University of North Carolina – Chapel Hill. His scholarship builds on his clinical, research and teaching background in mental health, practical theology, and public health about which he lectures widely and has published numerous publications including the co-authored book, Heal Thyself: Spirituality, Medicine, and the Distortion of Christianity. His academic work includes theological and conceptual exploration of the intersections of religion and health and empirical research regarding socio-cultural determinants of illness, health and human flourishing

Medical Humanities, Ethics and Policy

Students in this area are afforded guidance as they explore the ethical, legal and social dimensions of medicine, health care and health policy through multi-dimensional exploration of individual and social values, cultural dynamics, and legal and professional standards that impact clinical practice and biomedical research. They are guided by the team of faculty who are affiliated within the Center for Biomedical Ethics and Society.

COORDINATING THE FUTURE IN THE ICU: OBSTACLES TO PATIENT AND FAMILY PREPAREDNESS

Cristina Farkas
Medical Humanities, Ethics & Policy

Objectives

The purpose of this study is to explore obstacles to effective preparedness for the patient's course of care, specifically focusing on obstacles to effective communication between the healthcare team and patients' families, from both family and clinicians' perspectives. To our knowledge, no one has done an in-depth comparison of communication obstacles from the point of view of the clinician vis a vis the family point of view. We compare and contrast these differing perspectives, and offer suggestions for reconciling the two. Our long-term goal in undertaking this research was to begin developing an intervention that specifically addresses communication obstacles in an attempt to impact family preparedness (although we do not deal with this intervention in this presentation). Communication obstacles are important because they are barriers to family "preparedness" for taking on the role of surrogate for patients who are incapacitated or taking on a vital supportive role during the patient's recovery.

Summary

Clinicians in the ICU setting develop care plans structured by proximal and distal goals that mark intended pathways through the hospital stay. We know very little about patients/families' preparedness for the movements along these pathways. Reaching or failing to reach goals of care leads to important transitions for patients and their families. Pathways marked by progress involve achievement of milestones, movement to lower levels of care and eventually discharge to the next care setting. Pathways marked by persistent complications can lead to critical decisions that redirect a patient's course to outcomes of greater morbidity or mortality. We will present findings from semi-structured interviews that demonstrate how perspectival differences generate obstacles to family preparedness for ICU transitions, especially ones involving critical decision making about goals of care. As a part of this study, ten clinicians (five bedside nurse and five attending physicians) and twenty family members of patients in a Regional Burn ICU participated in a 45-minute semi-structured interview. The interview guide was designed to elicit perceptions of formation and communication of expectations about future medical care. Interview transcripts were coded by at least two researchers and inter-rater reliability was established using Cohen's kappa coefficient. In analyzing the distinct perspectives of clinicians and families, we found that perceptions of obstacles to preparedness for care transitions clustered around three major themes: Perceptions of Involvement, Perceptions of Information Needs and Perceptions of Coordination. Analysis of these domains showed that the obstacles are constituted by the differences in the ways families and clinicians understand factors like: a family's physical presence (or lack of presence) at the hospital, a family's socioeconomic status or the standardization of care pathways. Several implications for healthcare decision-making follow from these findings and these are especially true when patients' lack capacity to make their own decisions. Health care communication processes serving family preparedness need to be 1) responsive to surrogates who cannot be consistently present in the hospital 2) scripted at appropriate levels of health literacy and 3) attuned to upcoming transitions that require emotional and cognitive preparation.

Brief Description

Semi-structured interviews of 5 attending physicians, 5 bedside nurses and 20 family members revealed obstacles to communication involved three major themes: Perceptions of Involvement/Engagement, Perceptions of Family Education Level and Need for Information and Perceptions of Consistency/Coordination/Standardization.

References

References Available Upon Request

Mentor / Department

Joe Fanning, Center for Bioethics and Society

IMPACT OF REPEATED SURVIVORSHIP CLINIC VISITS ON PATIENTS' KNOWLEDGE OF THEIR TREATMENT HISTORY AND RISK OF LATE EFFECTS

Shannon Koh
Medical Humanities, Ethics & Policy

Objectives

Cancer survivorship clinics provide education regarding a patient's treatment history and risk of late effects, but the impact of survivorship care on patient knowledge remains unclear.

Summary

This is a prospective observational study of 48 childhood cancer survivors recruited prior to their first appointment at the cancer survivorship clinic at Vanderbilt University. Knowledge of treatment history and risk of late effects were assessed through a structured interview involving identification of chemotherapeutics and late effects from a cancer and treatment-specific list. Patients (21%) or parents of patients <15 years (79%) completed a baseline interview, before the first appointment, and one month and three months after the first clinic visit. Thirty-eight patients/parents completed a fourth interview, with a median time of 19 months (18.0-19.7) after the first clinic visit, and 8 months (6-16) since the last clinic visit. Longitudinal regression models were used to examine the effect of time since the last clinic visit on patients' knowledge, controlling for the time since last clinic visit and the percent correct at baseline.

Brief Description

Results: Knowledge of treatment history was maintained as the time since last clinic visit increased; no time-dependent effect was detected (p=0.465). In contrast, knowledge of risk of specific late effects declined as the time since last clinic visit increased (p=0.0043). Percent correct at baseline was significantly associated with percent correct on subsequent post-clinic interviews for both treatment history and late effects (p= <0.0001 and 0.0007 respectively). Conclusions: Attendance at survivorship clinic resulted in maintenance of knowledge of treatment history, whereas knowledge of late effects declined. The baseline interview score was a major predictor of performance on subsequent interviews. This suggests survivorship clinics have a positive effect on knowledge of treatment history, but repeated education regarding the risk of late effects is required to maintain patients' knowledge base and appropriate surveillance.

Mentor / Department

Debra L. Friedman, MD, MS Department of Pediatrics, Vanderbilt University School of Medicine and the Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA, Vanderbilt-Ingram Cancer Center

ASSESSING THE DISPARITIES IN NEEDS AND ASSETS OF CANCER SURVIVORS TREATED AT MINORITY SERVING INSTITUTIONS AND NCI-FUNDED INSTITUTIONS

Mobola Oyefule
Medical Humanities, Ethics & Policy

Objectives

Purpose: This study investigates the long-term differences in needs and assets of cancer survivors. It is the second part in a pilot study aimed at closing the gap between cancer survivors of different socioeconomic backgrounds and strengthening the partnerships between large NCI- funded cancer centers and municipal/minority serving institutions.

Summary

Methods: Cancer survivors (n=283) treated at Vanderbilt Ingram Cancer Center (NCI-funded institution) and Nashville General Hospital (minority serving hospital) were recruited from respective tumor registries (breast, colorectal, lung and prostate cancer). Quality of Life (QOL) was assessed through a combination methods including completion of a survey questionnaire packet and participation in a one-time focus group. Using multi-variate analysis, comparisons were made between the VICC and NGH group upon data collection. Psychological evaluations were performed based on self-reported data collected from survey information. Individuals identified to be at higher risk for psychological distress were referred to a specialist for follow-up. Results 283 responses were received from VICC participants (n=205) and NGH participants (N=78). 22.6% of VICC patients identified as minority vs. 60.3% of NGH patients Those treated at VICC reported a higher QOL ($P<0.0001$), less financial stress ($p<0.0001$), more emotional support ($p<0.0016$) and were less likely to be suffering from PTSD related to their cancer treatment ($p<.0001$). Conclusion: These results indicate that race, socioeconomic status and access to support post cancer treatment are related to long-term differences in QOL of cancer survivors. Interventions should be tailored to the specific needs of different groups of cancer survivors.

Brief Description

The study is still in the statistical analysis stage. More information will be updated as it becomes available

References

References Available Upon Request

Mentor / Department

Dr. Deb Friedman. Pediatric Hematology/Oncology

Terence S. Dermody, M.D., is the Dorothy Overall Wells Professor of Pediatrics and Microbiology and Immunology, Director of the Division of Pediatric Infectious Diseases, Director of the Lamb Center for Pediatric Research, and Director of the Vanderbilt Medical Scientist Training Program (MSTP). Dr. Dermody came to Vanderbilt in 1990 after completing his medical degree at Columbia University in New York, a residency of internal medicine at Presbyterian Hospital in New York, and fellowships in infectious diseases and virology at Brigham and Women's Hospital and Harvard Medical School in Boston. Dr. Dermody is a physician scientist with clinical interests in pediatric infectious diseases and research interests in viral pathogenesis. He has been directing the MSTP since 2003.

Medical Scientist Training Program

The central goal of the Medical Scientist Training Program (MSTP) at the Vanderbilt University School of Medicine is to train leaders in academic medicine. Our program is based on solid clinical and research training and is designed to foster the development of independent scientific careers.

The MSTP is a joint endeavor between the Vanderbilt University School of Medicine and the Vanderbilt University Graduate School. Students usually complete the first two years of Medical School, pursue graduate studies for three to four years, then return to Medical School to complete the final two years of clinical training. Successful completion of the program leads to both the M.D. and Ph.D. degrees.

Full-time laboratory research is performed in three rotations from the summer prior to the first medical year through the summer following the first year of Medical School. These cumulative research experiences provide MSTP students with the projects that are reported herein.

"The laboratory rotations that comprise the Emphasis experience are incredibly important for our students. They gain exposure to a variety of research opportunities and select a mentor, training environment, and scientific project best suited to their professional development. The poster presentation and the peer based feedback experience is incredibly helpful in training MSTP students in this form of scientific communication."

SPATIAL AND TEMPORAL DYNAMICS OF NUCLEAR ENVELOPE PROTEINS GOVERN STEM CELL DIFFERENTIATION THROUGH SPECIFIC CONFORMATION UNFOLDING OF CHROMATIN VIA MECHANOTRANSDUCTION

Daniel A. Balikov
Medical Scientist Training Program

Background
The study of mechanotransduction in living cells over the past three decades has provided new insight into how cells sense and interact with their microenvironments. In particular, stem cells have become a popular cell type of interest for their potential in therapeutic treatments for debilitating diseases. At present, it is known that stems cells interpret their physical environment and in turn, given the right set of conditions, will differentiate into a particular lineage conducive to that physical setting. However, the mechanisms that govern this transition are only now becoming clear. There is still a great deal of uncertainty as to how these physical forces transduced through a stem cell translate into meaningful gene expression corresponding to a differentiated state.

Hypothesis
The extracellular matrix serves as a physical “hard drive” that stores protein, cross linking and modulus information corresponding to different tissues types. Proteins of interest localized at the nuclear envelope (laminin; emerin; SUN; KASH; nesprin) become topographically organized to mimic properties of the extracellular matrix and transduce finite forces of varying degrees to the nucleus, and by extension the laminin associated domains of the chromatin. If a topographical position is held in place long enough for the exposed genes to be expressed to a critical level, the stem cell commences lineage differentiation into a cell type corresponding to the tissue type the extracellular matrix is representing.

Materials & Methods
Hydrogel cell assays will be used to screen for stem cell differentiation conditions. PCR analysis will evaluate gene expression. Confocal microscopy and structural illumination microscopy will image and model the cells.

Results
Variation in nucleus structure, at a superficial level, is present in different extracellular matrix settings.

Conclusions
To be determined.

Mentor and Department
Hak-Joon Sung, Ph.D
Department of Biomedical Engineering
Department of Medicine

LONG QT SYNDROME-ASSOCIATED CALMODULIN MUTATIONS IMPAIR KCNQ1 ACTIVITY

Kevin Bersell
Medical Scientist Training Program

Background
Long QT syndrome (LQTS) is an inheritable disorder with delayed repolarization of the heart causing an individual to be susceptible to cardiac arrhythmias. The most common type of LQTS is linked to loss of function mutations in the voltage-gated K+ channel, KCNQ1. Recently, diminished calcium binding affinity has been described in LQTS-associated missense mutations in the cytoplasmic calcium-sensor, calmodulin. Calmodulin is known to interact with two IQ domains on KCNQ1. Mutations that prevent the interaction of calmodulin with KCNQ1 lead to LQTS phenotypes.

Hypothesis
We hypothesize that the novel LQTS-associated calmodulin mutations with decreased affinity for calcium impairs KCNQ1 activity.

Methods
Mutant calmodulin with a single missense mutation to the fourth calcium-binding EF hand motif was inserted into a CMV promoter-driven plasmid. Chinese hamster ovarian (CHO) cell line stably expressing human KCNQ1 was used for all experiments. Whole cell patch clamping was performed on transfected CHO cells expressing wild type or mutant calmodulin and a current-voltage protocol was performed. The analysis of the patch clamp data included steady-state current density, instantaneous current density, and voltage-dependence of activation.

Results
Overexpression of wild-type calmodulin did not alter KCNQ1 activity. Mutant calmodulin displays a trend towards decreased steady-state current density and instantaneous current density. There is a statistically significant decreased in voltage-dependent activation in the range of voltages between -80 mV and +20 mV in the calmodulin mutant compared to the wild-type protein with a right shifted voltage-dependence of activation.

Conclusions
Impaired calcium-sensing capabilities of calmodulin have a detrimental effect on KCNQ1 activity. The channel has altered voltage-dependent activation in the presence of mutant calmodulin. Our findings suggest that the reduced activity of KCNQ1 contributes to the observed phenotype of the patients with LQTS-associated calmodulin mutations.

Acknowledgements
Alfred L. George Jr., MD, Courtney Campbell, Christopher Thompson, PhD, Rick Welch, Jennifer Kunic, and Carlos Vanoye, PhD

Mentor and Department
Alfred L. George Jr., MD
Department of Pharmacology

5-HT2B ANTAGONISM FOR THE TREATMENT OF TGF-B1 MEDIATED AORTIC VALVE CALCIFICATION IN VIVO

Nathaniel Bloodworth
Medical Scientist Training Program

Background

Calcific valve disease is the most common heart valve pathology worldwide, and in the United States contributes to over 28,000 deaths and 48,000 hospitalizations every year. The precise etiology of calcific valve disease remains unknown, though current evidence suggests that some combination of mechanical forces and extracellular signaling cues cause the pathological changes observed in diseased aortic valves that lead to fibrotic disease and valve calcification. Previous work in the Merryman laboratory has illustrated that administration of transforming growth factor β1 (TGF-β1) in conjunction with dynamic strain will induce a phenotypic transformation in valve interstitial cells from quiescent fibroblast to proliferating, contractile myofibroblasts. Characteristic of this transformation is the increased expression of α smooth muscle actin (α-SMA), collagen, and the formation of calcific nodules of dead cells. Recently it has also been demonstrated that inhibition of a serotonin receptor specific to cardiac tissue, 5-HT2B prevents TGF-β1 signaling that results in these pathologic changes.

Objectives

The Objectives of this study include further clarification of the mechanism in the implicated pathologic pathway of aortic valve calcification and evaluating the effectiveness of 5-HT2B antagonism in preventing valve fibrosis and calcification in an ex vivo tissue model and in an in vivo mouse model.

Materials and Methods

Aortic valve interstitial cell (AVIC) lines from immortalized Notch1+/- mice (as the animal model for aortic valve calcification) and isolated human AVICs will be used in all studies. To quantify biomechanical and morphological changes of porcine aortic valve (AV) leaflets due to 5-HT2B antagonism treatment in an ex vivo tissue model, we will examine the calcification response of AV leaflets exposed to combinations of 5-HT2B antagonists, TGF-β1, and strain. Small molecule inhibitors specific to TGF-β1 and Notch1 signaling pathways will be used to further assess tissue-level changes in leaflet biomechanics. Finally, the effects of long-term 5-HT2B treatment in Notch1+/- animals will be determined to evaluate if this strategy is appropriate to prevent calcific aortic valve disease.

Results

Results are forthcoming as studies are currently ongoing.

Conclusions

Preliminary results suggest that 5-HT2B antagonism is sufficient to arrest TGF-β1 signaling and prevent the development of pathologic cell nodules in vitro in conditions of physiologically relevant mechanical strain. Additional results including more details on the mechanism of this process and in vivo effectiveness of 5-HT2B antagonism in treating Notch1 haploinsufficient mice are forthcoming.

Acknowledgements

Merryman laboratory, Vanderbilt University MSTP

Mentor/Department

W. David Merryman
Department of Biomedical Engineering

ALTERED MULTISENSORY PROCESSING IN AUTISM SPECTRUM DISORDERS

Matthew A. De Niear
Medical Scientist Training Program

Background

Autism spectrum disorders are characterized by impairments of social interaction and communication. The features of this disorder suggest that information processing is altered in the brain. A recent study examining multisensory processing in autism spectrum disorders provided evidence that the length of the temporal binding window between two stimuli is increased for individuals with an autism spectrum disorder. The temporal binding window refers to the period of time during which two separate stimuli can occur and be perceived as a single stimulus; the period outside the temporal binding window is defined as the interstimulus interval at which two stimuli can be discriminated as separate stimuli. Additional evidence has suggested that sensory processing impairments in individuals with autism spectrum disorders is primarily related to multisensory stimulus as similar impairments have not been observed on tasks that assess unisensory processing.

Objective

This study sought to further investigate elements of multisensory processing that might be impaired in individuals with autism spectrum disorders.

Methods and Materials

The study investigated multisensory and unisensory processing in a typically developing adolescents and adolescents with an autism spectrum disorder. Various tests employed were multiple forms of temporal order of judgment task and simultaneity of judgment task. Future studies will be conducted to observe any differences in sensory processing using fMRI.

Results

To be determined.

Conclusions

The present study will hope to elucidate what forms of multisensory impairments exist for individuals with an autism spectrum disorder as knowledge of these impairments might have clinical applications for the diagnosis of autism spectrum disorders.

Mentor / Department

Mark Wallace, Ph.D.
Department of Psychology

SKF83959: A DOPAMINE D1 RECEPTOR AGONIST THAT ALTERS LOCOMOTION AND BEHAVIORAL DESPAIR IN RODENT MODELS

Aliya L. Frederick[1], Franklin D. Echevarria[2], LeAnne R. Kurela[2], Tommy P. Saborido[3] and Gregg D. Stanwood [3,4]
[1]Medical Scientist Training Program, [2]Neuroscience Graduate Program, [3]Department of Pharmacology, [4]Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville TN 37232

SKF83959 is a high affinity benzazepine-derived dopamine D1 receptor agonist that has been reported to preferentially activate D1 receptors linked to intracellular calcium mobilization, although the exact mechanism remains unclear. Behaviorally, SKF83959 has previously been shown to elicit intense grooming and orofacial movements in rodent models and can reverse some parkinsonian symptoms in animal models of Parkinson's disease. Here, we have extended the behavioral characterization of SKF83959 on motor output and additionally define SKF83959-induced effects on anxiety and depression-like behaviors.

In wildtype mice, a peripheral injection of SKF83959 (1mg/kg) produced a modest but significant increase in horizontal locomotor activity and orofacial grooming. The SKF83959-induced responses were blocked by the D1-like receptor antagonist SCH23390 and absent in D1 receptor knockout mice, confirming the role of the dopamine D1 receptor in mediating the effects. In the elevated zero maze, a useful task for assessing anxiety-related behavior in rodent models, there were no significant differences between SKF83959-treated and saline-treated mice tested 30 minutes after receiving an acute injection. There was, however, a small reduction in immobility observed in SKF83959-treated mice in the forced swim test, an assessment of behavioral despair. This acute effect of SKF83959 was confirmed in a second measure of behavioral depression, the tail suspension test. Finally, we evaluated chronic SKF83959 exposure (0.5 mg/kg for 21 days) and observed differences between treatment groups in a Novelty Induced Food Suppression test; a paradigm which is sensitive to chronic antidepressants. Taken together, these studies indicate that not only could SKF83959 have therapeutic implications for conditions of motor dysfunction but also could potentially define a novel class of antidepressants targeting the dopamine system. Support provided by RO1MH086629 (GDS) and F31DA029499 (ALF).

THE ROLE OF PGI2 MODULATION OF TLR4 EXPRESSION IN RSV PATHOGENESIS

Melissa T. Harintho
Medical Scientist Training Program

Background Problem

Respiratory syncytial virus (RSV) is the leading cause of respiratory failure in young children and severe RSV bronchiolitis has been identified as risk factor for the subsequent development of asthma in children. Our preliminary data suggest that PGI2 is a novel therapeutic target for RSV, however the mechanism by which prostacyclin (PGI2) and prostacyclin receptor (IP) signaling modulate RSV pathogenesis is currently unknown. Several studies show that RSV F protein activates toll- like receptor 4 (TLR4) and is a determinant of the inflammatory response to RSV infection.

Objectives

We will (1) define if PGI2 and IP signaling protects against RSV A2-induced illness, pro-inflammatory cytokine production and pathologic dysfunction by downregulating expression of TLR4, (2) test if PGI2 increases lung Tregs in the setting of RSV A2 infection through a TLR4-dependent mechanism, and (3) determine if PGI2 signaling decreases TLR4 expression and RSV-induced cytokine production in both an airway epithelial cell line and primary airway epithelial cells, the cells that line the airway and that are infected with RSV in vivo.

Materials and Methods

Mice: TLR4-/-, TLR4/IP doube KO, and WT BALB/c mice. Virus: RSV A2. Viral clearance: plaque assay, peak interferon gamma (IFN-γ) expression, and viral titers. Inflammation: histopathology. TLR4 expression: Western blot, flow cytometry, real time PCR, immunohistochemistry, and in-situ hybridization after gene amplification by polymerase chain reaction (PCRISH). Iloprost: Alzet mini-osmotic pump. Tregs: flow cytometry and Treg suppression assay. Cell line: 9HTEo. Cytokine expression: ELISA.

Conclusions

Our preliminary data reveal that PGI2 analogs decrease TLR4 expression in bone marrow-derived dendritic cells (BMDC), and that this effect is dependent upon signaling through IP. This is a major paradigm shift in our understanding of the mechanisms by which eicosanoids regulate host innate immune responses in that it is the first data to show that any prostanoid regulates expression of a TLR.

Acknowledgements

Dawn Newcomb

Mentor / Department

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Elizabeth and John Murray Chair in Medicine
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MACROPHAGE IRON HANDLING IN ADIPOSE TISSUE

Merla Hubler
Medical Scientist Training Program

Background

Macrophage phenotypic plasticity in adipose tissue (AT) leads to unique subpopulations in relation to the obesity state of the AT. M1 adipose tissue macrophages (ATMs) have been well classified to play an inflammatory role in AT, inducing insulin resistance and chronic inflammation. M2 ATMs are generally anti-inflammatory due to their cytokine milieu. The actual role of M2 ATMs, and their contribution to insulin senstivity is still relatively undefined. Iron metabolism has been highlighted as a contributor to the regulation of adipogenesis and overall AT insulin sensitivity. The possibility of iron metabolism regulation by ATMs has not been determined.

Objectives

Elucidating the differential handling of iron between M1 and M2 macrophages will help to delineate the role of M2 macrophages in maintaining anti-inflammatory and insulin sensitive homeostasis in lean AT.

Materials and Methods

The perfussion Perl's prussian blue method was used to detect a population of ATMs with high intracellular iron accumulation, which can be separated from the SVF via magnetic column sorting. Gene expression between ferromagentic (MFehi) and non-ferromagentic (MFelo) were compared to compare the expression of genes associated with iron handling. Wild-type Balb/c mice were compared on high fat diet (HFD) to low-fat diet (LFD) for 16 weeks to determine the relative presence of MFehi cells, the inflammatory state of the AT, hepatoctyes and spleen, and the expression profile of their ATMs.

Results

Studies in the Hasty lab have demonstrated that MFehi ATMs are a unique population of M2 ATMs, with a gene expression profile consistent with iron utpake, metabolism, storage and export. HFD is associated with an accumulation of MFelo ATMs with the expected inflammatory phenotype. Interestingly, the MFehi ATMs on HFD also shift towards an inflammatory profile with reduced intracellular iron accumulation and iron handling gene profiles. HFD mice have an increase in iron concentration in the adipocytes, not reflected in other tissues.

Conclusions

The novel identification of divergent iron handling in ATMs will be further explored by determining the influence of iron metabolism on preadipocytes differentiation and to characterize MFehi and MFelo with in-depth genomic and proteomic analysis.

Acknowledgements

Jeb Orr, PhD, Arion Kennedy

Mentor

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WHAT IS THE ROLE OF COPPER DETOXIFICATION AND TOLERANCE IN ACINETOBACTER BAUMANNII PATHOGENESIS?

Lillian Johnson
Medical Scientist Training Program

Background

Acinetobacter baumannii is a gram-negative non-fermenting coccobacillus that is an ever-increasing hospital threat due to its extensive and increasing antibiotic resistance. Relatively little is known about host-pathogen interactions during A. baumannii infection, underscoring the importance of research into these processes. In a process termed "nutritional immunity", hosts restrict essential transition metals to protect against infection, whereas toxic metals are directed against bacteria. To counteract this restriction and toxicity, pathogenic bacteria have evolved high-affinity metal uptake and detoxification systems. This struggle for transition metals plays a key role in determining the outcome of infection. Copper's antimicrobial properties have been known since ancient times. Research into Cu toxicity throughout the last several decades has identified two potential mechanisms by which Cu mediates its antimicrobial effects: (1) Cu accumulation within the cytoplasm leads to oxidative stress and resultant damage, or (2) Cu replaces cognate metals in bacterial enzymes, causing enzymatic dysfunction. However, A. baumannii tolerance to Cu has not been explored to date, despite the recent push to coat medical devices with Cu to prevent A. baumannii transmission.

Objective/Hypothesis

We hypothesize that tolerance to and detoxification of Cu is important for A. baumannii to survive within the host. The goal of this study is to determine what cellular components are required for A. baumannii to survive in copper-enriched media, and whether these components are important for the pathogenesis of this organism.

Materials & Methods

A genetic screen will be used to determine putative copper exporters and copper-induced transcription factors in A. baumanii. Genes of interest will be deleted and phenotypes of isogenic deletion mutants characterized in vitro for susceptibility to copper toxicity and intracellular survival. To determine whether virulence is impaired when Copper detoxification systems are deleted, a mouse model of A. baumannii pneumonia will be utilized.

Results

To be determined

References

Available upon request

Acknowledgements

Eric Skaar, Ph.D., M.P.H.
Skaar Lab, and the Vanderbilt MSTP

Mentor and Department

Eric Skaar, Ph.D., M.P.H.
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INTERROGATING THE NEUROPHYSIOLOGICAL BASIS OF DRAVET SYNDROME USING OPTOGENETICS

Daniel T. Kashima
Medical Scientist Training Program

Background Problem

Dravet syndrome (DS) is a severe, infant-onset epileptic encephalopathy with 70% of patients harboring mutations in the voltage-gated sodium channel SCN1A. The epilepsy and some behavioral features of DS are recapitulated in mice through targeted deletion of Scn1a. Electrophysiological studies of Scn1a+/- heterozygous null mice showed decreased activity of GABAergic interneurons. Thus, some hypothesize that central nervous system hyperexcitability brought about by decreased activity in inhibitory interneurons causes DS. In order to explore this idea, we generated a Scn1a+/- heterozygous null mouse expressing the light-driven cation channel rhodopsin in GABAergic interneurons (Scn1a+/-;VGAT-ChR2). Through electrophysiological recordings combined with light-induced excitation of spatially isolated groups of interneurons, we hope to learn more about the pathophysiology of epilepsy in the DS mouse.

Objectives

To determine if light-induced stimulation of specific groups of interneurons reduces seizure activity and network hyperexcitability in the Scn1a+/-;VGAT-ChR2 mouse line.

Materials and Methods

The Scn1a+/- null heterozygous mice were crossed with VGAT-ChR2 hemizygotes to generate Scn1a+/-;VGAT-ChR2 mice. We will implant fiber optic cables to modulate interneuron activity of DS mice in vivo and monitor seizure activity. Additionally, brain slice electrophysiology will be performed concurrent to light stimulation of specific groups of interneurons to determine the effect on network excitability in the hippocampus.

Results

To be determined

Conclusions

To be determined

Acknowledgments

Vanderbilt Medical Scientist Training Program

Mentor/Department

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CHARACTERIZATION OF THE MDM4 BINDING DOMAIN IN NBS1

Matthew V. Puccetti
Medical Scientist Training Program

Background

Mdm2 (murine double-minute two) and Mdm4 (Hdm2 and Hdm4 in humans) are structurally related proteins essential for the regulation of the p53 tumor suppressor; Mdm2 by ubiquitinating the protein and targeting it for degradation by the proteasome and Mdm4 by altering the transcriptional activity of p53. As negative regulators of p53, both proteins are classified as oncogenes and are frequently overexpressed in a subset of human cancers. Recently, a p53-independent function of Mdm2 has been identified. Previous studies from our lab have identified and characterized a role of Mdm2 in the regulation of the Mre11/Rad50/Nbs1 DNA break repair complex. Specifically, a direct interaction between Mdm2 and Nbs1 has been demonstrated to impair the ability of this complex to repair DNA double-strand breaks. Thus, overexpression of Mdm2 not only inhibits the tumor suppressive properties of p53, but also reduces chromosomal stability through this novel p53-independent function, which likely contributes to tumorigenesis. Recently, we determined that Mdm4 also associates with Nbs1. We hypothesize that Mdm4 has a role in inhibiting DNA double-strand break repair. This project sought to identify the amino acids in the domain of Nbs1 critical for Mdm4:Nbs1 binding.

Objectives

To generate point mutations in the Mdm4 binding domain of Nbs1 that are predicted to inhibit the interaction between Nbs1 and Mdm4.

Materials and Methods

The Mdm4 binding domain was previously localized to a small region in Nbs1. Primers were designed to induce specific amino acid substitutions within this region. Three point mutations were generated by overlap extension PCR.

Conclusions

Point mutations in three amino acids of Nbs1 were generated. Future studies will determine whether this mutant is unable to bind Nbs1 and alter the ability of Mdm4 to regulate the Mre11/Rad50/Nbs1 complex during DNA double-strand break repair.

Acknowledgments

Alexia Melo and the Vanderbilt University MSTP

Mentor and Department

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TREATMENT WITH THE SUGAR A-LACTOSE REDUCES VIRAL TITERS DURING HMPV LOWER RESPIRATORY INFECTION

Meredith Rogers
Medical Scientist Training Program

Background

Human metapneumovirus (hMPV) is a recently identified cause of serious lower respiratory infection (LRI) in infants, the elderly, and the immunocompromised, and accounts for up to 15% of pediatric LRI hospitalizations. CD8+ cytotoxic T lymphocytes (CTLs) function to kill virally infected cells leading to elimination of the pathogen. However, CTLs are functionally impaired in the respiratory tract during hMPV infection. We have previously identified PD-1 as an important mediator of this impairment. However, we hypothesized that other inhibitory receptors also play a role during viral LRI. One such receptor is TIM-3, which has previously been shown to be highly expressed on exhausted T cells present during chronic infections and cancer. Interaction of TIM-3 with its ligand Galectin-9 (Gal-9) suppresses CTL responses during other acute infections. The sugar α-lactose is a natural antagonist for this interaction.

Objective

To determine whether α-lactose disrupts the TIM-3/Gal-9 interaction during hMPV infection leading to reversal of CTL impairment and/or reduced viral titers.

Methods

Mice were infected intranasally with hMPV, then injected twice daily with 10% α-lactose. Noses, lungs, and spleens were harvested to assess viral titers and to quantify CTL functions by flow cytometry.

Results

α-lactose treated mice had lower hMPV titers in the lung and nose. Splenocytes and lung lymphocytes from α-lactose treated and control mice had equivalent CTL responses.

Conclusions

α-lactose treatment decreased hMPV titers, however the mechanism for this effect remains to be determined. TIM-3 may act synergistically with other inhibitory receptors, such as PD-1, to cause CTL impairment during hMPV infection. These data indicate that further exploration of a-lactose is warranted to determine if it may possess therapeutic potential for pediatric LRI.

Acknowledgements

John Erickson
Sharon Tollefson

Mentor and Department

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IMMUNOLOGICAL POLARIZATION IN RESPIRATORY SYNCYTIAL VIRUS INFECTION

Matt Stier
Medical Scientist Training Program

Background

Respiratory syncytial virus (RSV) is a major cause of acute respiratory infection in infants and young children. Strain-specific viral differen ces appear important for immunogenicity and the polarization towards either Th1 or Th2 responses. Known clinical variance in morbidity and mortality upon RSV infection may be related to this viral strain-dependent polarization. Moreover, the subsequent development of allergic asthma has been correlated with certain exposures to RSV infection as an infant, necessitating a clearer understanding of how the immune response develops in the context of heterogeneous RSV strains.

Objectives

1. Elucidate the initial precipitating factors in RSV-associated Th1 versus Th2 polarization. 2. Clarify the role of the RSV F protein variants in driving differential cytokine production.

Materials and Methods

RSV strains 0-1/2-20 (Th2), rA2-LongF (Th1), and rA2-Line19F (Th2) were administered intranasally at 1.5E6 PFU to Balb/c mice (Charles River). Mice were harvested up to 96 hours post-infection. Left and right lungs were processed for protein and cDNA, respectively. ELISA (R&D DuoSet) and quantitative PCR (SYBR Green) were used to measure IL-25, IL-33, and TSLP.

Results

Infection with RSV strain 0-1/2-20 led to detectable protein and mRNA levels. IL-25 mRNA and protein peaked at 3hr and 6hr post-infection, respectively. IL-33 mRNA and protein peaked at 12hr post-infection. TSLP mRNA and protein peaked at 12hr post-infection. Infection with RSV strains rA2-LongF and rA2-Line19F did not lead to detectable protein levels for TSLP and IL-25.

Conclusions

RSV strain 0-1/2-20 showed appreciable expression of IL-25, IL-33, and TSLP. Data for RSV rA2-LongF and rA2-Line19F were equivocal due to insufficient assay sensitivity. Other results were inconclusive, pointing to the need for additional data.

Acknowledgements

I am grateful for the technical and intellectual assistance of Shinji Toki, Kasia Goleniewska, Dan Dulek, and Dawn Newcomb and thankful for the support of Dr. Peebles and the Vanderbilt MSTP.

Mentor(s) and Department

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Department of Medicine

THE ROLE OF THE NOREPINEPHRINE TRANSPORTER IN GLOBAL BONE HOMEOSTASIS AND REMODELING

Yuantee Zhu
Medical Scientist Training Program

Background

Bone actively remodels to maintain integrity after micro/macroscopic injury. This process is regulated both systemically and locally. Deficits in these systems results in bone metabolic diseases such as osteoporosis. The central nervous system (CNS) plays a role in controlling bone remodeling, and is believed to act via the SNS.

Sympathetic signaling is controlled by the norepinephrine transporter (NET). Previous work in our lab suggests NET is required for peak bone mass; demonstrated by the osteopenia in mice with either globally or pharmacologic NET blockade. However, the low SNS outflow in these models suggests another mechanism independent of the peripheral SNS in regulating bone homeostasis.

Hypothesis

NET inhibition mediates bone loss primarily through a CNS mechanism.

Materials and Methods

WT and NET-KO mice were assessed for biochemical, functional, and histological phenotype. In brief, cellular mRNA and protein expression were measured using quantitative PCR and Western blotting, respectively. Serum hormone levels were detected by ELISA. Histological quantification of tissue sections was performed with image analysis software and cell- or bone-specific staining.

Results

Mice deficient in NET activity exhibit low bone mass yet have paradoxically decreased SNS outflow. Analysis of circulating hormones show decreased corticosterone, but without a compensatory increase in central CRF. Additional results are pending further experiments.

Conclusions

The low bone mass in NET-deficient mice can be partially explained by a central dysregulation of the CRF-ACTH-corticosterone axis. Further work needs to be done to determine whether NET in the CNS or the peripheral osteocytes is responsible for bone remodeling.

References

Available upon request

Acknowledgements

I would like to thank Dr. Yun Ma for her guidance, and extensive and ongoing work on this project.

Mentor and Department

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Jayant Shenai, M.D. is the Director of Educational Affairs for the Division of Neonatology, Vanderbilt Children's Hospital. His primary research interests include vitamin A in relation to chronic lung disease in pre-term infants and related clinical applications. As the Editor-in-Chief of Neo Reviews Plus, he contributes to the Self Assessment Program for neonatologists developed by the American Academy of Pediatrics. He participates in the grant review process at the National Institutes of Health as a member of the Study Section of Reproductive Biology. He is an Amos Christie Award winner for his outstanding teaching accomplishments and was a 2006 recipient of an Institutional Teaching Award for his contribution to continuing medical education. He was a founding member of the Academy for Excellence in Teaching.

Patient-Oriented Research

The area of Patient-Oriented Research addresses:

1. The mechanisms of human disease,
2. Therapeutic interventions,
3. Clinical trials,
4. The use of new technologies for the diagnosis, treatment, or prevention of disease, and
5. The emotional, social, development and behavioral mechanisms of health and disease.

In addition to standard randomized clinical trials, patient-oriented methodologies also include self-perception measures (e.g., patients completing questionnaires), interviews, and focus groups. The core of this focus group is the scientific study of human participants to understand the cause of disease, health, and function. This understanding contributes to therapy and prevention. Clinically derived scientific knowledge, laboratory science, and patient-oriented science are core disciplines of the medical profession.

"The Emphasis Program provides me a unique opportunity to nurture aspiring medical students in the field of clinical research. The motivation to learn from each clinical encounter, fostered by the patient oriented research of the Emphasis Program, is likely to transform each participating student into a life-long learner, effective problem-solver, and compassionate thinker. To paraphrase William Osler, 'No matter trifling the clinical question at hand, answer it with a feeling that is demands the best that it is in you, and when done look it over with a critical eye, not sparing a strict judgment of yourself.' Through the auspices of the Emphasis Program, I wish to inculcate such a spirit of reflection in each medical student."

"The Emphasis Program provides a unique opportunity to nurture aspiring medical students in the field of clinical research."

OBSERVING FACTORS CONTRIBUTING TO BLOOD WASTAGE IN THE PERIOPERATIVE ENVIRONMENT

Oluwaseun Arije, Bushrah Mushtaq
Patient Oriented Research

Background Problem

Multiple factors contribute to red blood cell (RBC) wastage in the perioperative environment. To assess potential areas of improvement, a comprehensive analysis was undertaken to identify non-value added steps and inefficiencies in blood delivery systems that increase the risk of product wastage. Because the margin between supply and demand continues to narrow and blood products costs continue to rise, the reduction of wastage is vital.

Objectives

To identify problems in the blood supply chain that could have a impact on financial costs to the medical center and potentially patient safety.

Materials and Methods

Study design and methods: A time-and-motion study was conducted to determine the process steps used to deliver units of RBCs from the hospital blood bank to surgical patients in the operating room. Observations started at the time RBC orders were received by the blood bank and ended when the RBCs were transfused into the patient or were returned to the blood bank. Temperature data was also recorded at key transition points during the delivery process in the blood bank and perioperative environment. Retrospective audits of reported data and required regulatory documentation surrounding RBCs were performed.

Results

Pneumatic tube delivery caused RBC wastage in surgical cases that did not have a cooler already present in the room from a previous order because minimum turnaround times exceeded 15 minutes.

Conclusions

We have demonstrated that it is possible to implement complementary human factors engineering and quality improvement methods to garner a systems view of the perioperative transfusion processes to inform the prioritization and development of improvement strategies at a large academic medical center.

References

References Available Upon Request

Acknowledgements

Christopher S. Baker, Daniel J. France, Bushrah Mushtaq, Oluwaseun Arije, Michael A. Pilla,Eileen Ricker, Stephanie Sephel, Garrett S. Booth

Mentor / Department

Dan France Anesthesiology

DECODING THE ANTICIPATION OF MONETARY AWARDS: A MULTIVARIATE PATTERN ANALYSIS

Daniel F. Arteaga
Patient Oriented Research

Background Problem

The anticipation of potential rewards or losses modulates broad neural networks involved in motivation and task execution. To date, distinctions between the neural representations underlying the motivational effects of potential monetary rewards and losses have yet to be clearly elucidated using conventional univariate analyses of fMRI data.

Objectives

Here, we investigated the ability of multivariate pattern analysis (MVPA) to discriminate between the anticipation (preparation to respond for) and feedback of monetary gains and losses.

Materials and Methods

Data was obtained from twenty-five healthy subjects who performed a monetary incentive delay (MID) task while undergoing fMRI. Whole-brain multivariate analyses were initially performed to establish the predictive capabilities of the multivariate classifier. Multivariate searchlight maps were then computed and compared with a parallel set of GLM-based univariate analyses.

Results

Our results reveal that MVPA is capable of reliably decoding between an anticipated monetary gain and loss (accuracy=56.3%, p=3.33x10-7). While there was overlap in significant voxel clusters detected by both univariate and multivariate methods, the MVPA results were much more robust. Notably, MVPA revealed the involvement of medial frontal and occipital regions that were substantially more active under conditions of large potential rewards than large potential losses. By contrast, ventral striatal areas that are robustly modulated when there are incentives showed little or no discrimination of the valence of monetary incentives.

Conclusions

These data indicate that specific cortical areas are differentially recruited in valence-dependent reward processing. Our findings further demonstrate the potential utility of a multivariate approach in affective neuroscience.

Mentor / Department

David H. Zald, Department of Psychology

A GAIT-ACTIVATED NEUROMUSCLAR STIMULATION (GANMS) DEVICE IMPROVES STRENGTH, BALANCE AND MUSCLE CHARACTERISTICS OF CHILDREN WITH HEMIPARETIC CEREBRAL PALSY

Jeremy Chan
Patient Oriented Research

Background Problem
Every year 11,000 US infants and children receive a new diagnosis of cerebral palsy but evidence-based therapies to improve functional outcome are extremely limited. Currently, rigid ankle-foot orthoses (AFOs) are the standard of care for gait improvement. Unfortunately, AFOs do little to improve muscle strength, growth, and spasticity.

Objectives
To measure the effectiveness of a Gait-Activated Neuromuscular Stimulation (GANMS) device in improving muscle functionality, strength and elasticity in children with cerebral palsy who are currently using AFOs.

Materials and Methods
This was a prospective interventional study of a single-unit GANMS device worn daily after a 2 week ramp-up. Ten children ages 5-17 years (median 10) with hemiparetic spastic cerebral palsy (GMCSF 1-2), all of whom wore AFOs prior to the start of intervention, participated in the study. Two baselines were obtained, 6 week prior and one day prior to the start of the intervention. During the study period a stretching AFO was worn every night. Statistical analysis was performed using paired samples T-Tests. Manual muscle test results and ultrasound measures wer referenced to the unaffected limb. Six weeks post-intervention assessments are reported.

Results
There were no changes in any measures between baseline timepoints. There were significant improvments in knee extension (77.4 Nm vs. 89.4 Nm, p =0.03), ankle dorsiflexion (37.6 Nm vs. 53.2 Nm, p=0.04), and balance (Pediatric Berg Balance Score: 49 vs. 51, p=0.02) after 6 weeks of GANMS use to the affected extremity. Patients also showed decrease fiber strain in the tibialis anterior muscle after GANMS use (25.6 degrees/mm2 vs. 1.4 degrees/mm2, p=0.05). All range of motion measures were stable after the intervention despite lack of daytime AFO.

Conclusions
This is the first report of a therapy for children with cerebral palsy which improves strength, balance and muscle elasticity while decreasing spasticity and without range of motion loss.

Acknowledgements
Shirley Gogliotti, Cherri Rooks, Laura Flynn, Heidi Kessler, Ellen Shaw Ashley Schilling, Donna Trotter, Gena Henderson Amy Rosen, Bruce Damon, Theodore Towse

Mentor / Department
Nathalie Maitre Department of Neonatology

MDMA USE IS ASSOCIATED WITH LOWER GRAY MATTER VOLUME IN WIDESPREAD CORTICAL REGIONS

Andrew Dornan
Patient Oriented Research

Background Problem

MDMA (Ecstasy) has been a popular recreational drug for 25 years and is now in trials as an adjunct to psychotherapy. Animal models show serotonergic neurotoxicity at high doses, while human studies suggest that recreational exposure is correlated with lower serotonin signaling and long-term cognitive changes.

Objectives

To determine whether lifetime MDMA use is associated with cortical gray matter volume. Prior studies have been equivocal, with some showing lower gray matter in MDMA users and others showing no difference.

Materials and Methods

We recruited 41 MDMA users (mean 31.3 lifetime MDMA episodes) and 30 non-users aged 18-34 and abstinent from recreational drugs (excluding nicotine and caffeine) for at least two weeks. Cortical gray matter, white matter and CSF volume were measured using structural MRI scans and analyzed using voxel-based morphometry (VBM) with DARTEL, controlling for age, polydrug use and total intracranial volume. We examined both exposure-response correlation and between-group differences.

Results

Lifetime MDMA use was negatively associated with gray matter volume in bilateral regions of the frontal, temporal, and limbic lobes (correlation coefficients ranged from -0.55 to -0.71), with no regions featuring a positive association. In the between-group analysis, MDMA users had lower gray matter volume in all lobes, with the largest differences in the right supplementary motor area and left middle temporal gyrus. Over the entire brain, the ratio of gray and white matter volume to total intracranial volume was 3.5% lower in MDMA users.

Conclusions

Recreational use of MDMA is associated with lower cortical gray matter volume. Further research is needed to determine the functional consequences of lower gray matter volume and whether the difference pre-exist MDMA use or result from MDMA exposure. MDMA neurotoxicty in rats involves destruction of serotonergic axons, not cell bodies, so a causal link is likely to depend on serotonin's possible neurotrophic role rather than direct cytotoxicity.

References

References Available Upon Request

Acknowledgements

TJ Watkins, MS Dietrich, MM Benningfield, JU Blackford, RM Salomon

Mentor / Department

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UTILIZING ACCELEROMETRY TO MEASURE PHYSICAL ACTIVITY IN PEDIATRIC PATIENTS WITH IMPAIRED CARDIOPULMONARY FUNCTION

Stessie Dort
Patient Oriented Research

Background Problem

Nearly 1% of newborns in the United States are diagnosed with congenital heart disease and have symptoms that vary in severity including pulmonary arterial hypertension [1].This destructive pulmonary vascular disease often results in right heart failure and transplantation or death within 5 years. There are no FDA approved drug treatments for children diagnosed with PAH [2]. In adults, the six-minute walk distance (6MWD) is used clinically and by the FDA to assess the progression of symptoms and response to treatment in PAH and has been correlated with mortality [3]. However, this test is unreliable and impractical in children. Studies performed in the adult population using accelerometry have been shown to positively correlate with 6MWD and PAH functional class [4]. No similar study has been conducted in children or to correlate physical activity measures with quality of life in all ages.Accelerometers are small and non-invasive devices that have the capacity to measure physical activity in ambulatory free-living individuals [6,7].Parental-report measures of outdoor playtime have been shown to positively correlate to accelerometry measures [8].

Objectives

We tested whether Actigraph accelerometers could be used to measure physical activity in children with impaired cardiopulmonary function secondary to congenital heart disease and correlated to invasive pulmonary hemodynamic measures and parent-reported child outdoor playtime. We assessed whether baseline activity measures of subjects with congenital heart disease is significantly different then healthy controls.

Materials and Methods

Children (2-7 years old) with atrial septal defects were recruited from Monroe Carell Jr. Children's Hospital at Vanderbilt. Healthy controls (2-7 years old) After obtaining consent, parents and children were instructed on the proper use of the ActiGraph accelerometer device and asked to complete a validated outdoor playtime questionnaire. After at least 2 days of ActiGraph wear, metrics were obtained from the device and scrutinized using the Actigraph 6 data analyzing software. Invasive pulmonary hemodynamic measures were obtained from patient charts. All sensitive information was properly stored in a REDCap database.

Results

Mean age of the children in the control group was 5.3 years of age. Mean age of subjects with ASD is 5.5 years of age. All children are Caucasion and resided in Tennessee or Kentucky.None of the subjects had a diagnosis of PAH at baseline. Subjects with ASD wore accelerometers for an average of 591.3 minutes (95% CI 648.58 to 533.9) per day over two consecutive days compared to controls which average 761.2 minutes (95% CI 767.4 to755.0). Subjects with ASD spent 78% of ActiGraph wear-time sedentary or at rest. Subjects with ASD recorded 69.1 (95% CI 84.5 to 53.61) light activity counts verses 119.25 (95% CI 143.4 to 95.1) in healthy controls. Subjects with ASD recorded 45.3 (95% CI 62.0 to28.7) moderate activity counts verses 98.5 (95% CI 115.9 to 81.0) in healthy controls. Subjects with ASD recorded 15.8 (95% CI 23.8 to 7.9) vigorous activity counts verses 60.1 (95% CI 71.0 to 49.1) in healthy controls. Parents of participants with ASD reported that their child spend a mean 345 minutes (95% CI 374.4 to 315.6) playing outdoors each day compared to 330 minutes reported by parents of healthy controls.

Conclusions

Unique barriers exist for children with ASD that impact accelerometer wear-time that are not present in healthy controls. Additionally, children with ASD participate in significantly less light, moderate, and vigorous physical activity than their healthy controls counterparts. Accelerometry does not correlate with the parental reported outdoor playtime checklist in children with ASD. Furthermore, parents of children with ASD over-report their child's outdoor playtime. This should be considered in clinical encounters when quality of life is being assessed.

References

References Available Upon Request

Acknowledgements

I would like to acknowledge Eric Austin M.D., Drew Ammons M.D., Maciej Buchowski PhD., and Dr. Anna Hemnes M.D. for their mentorship and support and the Vanderbilt Institute for Clinical and Translational Research and the Vanderbilt School of Medicine Emphasis Program.

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REDEFINING SOFT TISSUE SARCOMA SURGICAL MARGINS WITH OPTICAL SPECTROSCOPY

Zain Gowani
Patient Oriented Research

Background Problem

Soft tissue sarcomas (STS) are a heterogeneous group of malignant mesenchymal tumors that are treated by surgical excision with a wide margin of surrounding tissue. Margin status is a central prognostic factor for curative treatment and patient survival. Current clinical practice employs frozen section pathology to evaluate margins, but this method prolongs procedure time, can increase surgical complication risk, and has limited utility near challenging anatomy and critical structures. Raman spectroscopy, a non-invasive optical technique, may be a more functional alternative. This method yields a biochemical fingerprint for tissues and can identify subtle cancer-associated biochemical changes. The technique is ideal for in vivo clinical diagnosis because it is rapid, specific, and non-destructive, and allows for intraoperative detection of residual tumor cells. This study explored the feasibility of evaluating STS margins by Raman spectroscopy.

Objectives

The goal was to determine whether biomolecular data collected by Raman spectroscopy can accurately discriminate between tumor and control tissue in STS margins.

Materials and Methods

Raman spectra were collected using a portable fiber-optic system. STS margin biopsies from 20 patients were tested, yielding 44 spectra from tumor tissue and 33 spectra from muscle tissue.

Results

Multivariate statistical analysis discriminated tumor and muscle spectra from in vitro and preliminary in situ data with 100% sensitivity and 100% specificity.

Conclusions

These results underscore the potential of Raman spectroscopy in evaluating STS margins, opening a new avenue for rapid intraoperative margin assessment.

References

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Acknowledgements

Quyen Nguyen, PhD; Anita Mahadevan-Jansen, PhD; Isaac Pence; Evelyn Okediji

Mentor / Department

Dr. Ginger Holt, Department of Orthopaedic Surgery & Rehabilitation; Dr. Xiaohong Bi, Department of Biomedical Engineering

MELATONIN SUPPRESSES TACHYCARDIA IN POSTURAL TACHYCARDIA SYNDROME (POTS): A RANDOMIZED, CROSSOVER TRIAL

Beth Green
Patient Oriented Research

Background Problem

Postural Tachycardia Syndrome (POTS) induces disabling chronic orthostatic intolerance with an excessive increase in heart rate (HR) upon standing, and many POTS patients have a hyperadrenergic state. Medications that restrain heart rate are a promising approach to this problem. Melatonin is an endogenous indoleamine secreted by the pineal gland that is involved in the regulation of the circadian rhythm and acts as a signal for darkness. Melatonin is also involved in the regulation of the cardiovascular system. In previous studies, exogenous melatonin has produced varying effects on HR and blood pressure (BP) in healthy adults, and significantly decreased standing plasma norepinephrine levels in healthy women.

Objectives

We tested the hypothesis that melatonin will attenuate the tachycardia and improve symptom burden in patients with POTS.

Materials and Methods

In this protocol, patients with POTS (n=78) underwent acute drug trials with melatonin 3 mg orally and placebo, on separate mornings, in a randomized crossover design. Blood pressure, HR and symptoms were assessed while seated and after standing for up to 10 minutes prior to and hourly for 4 hours following study drug administration.

Results

Standing HR was significantly lower two hours after melatonin compared to placebo (102±17 vs. 109±17 bpm; $P<0.001$). Standing systolic blood pressure was not affected (PInt=0.536). The symptom burden was unchanged with melatonin compared with placebo (PInt=0.117).

Conclusions

Oral melatonin produced a modest decrease in standing tachycardia in POTS. Further research is needed to determine the effects of regular night-time use of this medication in POTS.

Acknowledgements

Bonnie K Black RN CNP, Italo Biaggioni MD, Sachin Y Paranjape BS, Kanika Bagai MD MSCI, Cyndya Shibao, MD, MSCI, Miriam C Okoye, William D. Dupont PhD, David Robertson MD

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THE ASSOCIATION OF NGAL AND CYSTATIN-C WITH WORSENING RENAL FUNCTION AND 5 AND 30-DAY EVENTS IN ACUTE HEART FAILURE PATIENTS

Brendan Hayes
Patient Oriented Research

Background Problem

Acute heart failure (AHF) represents the leading cause of hospitalization for patients over 65. Although only 10% of admitted AHF patients are acutely ill, over 80% of ED patients with AHF are admitted to the hospital. Moreover, those discharged primarily from the ED have a 90-day adverse event rate of over 60%. Determining which patients can be safely discharged from the ED and avoid hospitalization is problematic. Renal dysfunction has been associated with an increased risk for adverse events in AHF patients. Urine neutrophil gelatinase-associated lipocalcin (NGAL) and serum cystatin-C (CysC) are renal biomarkers that have been shown to be elevated in worsening renal function (WRF) earlier than creatinine.

Objectives

Investigate the individual and combined utility of both urinary NGAL and serum CysC in predicting WRF over 72-96 hours and 5-day and 30-day adverse events in AHF patients presenting to the ED.

Materials and Methods

Patients (n=302) were chosen from a previous prospective, observational cohort study of adults presenting to Vanderbilt and four Cincinnati EDs with AHF signs and symptoms. Adverse events were defined as the following: death, ED visit for AHF, hospital admission for AHF, or emergent dialysis. The sensitivity and specificity of NGAL, CysC, and GFR were calculated. NGAL and CysC “positive for disease” were respectively defined as baseline values above the cohort medians.

Results

The sensitivities of NGAL and CysC separately for predicting WRF were 0.64 and 0.56, while the combination of NGAL-CysC yielded a sensitivity at 0.82. The sensitivities of NGAL, CysC, and GFR for 5-day events were 0.63, 0.50, and 0.44, respectively, while the NGAL-GFR combination yielded the highest sensitivity at 0.81. The sensitivities of NGAL, CysC, and GFR for 30-day events were 0.54, 0.48, and 0.54, respectively, while the NGAL-GFR combination yielded the highest sensitivity for 30-day events at 0.72.

Conclusions

In AHF patients, the combination of urinary NGAL and serum CysC is useful for detecting WRF, but the NGAL-GFR combination is more useful for 5-day and 30-day events than the combination of NGAL-CysC.

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Acknowledgements

Dandan Liu, PhD Edward Siew, MD Alp Ikizler, MD Gregory J. Fermann, MD Kimberly Hart, MS Christopher J. Lindsell, PhD Karen Miller, RN Matthew I. Sperling Sue Roll, RN Doug Sawyer, MD

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INVESTIGATING SERUM HCG, AFP, CA-125, CRP, AND MATERNAL AGE AS PREDICTORS OF ECTOPIC PREGNANCY

Tenisha James
Patient Oriented Research

Background Problem
Ectopic pregnancy (EP) causes significant morbidity and mortality. No single serum biomarker can identify EP in symptomatic pregnant women at emergency department (ED) presentation.

Objectives
To determine the diagnostic utility of hCG, AFP, CA-125, CRP, and maternal age (age) to predict EP at presentation to the ED in pregnant women with symptoms of vaginal bleeding, abdominal pain, or cramping.

Materials and Methods
This retrospective case-control pilot study enrolled 93 pregnant women < 10 weeks gestation presenting to the ED with vaginal bleeding, abdominal pain and/or cramping (12 EP, 30 spontaneous abortions (SA), 51 viable intrauterine pregnancies (VIP)). Residual serum specimens sent to the VUMC laboratory for hCG testing were utilized. Age and diagnosis were determined by review of the electronic medical records. Diagnoses were verified by ultrasonic or laparoscopic visualization, serum hCG trends, and assessment of fetal cardiac activity. Serum hCG, AFP, CA-125, and CRP were measured on the Siemens Immulite. Areas under receiver operator characteristic curves (AUCs) were used to evaluate diagnostic utility of age and biomarkers to predict EP. Kruskal-Wallis Test was used to detect statistically significant differences in age, hCG, AFP, CA-125, or CRP concentrations among EP, SA and VIP.

Results
The AUCs for age, hCG, AFP, CA-125, and CRP were 0.63, 0.71, 0.57, 0.80, and 0.51, respectively. At 92% sensitivity, specificities were 11%, 53%, 15%, 62%, and 9.8%, respectively. Median hCG concentrations were significantly different ($p<0.05$) between viable and non-viable pregnancy (EP or SA), but not between EP and SA. Median CA-125 concentrations were significantly different between EP and non-EP, but not between SA and VIP. Median CRP and AFP concentrations and age were not significantly different between EP, SA, and VIP.

Conclusions
Serum hCG demonstrated moderate clinical utility to predict EP in symptomatic patients. CA-125 demonstrated clinical utility superior to all tested biomarkers and age. Future plans include logistic regression analysis.

References
References Available Upon Request

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ASSESSING BILATERAL VOLUMETRIC DIFFERENCE IN THE AMYGDALA OF SHY CHILDREN

Michael Maggart
Patient Oriented Research

Background Problem

Temperamental shyness, which includes wariness and avoidance of new people and situations, bears an increased risk of developing social anxiety, depression, and substance abuse. Shyness likely has a biological basis, given the greater incidence of monozygotic twins that both exhibit the inhibited behavior, as well as an intergenerational tendency for shyness. Research in the neural basis of shyness has implicated greater amygdala activation in adults and a recent study suggests that increased amygdalar activation is the result of increased gray matter volume in the amygdala. While it is well established that shyness is relatively stable across development, it remains unknown whether the amygdala is enlarged in shy children.

Objectives

We sought to determine whether amygdala gray matter volume is larger in shy children. To quantify amygdala gray matter volume differences, we compared volumes of socially inhibited and uninhibited children, aged 8 to 15 years, using MR imaging.

Materials and Methods

Subjects were twenty-eight children, aged eight to fifteen years (8 shy, 20 non-shy). Structural Magnetic resonance images (MRI) were collected on a 3T scanner at the Vanderbilt University Institute for Imaging Sciences. Two single-blinded raters manually segmented left and right amygdalae using standard methods. An analysis of covariance was used to test for group differences in amygdala volume with sex, age, and intracranial volume included as covariates.

Results

No significant difference was found between the shy and control groups of children.

Conclusions

Failure to find any change in amygdala gray matter volume of socially inhibited children suggests that amygdalar hypertrophy viewed in adults could be a consequence, rather than cause, of shyness.

Acknowledgements

Dr. Jennifer Blackford, Jacci Clauss, Ross Van Der Klok, and Dr. Margaret Benningfield

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NEUROPSYCHOLOGICAL EFFECTS OF DEEP BRAIN STIMULATION IN EARLY STAGE PARKINSON'S DISEASE

Alexandra May
Patient Oriented Research

Background Problem

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an effective treatment for motor system fluctuations in advanced Parkinson's disease (PD) that can no longer be controlled by dopaminergic replacement therapy. STN DBS improves quality of life, reduces requirement for high doses of dopamine medication, and reduces financial burden (1-3). There may be benefit to starting STN DBS in early stages if long-term stimulation is safe.

Objectives

The purpose of the clinical trial is to determine the safety and tolerability of chronic stimulation in early stage PD. Cognitive and neurobehavioral changes will be assessed over a two-year follow-up.

Materials and Methods

We conducted a single-blind randomized controlled clinical trial in early PD comparing fifteen patients on STN DBS and optimal drug therapy (ODT) to fifteen people on ODT alone. While off stimulation and after a 7 day medication wash out, participants were evaluated on a battery of 12 tests yielding a total of 22 specific neuropsychological variables every 6 months for two years.

Results

At 12 months, the ODT alone group performed slightly better on phonemic (letter) fluency ($p = 0.047$) and Stroop Color/Word tests ($p = 0.035$) compared to baseline. The change in scores from baseline to 12 months between the two groups was also significant for phonemic fluency and Stroop Color/Word tasks ($p = 0.036$ and $p = 0.002$, respectively) with the ODT group performing better on both tests. At 24 months, most of the differences seen at 12 months were resolved with no differences in the change in scores over time between the two groups.

Conclusions

STN DBS in early stage PD does not significantly impair neuropsychological performance within a two year follow-up. This is an ongoing study that is still undergoing analysis and will follow patients for 5 years.

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Acknowledgements

Tramontana MG, Molinari AL, Konrad PE, Davis TL, Wylie SA, Neimat JS, Phibbs FT, Hedera P, Gill CE, Salomon R, Want L, Charles PD

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Dr. David Charles (Department of Neurology), Dr. Tramontana (Department of Psychiatry), Anna Molinari,

METABOLIC SYNDROME IN ELITE ATHLETES

E. Michael Powers
Patient Oriented Research

Background Problem

Metabolic syndrome (metsyn) is caused partly by insulin resistance and oxidant stress and is linked to obesity and physical inactivity. Previous studies of collegiate football linemen have shown that 50% have metsyn during their playing career.

Objectives

The objective of this study is to test the hypothesis that the type of training lineman undertake, together with weight gain achieved through positive energy balance via a high-fat, high-calorie diet, generates oxidant stress and, thereby, the metabolic syndrome.

Materials and Methods

Clinical metsyn was assessed via AHA/NCEP guidelines along with research biomarkers (resting energy expenditure, flow-mediated brachial artery dilation (FMD), radial arterial tonometry, body composition, and oral glucose tolerance) and diet composition in the Vanderbilt Clinical Research Center.

Results

Preliminary analysis shows the prevalence of clinical metsyn in linemen was 80% (12/15) and 6% (1/18) in non-linemen. Significant differences were found in in FMD in metsyn (0.029 +/- 0.004 cm) vs. non-metsyn (0.040 +/- 0.003 cm; p=.03), small artery elasticity in metsyn (13.5 +/- 0.6 mL/mm Hg x100) vs. non-metsyn (11.6 +/-0.6 mL/mm Hg x100; p=.04)), F2-isoprostanes in metsyn (0.46 ± 0.03 ng/mg Cr) vs. non-metsyn (0.35 ± 0.03 ng/mg Cr), and C-reactive protein in metsyn (1.53 +/- .37 mg/L) vs. non-metsyn (.58 +/- .77 mg/L; p=.02), which is strongly correlated to trunk fat mass (R=.75, p=.0006). Typical elevation in respiratory quotient was not observed in metabolic syndrome cases.

Conclusions

Collegiate linemen have metsyn at an alarming rate with a unique set of risk factors, but the long-term implications are unknown. Elevated F2-isoprostanes suggest that increased oxidant stress may have an etiological role in metabolic syndrome in this population. These results provide strong rationale to conduct larger, longitudinal studies.

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Acknowledgements

Vanderbilt CTSA grant UL1 TR000445 from NCRR/NIH, Vanderbilt Diabetes Research and Training Center (DRTC) and Vanderbilt Center for Human Nutrition (VCHN), Vanderbilt Summer Research Training Program (T35 DK007383)

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RISK OF SECONDARY MALIGNANCIES IN SURVIVORS OF CHILDHOOD LEUKEMIA

Mythri Reddy
Patient Oriented Research

Background Problem

The survival rate for childhood leukemias has improved dramatically since 1975. For acute lymphoblastic leukemia (ALL), the most common childhood cancer, survival rates for patients treated with contemporary protocols have reached over 80%. For acute myeloid leukemia (AML), survival rates have increased from 20% in the 1970s to 55% currently. However, survivors of any childhood cancer are at increased risk of subsequent neoplasms. Identification of risk groups for the development of secondary malignant neoplasms will affect prognosis, follow-up and treatment for children with leukemia.

Objectives

The purpose of this study is to evaluate risk and characteristics of secondary malignant neoplasms in survivors of all childhood leukemias.

Materials and Methods

Incidence of secondary malignancy in survivors of childhood ALL and AML were analyzed using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. Patients diagnosed with AML or ALL between the ages of 0-18 years who survived at least 5 years after diagnosis were included in analysis. Cumulative incidence of secondary malignancy at 30 years was calculated along with comparisons based on type of leukemia, age, gender, race and treatment era.

Results

A total of 4,806 patients were included in the analysis. Median follow-up was 14.5 years (range 5.0-35.9 years). A total of 91 patients developed a second malignancy. The most common second tumor was brain (23.0%) followed by thyroid (20.9%). Cumulative incidences of secondary malignancy at 30 years for all patients, for ALL patients and for AML patients were 5.8%, 5.6%, and 7.7%, respectively (p=0.046). Patients were at an increased risk of malignancy compared to the general US population with an SIR of 3.9 (95% CI 3.2-4.8). Cumulative incidence of second malignancy at 10 years was increased for patients treated after 1995 (0.622% vs. 0.293%, p = 0.002).

Conclusions

Survivors of childhood leukemia are at an increased risk of secondary malignancies compared to the general population while patients with AML have the highest risk. Continued follow-up will be needed to assess whether the curve will plateau for patients treated with modern therapy.

References

References Available Upon Request

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CONTROLLING WASTE WITH MASSIVE TRANSFUSION PROTOCOLS

Vasanth Sathiyakumar
Patient Oriented Research

Background Problem

One avenue in lowering healthcare expenditure may be controlling preventable waste with blood product utilization and transfusion practices in the OR, particularly in the setting of massive transfusion for patients with major hemorrhage. While intraoperative transfusion protocols have streamlined the process of blood product delivery, it is unknown whether they may increase waste.

Objectives

We sought to identify which blood components were wasted in two large blood-requiring procedures – a standardized protocol in MTP for traumatic patients and a non-standardized protocol in orthostatic liver transplants (OLT). By identifying specific areas of wastage associated with the process of blood product administration, we propose a simple intervention to reduce product waste.

Materials and Methods

After approval, we reviewed MTP cases from 2008 to 2009 and OLT cases in 2009. Blood bank and medical records were reviewed for demographic information, number of products sent from the blood bank and transfused in the OR, and number of blood products returned to the blood bank or wasted. MTP and OLT cases were compared using rank sum, Fisher's exact tests, and multivariate analysis.

Results

We reviewed 202 MTP cases and 52 OLT cases. For OLT cases, there were no significant odds predicting wastage when controlling for blood products transfused or returned. However, for MTP cases, platelet transfusion resulted in a 5.0 lesser chance of wastage ($p<.05$). Returning platelets resulted in a 10.0 greater chance of wastage ($p<.05$). The majority of platelet wastage occurred due to unacceptable temperature ranges of unopened platelets upon return to the blood bank.

Conclusions

This is the first study of its kind to investigate in a process improvement standpoint wastage associated with MTP and OLT protocols in terms of transfusion and returns to the blood bank. A simple intervention of reminding operative room technicians to return unopened platelets outside of coolers can result in reducing wastage.

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THE ROLE OF RADIATION IN CARCINOMA EX PLEOMOPHIC ADENOMA

Arnold Silverberg
Patient Oriented Research

Background Problem

Carcinoma ex pleomorphic adenoma (CXPA) is a rare, aggressive tumor that accounts for approximately 11% of salivary gland malignancies (1). These tumors most commonly occur in the parotid and submandibular glands, but can also affect the minor salivary glands, lacrimal glands, and breast tissue (2). Treatment consists of surgical resection with or without post-operative radiation therapy. The role of radiation therapy has not been well defined, and little data is currently available to guide clinical decision making (2). Single institution retrospective reviews have suggested that post-operative radiation therapy can improve both local control and overall survival in node negative patients (3).

Objectives

We investigated the patient and tumor characteristics as well as treatment modality in the outcome of patients with CXPA using the National Cancer Institute's Surveillance Epidemiology and End Result (SEER) database with the hypothesis that radiation therapy would afford survival benefit to a subset of patient. Our goal was to provide additional evidence to help guide clinicians' decision making in caring for patients with CXPA

Materials and Methods

The present study is a retrospective review of patients with CXPA extracted from the National Cancer Institute's SEER database. Patients from 1986-2008 provided by 17 registries were identified using the November 2010 submission. Cases of CXPA were identified using the International Classification for Childhood Cancer site recode extended ICD-0-3 histology code 8941/3. Patients were excluded if their CXPA originated at a site other than the parotid or submandibular glands, if they had distant disease, or if they did not receive surgical resection.

Results

A total of 246 patients (median age=62) were identified who were diagnosed with CXPA of the parotid or submandibular glands. Parotid tumors (n=200) were more common than submandibular tumors (n=46) in this cohort. Median overall survival for the cohort was 46.5 months. Overall survival was 56.5 and 29 months for parotid and submandibular CXPA, respectively ($p<0.05$). Of patients with known tumor grade (n=127), the majority had high grade disease (n=87). Most patients had localized disease (n=195). Median survival for patients who received surgery with adjuvant radiation was 46 months, compared to 53 months for those who only received surgical resection. Patients were more likely to receive surgery with post-operative radiation if they had high grade disease (83%), compared to 57% for those with low grade CXPA. Further, patients were also more likely to receive radiation if they had regional compared to localized disease (88% and 58%, respectively). Significant negative prognostic factors by univariate analysis were older age (HR=2.36), male sex (HR=1.70), and regional lymph node involvement (HR=3.41). Survival for high grade tumors was significantly less than for low grade or unknown tumors ($p=0.001$). CXPA location, use of adjuvant radiation, and capsular invasion were not significant prognostic factors.

Conclusions

This review of the SEER database provides prognostic information for patients with non-metastatic CXPA of the parotid or submandibular glands. Older age, male sex, and lymph node involvement were negatively associated with survival. Lymph node involvement was the poorest prognostic factor. Though patients with CXPA of the submandibular gland had shorter median survival, this relationship did not hold through in univariate analysis. Tumors of the submandibular gland tended to be of higher grade and more likely to have capsular penetration, likely accounting for this observed survival discrepancy. Radiation therapy was utilized more frequently in patients with more advanced disease, which may explain the trend toward shorter median survival for patients who received radiation. Patients with high grade disease derived significant survival benefit from adjuvant radiation; this did not hold true for patients with regional, localized, or low grade disease.

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Acknowledgements

K.O. Arneson

Mentor / Department

S.M. Perkins- Radiation Oncology (now at Washington University in St. Louis) E.T. Shinohara- Radiation Oncology

COMPARATIVE MUSCULOSKELETAL IMPAIRMENT IN PATIENTS WITH HEAD AND NECK CANCER UNDERGOING SURGICAL RECONSTRUCTION WITH PECTORALIS MAJOR MYOCUTANEOUS FLAP VS REVASCULARIZED FREE TISSUE TRANSFER

Kristin Stevens
Patient Oriented Research

Background Problem
Surgical therapy for head and neck cancers may directly disrupt or remove neck musculature, and reconstructive techniques may further impair function. Although pectoralis major myocutaneous flaps (pectoral flaps) and revascularized free tissue transfers (free flaps) are both commonly used reconstructive techniques, there is no data available comparing the adverse effects of these two techniques on musculoskeletal function.

Objectives
The purpose of this study is to compare the impact of pectoral flaps and free flaps on patient-reported symptom burden, cervical range of motion, trismus, posture, and pulmonary function in head and neck cancer patients who have completed curative intent therapy a minimum of three months prior to study entry.

Materials and Methods
This is a cross-sectional study. Disease and treatment information is gathered from the patient's electronic medical record. Patients are asked to fill out a demographic form, the Vanderbilt Head and Neck Symptom Survey version 2.0, the Neck Disability Index, and the Shoulder Pain and Disability Index. Cervical range-of-motion (ROM) is measured using the Dynatronics CROM-D and jaw ROM is measured using the OraStretch ROM scale. Pictures are taken of each patient standing in front of a posture grid. Finally, patients complete a pulmonary function test. A REDCap database was created for data collection and statistical evaluation.

Results
Herein, we report preliminary data for CROM, trismus, and patient-reported symptoms for the initial 22 patients. Data was double entered into and analyzed using the statistical software package SPSS version 21.0. Chi-Square tests of independence (nominal, ordinal) and Mann-Whitney tests (continuous data) were used to test group differences.

Conclusions
Because this study is still in progress, it is premature to make definitive conclusions about our findings. However, current trends suggest that both procedures negatively impact CROM and trismus measurements.

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Acknowledgements
Barbara Murphy MD, Kyle Mannion MD, Mary Dietrich PhD, Sheila Ridner PhD, Melissa Adair RN, James Tolle MD, and Jie Deng, PhD RN

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COMPARING REFRACTIVE ERROR RATE OF CHANGE: EMMETROPIZATION AFTER CATARACT REMOVAL IN CHILDREN

Diana Thiara
Patient Oriented Research

Background Problem

Emmetropization describes the process that reduces refractive error during eye development, it is highly dependent on visual stimulation. Animal models show that visual deprivation results in postnatal elongation of the eye, known as axial myopia. Human deprivation of patterned vision due to cataractous lenses results in varying patterns of axial elongation. Power of the intraocular lens is estimated based on future elongation of the eye. Thus it is important to know how the globe develops differently in children with cataracts.

Objectives

Compare rate of change of refractive error in aphakic and pseudophakic children with that of children with normal vision.

Materials and Methods

We reviewed clinical records for an eight-year period of patients who had cataract surgery in childhood. The sample size was 89 eyes. We extracted data regarding: presence of secondary intraocular lens, laterality of cataract, cataract type, and yearly measurements of postoperative visual acuity and refractive error. We excluded children with traumatic and secondary cataract, lens subluxation, or postoperative glaucoma. We then calculated yearly rate of change of refractive error for each eye. The rates of change of refractive error for each age group were compared with refractive error changes in healthy eyes as reported by Mayer et al and Zadnik et al. A Wilxcoxon test was used to determine difference between groups.

Results

For the right (OD) and left (OS) eyes 0-1 age group, the refractive error rates of change after the 1st and 2nd years post-cataract extraction were not equal to the rates of refractive error change seen in healthy eyes.

Conclusions

The rate of refractive error change in children who have cataract removal before the age of 2 is different from normal eye development, and this has implications for current intraocular lens (IOL) power calculations. For children who have surgery at a later age, refractive error change is similar to normal. The small sample size for older children makes it difficult to draw strong conclusions about refractive error changes.

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References Available Upon Request

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CONSTRAINT-INDUCED MOVEMENT THERAPY IMPROVES NEUROBEHAVIORAL FUNCTION AND NEURAL PROCESSING EFFICIENCY IN CHILDREN WITH HEMIPARETIC CEREBRAL PALSY

Lulu Wang
Patient Oriented Research

Background Problem

Despite the prevalence of cerebral palsy (CP), few treatments focus on rehabilitation of the sensorineural pathways impaired in this disease, due to a lack of systematic approach and appropriate tools to measure brain reorganization.

Objectives

In this study, we used a novel application of event-related potential (ERP) methodology to study the efficiency of neural processing in a pediatric population. Previous studies have shown a high degree of connectivity between the motor, sensory and language neural systems. Thus, we hypothesized that ERP, along with standard assessments of motor function, would allow us to characterize changes in cortical processing following Constraint-Induced Movement Therapy (CIMT).

Materials and Methods

Twenty children (ages 5-12 years) diagnosed with hemiparetic CP underwent a 5-day course of CIMT at the Vanderbilt Pediatric Rehabilitation Center, totaling 20 hours of sensory and motor exercises and 120 hours of constraint. Two ERP paradigms were selected: computer-generated speech sound discrimination and visual-auditory match-mismatch discrimination. Study participants were assessed immediately pre- and post-intervention, and at 6 months, for muscle strength and ERP responses.

Results

ERP mean peak amplitudes and latencies showed increased discrimination in the primary auditory cortex contralateral to the lesion (2.4 μV increase in N250 amplitude, $p = 0.045$) and increased picture-word match-mismatch discrimination in the parietal cortex ipsilateral to the lesion (9.3 μV increase in N400 amplitude, $p = 0.001$). Neurobehavioral tests showed gains in spontaneous movement and muscle strength of the affected extremity. Using these simple speech-sound and visual-audio tasks, we were able to identify strong correlations between the efficiency of signal processing and neurobehavioral measures.

Conclusions

This study demonstrated for the first time that ERP methodology could measure changes in the speed of complex language task processing and efficiency of cross-hemispheric signaling. This makes ERP a promising tool to objectively quantify the effectiveness of sensorimotor therapies in pediatric populations.

Acknowledgements

Dr. Nathalie Maitre, Ashley Simmons, Gena Henderson, Shirley Gogliotti, Amber Vinson, Dorita Jones, and Alexandra Key

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RETROSPECTIVE ANALYSIS OF COAGULOPATHY IN PEDIATRIC TRAUMA PATIENTS AND ASSOCIATED CLINICAL CHARACTERISTICS

Emily Zern; Courtney Horton, MD; Candace McNaughton, MD MPH
Patient Oriented Research

Background Problem

The study of Acute Traumatic Coagulopathy (ATC) in adults has led to the implementation of a Massive Transfusion Protocol (MTP) in Adult Emergency Departments. Metrics of shock such as hypotension and tachycardia are not as reliable in directing the care of pediatric patients. Preliminary data suggests that coagulopathy is present in pediatric populations and, more importantly, is associated with adverse outcomes and increased mortality. Further studies are necessary to determine if ATC in pediatric trauma patients is an indicator for initiation of MTP.

Objectives

To evaluate coagulopathy in pediatric trauma patients at the time of presentation to the pediatric emergency department (PED) at Monroe Carell Jr. Children's Hospital at Vanderbilt from February 29th, 2008 to February 29th, 2012.

Materials and Methods

Included in this retrospective chart review were all pediatric trauma patients who met Level I or Level II trauma criteria and who had coagulation studies during initial PED evaluation. Of all patients with coagulopathy, as defined by an International Normalized Ratio (INR) of prothrombin time (PT) > 1.5, clinical characteristics were reviewed. A SQL query on the Vanderbilt University Medical Center (VUMC) Electronic Data Warehouse of eligible patients produced a data set of vital signs, demographic data, injury mechanism, arrival method, Glasgow Coma Scale, length of stay and disposition, laboratory data, and transfusion data.

Results

Out of a total of 941 pediatric patients (< 18 years), 39 (4.1%) patients were coagulopathic. Injury mechanisms of those who were coagulopathic included blunt trauma (68%), penetrating trauma (10%), burns (10%), closed head injuries (2%), and hanging (2%). 30% arrived by ground ambulance and 70% by air transport, with 41% of cases coming from an outside institution. Upon arrival to the PED, coagulopathic patients had an average Glasgow Coma Scale (GCS) of 7, 18% were hypotensive, and 26% were hypothermic. In the first 24 hours, transfusion data revealed that 44% received packed red blood cells, 38% fresh frozen plasma, and 15% platelets. Disposition from the PED was evaluated: 54% admitted to the Pediatric Intensive Care Unit (PICU), 28% to the operating room, 8% admitted to the hospital (not to the PICU), 5% discharged, and 5% died. At 30 days, 54% had been discharged home, 41% were deceased, and 5% remained hospitalized.

Conclusions

Coagulopathy was present in 39 (4.1%) of pediatric Level I and Level II trauma patients over the time period of February 29, 2008 to February 29, 2012. The major mechanism of injury was blunt trauma (68%). Ongoing studies with this data set will compare coagulopathic to non-coagulopathic patients and determine the statistical variation of hypotension, hypothermia, acidosis, GCS, transfusion, and disposition. These future studies will help elucidate whether abnormal coagulation studies upon arrival to the PED can be used as a marker for increased morbidity and mortality and whether interventions addressing coagulopathy may improve patient outcomes.

Acknowledgements

IRB#: 120364 "Acute Traumatic Coagulopathy in Pediatric Trauma Patients: incidence and association with increased mortality"

Mentor / Department

Mentor: Courtney Horton, MD, Clinical Fellow, Division of Pediatric Emergency Medicine

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