Translational Science Research: Towards Better Health
Effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease, which is essential for improving health.
CONTENTS

Editorial
Translational Science Research: Towards Better Health
Emir Festic, Ognjen Gajic .......................................................... 52

Immunomodulatory Compounds (IMIDS')
in the Treatment of Multiple Myeloma
Gordan Srankovic, Mohamad Hussein ........................................ 54

Towards Individualized Medicine: Insights Gained from Genomic Studies
Salman Kirmani, Dusica Babovic-Vukasinovic .................................. 512

Clinical Significance of the Kras Mutation
Sead Beganovic ........................................................................... 518

Red Blood Cell Storage Lesion
Daryl J. Kor, Camille M Van Buskirk, Ognjen Gajic .............................. 522

Thigh Compartment Syndrome, Presentation and Complications
Eric G. Verwiebe, Ees M. Kadic, Jeremy Saller, Amr Abdelgawad ........... 529

Medical Informatics:
An Essential Tool for Health Sciences Research in Acute Care
Man Li, Brian W. Pickering, Vernon D. Smith, Mirsad Hadzikadic, Ognjen Gajic, Vitaly Herasevich ............................. 535

Extramedullary Intradural Spinal Tumors: a Review of Modern
Diagnostic and Treatment Options and a Report of a Series
Kenan Arnautovic, Aska Arnautovic .............................................. 541

Current Prophylactic Perioperative Antibiotic Guidelines in
Trauma: a Review of the Literature and Outcome Data
Lejla Hadzikadic ........................................................................... 547

When Less is More in the Intensive Care Unit; Lessons Learned
Emir Festic, Ognjen Gajic .......................................................... 555

Acute Respiratory Distress Syndrome:
Insights Gained from Clinical and Translational Research
Marija Kojicic, Emir Festic, Ognjen Gajic ........................................ 560

From Mechanical Ventilation to Intensive Care Medicine:
A Challenge for Bosnia and Herzegovina
Guillatame Thievy, Prisca Kivancoue, Slavenka Stras, Jadranska Vatrovic, Amer Ipiipa, Emir Festic, Ognjen Gajic ........................................... 570

Evaluation of the Intrinsic Properties of Pedicle Screws: Do Diameter,
Manufacturing and Screw Design Affect Resistance and/or Resistivity
Worawat Limthongkul, Jason Savage, Emmanuel K. Nenonene, Eldin E. Karaikovic .............................................................. 578

Depression in Adolescents: Current Treatments,
Suicidality and Evaluation of Novel Treatment Strategies
Amer Smajkic ................................................................................ 584

Environmental Impact of Nuclear Industry Karlis Brijbasi
Sarajevo Environmental Protection Agency .............................. 594

Mendelian Factors in the Development of Neurologic Disease
Agnieszka Kruk, Mohammad Atieh, Hans-Peter Moller, Emir Festic, Ognjen Gajic, Vitaly Herasevich ............................. 598

The Impact of Social Media on Healthcare Information
Sukumar Pal, Cristián Álvarez-Ibarra, Francesco Longo, Vincenzo De Santis, Vitaly Herasevich .............................................. 604

Pathological and Molecular Assessment of the Tuberculosis Treatment
Failure
Jovan Vucinic, Mladen Lonja, Milan Maric, Mladen Ilic, Vojislav Rajkovic, Dusica Babovic-Vukasinovic, Emir Festic, Ognjen Gajic, Vitaly Herasevich ........................ 611

The Role of Mitochondria in the Pathogenesis of Type 2 Diabetes
Meryem Aydogdu, Selma Batur, Esra Bilginer, Emir Festic, Ognjen Gajic, Vitaly Herasevich .......................................................... 616

The Impact of the Food Industry on Childhood Obesity
Aminur Rahman, Saima Parveen, Asma Karim, Emir Festic, Ognjen Gajic, Vitaly Herasevich .................................................... 620
TRANSLATIONAL SCIENCE RESEARCH: TOWARDS BETTER HEALTH

Even though it is considered a 21st century term, translational research has been present for much longer. The idea of translating experimental discovery to its clinical application and use is old as research itself. However, it is the understanding of missing links between the basic science research and clinical research that emerged in the past decade and mobilized scientific and clinical communities and organizations worldwide. Hence term, translational research, which represents an "enterprise of harnessing knowledge from basic sciences to produce new drugs, devices, and treatment options for patients" (1). It has been also characterized as "effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease, which is essential for improving health" (2).

This translation is a complex process and involves more than one step for transfer of research knowledge. At least 3 such roadblocks have been identified (Figure 1); T1 translation: "The transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans", T2 translation: "The translation of results from clinical studies into everyday clinical practice and health decision making", and T3 translation: "Practice-based research, which is often necessary before distilled knowledge (e.g., systematic reviews, guidelines) can be implemented in practice" (3-5). The international research community rapidly recognized importance for promotion of translational research and made it their priority (5). In the USA, National Institutes of Health (NIH) expects to fund 60 translational research centers with a budget of $500 million per year by 2012 (6). Besides academic centers, foundations, industry, disease-related organizations, and individual hospitals and health systems have also established translational research programs and at least 2 journals (Translational Medicine and the Journal of Translational Medicine) are devoted to the topic. In Europe,
translational research has become a centerpiece of the European Commission’s €6 billion budget for health related research, and the United Kingdom has invested £450 million over 5 years to establish translational research centers (7). In this issue of Bosnian Journal of Basic Medical Sciences, members of medical section of Bosnian and Herzegovinian-American Academy of Arts and Sciences (BHAAAS), contributed their own work and expertise to bridge the gap between basic and clinical research, between inventing the treatments and getting them used in practice, and laid down foundations for future collaborative development of translational research in Bosnia and Herzegovina, as well as in the region (8). At the first glance of this issue’s table of content, a reader will easily notice the variety and breadth of topics and themes, from medical informatics and genetics, to hematology and oncology, pulmonary and critical care medicine, orthopedics, trauma surgery and neurosurgery. However, all of the articles share common ideas of translation of knowledge, from bench to bedside and back, and individualized approach to medicine, which are the true hallmarks of the 21st century medicine. Deeper under the surface and titles, there lies our common privilege and honor to be part of a broader mission of BHAAAS: to connect with our fellow physicians and scientists, and to build bridges of cooperation with our homeland, to promote the spirit of intellectual diversity and free exchange of ideas with the strong belief that this knowledge sharing will promote betterment of health in Bosnia and Herzegovina.

Invited Editors from BHAAAS Emir Festic (Mayo Clinic, Jacksonville, FL USA), Ognjen Gajic (Mayo Clinic, Rochester MN USA)

REFERENCES


This journal is indexed in:
Index Medicus /MEDLINE,
CAB abstract / Global Health databases;

THOMSON REUTERS
http://thomsonreuters.com/
Web of Science
Science Citation Index Expanded
EBSCO HOST
Academic Search Complete

S2
Abstract

The design of innovative, more effective, less toxic therapy of multiple myeloma (MM) is emerging in parallel to a better understanding of the underlying pathophysiology of this common hematologic malignancy. Thalidomide has changed the treatment paradigm of patients with MM. Its efficacy, however, has been compromised by significant side effects. IMiDs® (immunomodulatory compounds) are structural and functional analogs of thalidomide that were specifically designed to create new agents with enhanced immunomodulatory and anticancer properties and better tolerability profiles. In this article, we review the clinical trial development of the second-generation IMiDs®, lenalidomide and pomalidomide. Both agents demonstrate potent activity and are highly effective and well tolerated treatment options for patients with MM.

KEY WORDS: lenalidomide, thalidomide, multiple myeloma, pomalidomide, IMiDs®
INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy and is invariably fatal (1, 2). Each year, 19,920 new cases of MM are diagnosed, resulting in nearly 11,000 deaths annually (2). Despite available therapies such as high-dose chemotherapy and autologous stem cell transplantation (ASCT), MM remains an incurable disease with a median survival of 3 to 5 years depending on disease stage (3), and a 5-year relative survival rate of approximately 35% (4). The role of high-dose chemotherapy and ASCT continues to be controversial, with overall survival (OS) only minimally improved if any (5, 6). Patients with progressive disease can achieve a 50-75% response rate to salvage regimens such as vincristine, doxorubicin, and dexamethasone (VAD) (7, 8); however, these responses are often short-lived. Therefore, the need for novel agents and therapeutic modalities in MM remains critical. The introduction of the IMiDs®, such as lenalidomide and pomalidomide, for the treatment of various malignancies has gained momentum, especially in the management of MM (9). The re-discovery of thalidomide not only improved response rates and provided a new class of agents for MM patients, but also instigated a wide range of bench and clinical research activities that enriched the understanding of MM pathophysiology (10).

Thalidomide

The discovery that thalidomide had anti-angiogenic (11) and T-cell co-stimulatory (12) activity led to the clinical investigation of thalidomide for therapy in MM. In relapsed and refractory MM, thalidomide produced response rates of approximately 30% as a single agent (9). In newly diagnosed patients, thalidomide achieved response rates of 36% alone and 64-72% in combination with dexamethasone (13, 14). As a result, thalidomide in combination with dexamethasone received United States Food and Drug Administration (US FDA) approval for the treatment of newly diagnosed MM in 2006. In addition, recent phase III studies have investigated various thalidomide-containing regimens and reported improvements in quality of response with: thalidomide, adriamycin and dexamethasone compared to VAD (15); bortezomib, melphalan, prednisone and thalidomide (VMP) compared to bortezomib, melphalan and prednisone (VMP) (16), melphalan, prednisone and thalidomide (MPT) compared to melphalan and prednisone (MP) (17), and bortezomib, thalidomide and dexamethasone (VTI) compared to thalidomide and dexamethasone (TD) (18). However, the encouraging effects of thalidomide are hampered by toxicity, which often compromises the dose or leads to discontinuation of therapy. Common adverse events include fatigue, somnolence, constipation, fluid retention, peripheral neuropathy, venous thromboembolism (VTE), and rash (9, 19). Given the promising activity of thalidomide, synthetic analogs were developed and introduced in an effort to provide equal or greater immunomodulation, but a better tolerability profile. Clinical data indicate that the incidence of peripheral neuropathy, which is common with thalidomide, is low with lenalidomide and pomalidomide, (20-24).

Lenalidomide and pomalidomide

The IMiDs® are a group of unique, orally bioavailable agents that have been refined, using thalidomide as a structural template (Figure 1).

Modification of the thalidomide structure through removal of a carbonyl on the ring formed lenalidomide (CC-5013, Revlimid®), and addition of an amino group at the 4 position of the phthaloyl ring formed pomalidomide (CC-4047). These IMiDs® were specifically designed to enhance immunomodulatory and anticancer properties of thalidomide with fewer side effects. Preclinical studies have shown that lenalidomide and pomalidomide are 50 000 times more potent, in vitro, than thalidomide at inhibiting tumor necrosis factor alpha (TNF-α) (25, 26).

FIGURE 1. Molecular structure of thalidomide, lenalidomide and pomalidomide
Studies have revealed that IMiDs not only inhibit angiogenesis, but also stimulate T-cell proliferation and induce apoptosis and growth arrest in resistant myeloma cells (Table 1) (27-29). These compounds also prevent the adhesion of myeloma cells to bone marrow stromal cells, and thereby inhibit the enhanced secretion of migratory factors, such as interleukin (IL)-6, TNF-α, and vascular endothelial growth factor (VEGF) (30-35). Lenalidomide has more potent activity than thalidomide in the preclinical setting (25, 36), and has also demonstrated impressive clinical activity in both newly diagnosed and relapsed or refractory MM (23, 37-39). Pomalidomide also demonstrates potent activity against TNF-α in vitro, indicating greater synergy than lenalidomide with rituximab in vivo (40). It also promotes T-cell differentiation and cytokine production via the transcription factor T-bet (41), and has demonstrated promising activity in clinical trials (24, 42).

Studies among patients with relapsed or refractory MM have demonstrated that lenalidomide can overcome resistance to prior MM therapy, including thalidomide (43-45). In addition, time to progression (TTP) and progression-free survival (PFS) are superior when lenalidomide is given at first relapse rather than given later as salvage therapy (45). Two phase I trials of lenalidomide have demonstrated promising activity as well as decreased toxicity in heavily pretreated patients with relapsed or refractory MM [42, 43].

These studies established 25 mg/day as the maximum tolerated dose (MTD) for lenalidomide in relapsed or refractory MM, and provided a firm foundation for continuing trials with lenalidomide, either alone or in combination with other active agents in MM. Two large, randomized, phase III, double-blind, placebo-controlled clinical trials (North American MM-009 and European MM-010) have compared the efficacy and safety of lenalidomide plus dexamethasone (Len+Dex) with placebo plus dexamethasone in patients with relapsed or refractory MM (23, 37). In both trials, lenalidomide 25 mg/day or placebo was administered on days 1-21 of each 28-day cycle and oral dexamethasone 40 mg was administered on days 1, 4, 9-12, 17-20 of each 28-day cycle. The MM-009 trial enrolled 353 patients (Len+Dex n=177; placebo+Dex n=176) and the MM-010 trial enrolled 351 patients (Len+Dex n=176; placebo+Dex n=175). The Len+Dex combination achieved a significantly higher overall response rate (ORR) (MM-009: 61% vs. 20%; MM-010: 60% vs. 24%; both p<0.001) and complete response (CR) rate (MM-009: 14.1% vs. 0.6%; MM-010: 15.9% vs. 3.4%; both p<0.001), (Figure 2). The median TTP was significantly prolonged by the addition of lenalidomide to dexamethasone (MM-009: 11.1 months vs. 4.7 months; MM-010: 11.3 months vs. 4.7 months; both p<0.001), (Figure 3) and the median OS was significantly longer in the Len+Dex arm (MM-009: 29.6 months vs. 20.2 months; p<0.001; MM-010: not reached vs. 20.6; p=0.03).

<table>
<thead>
<tr>
<th>Activity</th>
<th>Thalidomide</th>
<th>Lenalidomide</th>
<th>Pomalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-angiogenic activity (human explant model)</td>
<td>++++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Anti-inflammatory activity against monocytes</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>T cell/NK cell costimulation</td>
<td>+</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>T regulatory cell inhibition</td>
<td>-</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Antibody-dependent Cellular Cytotoxicity (ADCC)</td>
<td>-</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>

TABLE 1. Comparative table of IMiDs’ activity in preclinical studies

* = potency factor of 10

FIGURE 2. Response rates with Len+Dex versus Dex alone in the pivotal phase III trials. MM-009 and MM-010.
In the MM-009 and MM-010 studies, grade 3/4 hematologic adverse events were more common with Len+Dex and included neutropenia (41.2% and 29.5% vs. 4.5% and 2.3%, respectively), anemia (13.0% and 8.6% vs. 5.1% and 6.9%), thrombocytopenia (14.7% and 11.4% vs. 6.9% and 5.7%), and febrile neutropenia (3.4% vs. 0%). Other common grade 3/4 adverse events included infection (21.4% and 11.3% vs. 12.0% and 6.2%, respectively), and fatigue (6.2% and 6.8% vs. 6.3% and 3.4%). The incidence of VTE in the MM-009 and MM-010 studies was higher in the Len+Dex arm (14.7% and 11.4% vs. 3.4% and 4.6%, respectively); however, it was comparable to the incidence of 10% observed for the general MM population in retrospective analyses (46). On the basis of these studies, lenalidomide was approved by the US FDA in June 2009 and by the European Medicines Agency in June 2010 for use in combination with dexamethasone in the treatment of MM in patients who have received at least one prior therapy. Due to encouraging results in the relapsed or refractory setting, a phase II trial was undertaken to assess the efficacy and safety of the Len+Dex combination therapy in the front-line setting (21). In this phase II trial, lenalidomide (25 mg/day orally on days 1-21 of each 28-day cycle) was combined with dexamethasone (40 mg/day orally on days 1-4, 9-12, and 17-20 of each 28-day cycle) in 34 newly diagnosed, previously untreated MM patients. The ORR was 91%, with CR in 6% and very good partial response (VGPR) and near CR in 32%. Grade 3 or greater non-hematologic adverse events were reported in 47% of patients and included fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). Myelosuppression was minimal, most likely reflecting the preserved bone marrow reserve in this group of previously untreated patients. All patients were placed on low dose aspirin prophylaxis, based on the efficacy of low dose aspirin in preventing VTE among patients treated on the thalidomide plus dexamethasone regimen (47), and only one patient developed a VTE. In addition, Len+Dex combination therapy appeared to be a useful pre-transplant conditioning regimen, as there was no adverse effect on stem cell mobilization among these patients. With successful responses and better tolerability obtained from early trials, lenalidomide is rapidly being incorporated into front-line regimens. The Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG) have ongoing randomized, phase III trials assessing Len+Dex as primary therapy in the front-line setting. The SWOG trial compared Len+Dex to dexamethasone alone in patients with newly diagnosed MM (38). In this study, 198 patients were randomized, 100 received lenalidomide 25 mg/day (28 of 35 days for 3 induction cycles, then 21 of 28 days as maintenance thereafter) plus dexamethasone 40 mg/day (days 1-4, 9-12, and 17-20 as induction, then days 1-4, and 15-18 as maintenance) and 98 received dexamethasone plus placebo. In the 133 patients who were assessable for response, the ORR was significantly higher (85.3% vs. 51.3%; p=0.001) and 1-year PFS was significantly longer (77% vs. 55%, p=0.002) with Len+Dex. The 1-year OS was high and there was no difference between arms (93% vs. 91%). Grade 3/4 neutropenia (13.5% vs. 2.4%, p=0.010) and infections (all grades: 38% vs. 24%; grade 3 or higher: 14% vs. 8%, p=0.003) were more common with Len+Dex. VTE was reported in 25% of patients treated with Len+Dex vs. 7% of patients treated with dexamethasone alone; most patients (81%) who experienced VTE received aspirin as thromboprophylaxis, however it is to be noted that those patients received the full dose of aspirin at 325 mg daily which his known to be thrombogenic as it inhibits the prostacyclin activ-
ity this negating its anti-platelet role (48, 49). Patients in the dexamethasone arm who progressed were allowed to cross over to the Len+Dex arm. Of 40 patients who crossed over, the ORR in 23 who were assessable for response was 70.4%. These data confirm the superior efficacy with Len+Dex in newly diagnosed patients. The ECOG trial compared lenalidomide plus standard-dose dexamethasone (RD) to lenalidomide plus low-dose dexamethasone (Rd), in an attempt to further diminish adverse events while maintaining the response rate. In this study, patients in the RD arm were treated with lenalidomide 25 mg/day on days 1-21 of each 28-day cycle and dexamethasone 40 mg/day on days 1-4, 9-12, and 17-20 of each 28-day cycle, and patients in the Rd arm received dexamethasone 40 mg on days 1, 8, 15, and 22 of each 28-day cycle (50). A total of 445 patients were randomized, 223 to RD and 222 to Rd. Grade 3 or higher adverse events were more common in the RD arm (49% vs. 32%; p=0.001), including neutropenia (10% vs. 19%; p=0.01), VTE (25% vs. 9%; p=0.001), and infections (16% vs. 6%; p=0.001). Although response rates during the first 4 cycles were higher with RD (ORR: 82% vs. 70%; p=0.007; CR + VGPR: 52% vs. 42%; p=0.06), OS was significantly higher in the Rd arm, p=0.006, (1-year OS: 96% vs. 88%; 2-year OS: 87% vs. 75%). The 2-year OS rate for the 102 patients who underwent stem cell transplant (94%) was comparable to the 2-year OS for patients in the Rd arm who continued primary therapy beyond 4 cycles (91%). These data demonstrated superior outcome with lenalidomide plus low-dose dexamethasone in patients with newly diagnosed MM compared to lenalidomide plus high-dose dexamethasone. The dose and schedule of dexamethasone will need to be evaluated further in light of the differences between the results of the SWOG and ECOG studies. There is probably a group of patients that could benefit from high dose dexamethasone administered according to the SWOG schedule and for others a lower dose may achieve similar disease outcome with less toxicity and mortality. Baz et al. combined pegylated liposomal doxorubicin, vincristine, and dexamethasone (DVd) regimen with lenalidomide (DVd-R) in a phase I/II study among patients with relapsed or refractory MM (51). The study objectives were to determine the MTD and evaluate the safety and efficacy of DVd-R. Lenalidomide was administered orally at doses of 5, 10, and 15 mg/day for 21 days of each 28-day cycle in cohorts of 3-6 patients. Patients were treated for at least 4 cycles, and a maximum of 2 cycles after best response. Maintenance therapy included continuation of lenalidomide with the addition of prednisone 50 mg every other day until disease progression. Low-dose aspirin (81 mg) was administered as VTE prophylaxis. Sixty-two patients were enrolled in the study (40 refractory to prior therapy). The MTD of lenalidomide with DVd chemotherapy was 10 mg. The ORR was 75% with CR or near CR in 29%. After a median follow-up of 7.5 months, the median PFS was 12 months and the median OS had not been reached. Grade 3/4 adverse events included neutropenia (32%), febrile neutropenia (7%), peripheral neuropathy (5%), and VTE (9%). This novel combination appears to be well tolerated, and resulted in a high response rate in a group of patients with MM, most of whom were refractory to prior therapy. In addition to the ability of lenalidomide to exert an effective anti-tumor activity through direct anti-malignant plasma cell effects, it also exerts immune modulatory effects. Lenalidomide stimulates the immune cellular system leading to a beneficial impact on infectious complications, especially those that rely on the cellular immune system. One of the major viral infections in patients with multiple myeloma is herpes zoster that occurs in 15% of multiple myeloma patients over the course of the disease. Herpes zoster has high morbidity especially in this age group where post herpetic neuralgia could be crippling to the patients. With lenalidomide based therapy the incidence of herpes zoster is less than 5% as compared to other regimens that include proteasome inhibitors, where the incidence ranges from 15-60% (52, 53). The clinical activity of pomalidomide was first demonstrated in a phase I study in which 24 patients with relapsed or refractory MM were treated with pomalidomide as a single agent (42). The MTD was established at 2 mg/day. The ORR was 54%, including CR in 17%. Four patients (17%) experienced VTE. Pomalidomide therapy was associated with significantly elevated serum IL-2 receptor and IL-12 levels, which is consistent with activation of T cells, monocytes and macrophages. Based on these results, a recent phase II study has evaluated the safety and efficacy of pomalidomide (2 mg/day) combined with low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22 of each 28-day cycle) in 37 patients with relapsed or refractory MM (24). Most patients had received prior ASCT (76%) and prior IMiD® therapy (62%). The ORR was 62%, including VGPR in 24%. Objective responses were also reported 4 of 13 patients (29%) who were refractory to lenalidomide. Grade 3 hematologic adverse events included neutropenia (31%), thrombocytopenia (3%), and anemia (3%). There was no grade 4 neuropathy, but grade 1-2 neuropathy was reported in 16% of patients. Due to the incidence of VTE in the phase I study, all
patients received aspirin as thromboprophylaxis and there were no cases of VTE. Pomalidomide appears to be another promising agent with a role for further studies as an immunostimulatory modality of treatment among patients with relapsed or refractory MM.

**CONCLUSION**

The treatment paradigm for MM has evolved rapidly in recent years, with significant advances in the translation of novel biologically derived therapies from research to clinical application. Studies of lenalidomide and pomalidomide have demonstrated significant clinical benefits in patients with MM, along with an improved safety profile compared to thalidomide. Both IMiDs® are significant additions to the therapeutic armamentarium for MM therapy due to their more potent immunomodulatory properties, as well as their improved tolerability. Further studies of these orally bioavailable IMiDs® in MM patients are warranted, not only in combination with other biologics and chemotherapeutic agents, but with thalidomide as well.

G. Srkalovic has no potential conflict of interest relevant to this article. M.A. Hussein is employee of Celgene Corporation, manufacturer of IMiDs®

**Acknowledgement:** Authors would like to thank Mindy Yang, Pharm.D. for her assistance in preparation of the manuscript

**REFERENCES**

18. Cavo M., Tacchetti P., Patriarca F., Petrucci M.T., Pantani L., Ceccoln M., et al. Superior complete response rate and progression-free survival after autologous transplantation with up-front velcade-thalidomide-dexamethasone compared with thalido-


GORDAN SRKALOVIC, MOHAMAD HUSSEIN: IMMUNOMODULATORY COMPOUNDS (IMIDS) IN THE TREATMENT OF MULTIPLE MYELOMA


TOWARDS INDIVIDUALIZED MEDICINE: INSIGHTS GAINED FROM GENOMIC STUDIES

SALMAN KIRMANI*, DUSICA BABOVIC-VUKSANOVIC

Department of Medical Genetics, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

* Corresponding author

ABSTRACT

Advances in the field of human genetics have made it possible to develop specific management and prevention strategies for rare genetic disorders, and tailor pharmacotherapeutic approaches to anticoagulation and certain cancers. The role that genetic variation plays in influencing the risk and outcome of the most common diseases are still unclear. Data from genome-wide association studies is just beginning to answer these questions. We review the role of genome-wide association studies in the quest towards individualized medicine, and examine the promises and challenges that lie ahead.

KEY WORDS: personalized medicine, genome-wide association studies, single nucleotide polymorphism
**INTRODUCTION**

*One size fits all?*

One of the biggest challenges in practicing medicine is the variability in phenotypes and responses to applied treatments, leading to different, often unpredictable outcomes. The idea about individualizing medical care and treating each person in the way that will fit them best is very appealing, but is not novel. In daily practice, clinicians routinely tailor diagnostic and therapeutic interventions according to individual patients’ characteristics and preferences, and thus have been practicing a form of individualized medicine for many years. The unraveling of the human genome at the turn of the century now promises to revolutionize this entire concept. The terms personalized or individualized medicine as they are understood today refer to the use of preventative and therapeutic interventions to manage the individual’s disease or predisposition to disease, based on the patients unique molecular risk profile. We describe here a few examples of the successful application of genetic information to achieve optimal health outcomes in different settings. We also discuss the role of genome-wide association studies in furthering the practice of individualized medicine.

**Individualized medicine in newborn screening**

One of the examples of successful individualized medicine is newborn screening. Detecting a newborn with phenylketonuria and making an immediate change to a phenylalanine-restricted diet will prevent manifestations of the metabolic disorder and allow for normal psychomotor development in the child who would otherwise be mentally retarded if managed like other children. Currently, genetic screening is available for more than 50 conditions, and great successes have been achieved in preventing adverse outcomes in previously fatal conditions.

**Pharmacogenomics**

Another example of successful implementation of genomic data is the use of pharmacogenomic information in selecting appropriate therapy and dosage for an individual. Based on genetic markers, one can determine how the person will metabolize a drug, and thus predict response to some medications. This strategy has already been introduced for dosing Warfarin (1) (Figure 1.), some psychotropic medications (2) or for selecting patients with breast cancer who will benefit from chemo-prophylactic therapy with Tamoxifen (3). Warfarin is administered as a racemic admixture of R- and S-enantiomers. The more potent S-enantiomer is metabolized principally by cytochrome P450 (CYP) 2C9. The pharmacologic effect of warfarin is mediated by the inhibition of vitamin K epoxide reductase complex 1 (VKORC1). This results in the decreased concentrations of activated clotting factors (II, VII, IX and X) producing therapeutic anticoagulation. Genetic variations in the above-mentioned genes can lead to inter-individual variation in effective warfarin dose. Profiling an individual based on these genetic variations leads to the choice of the safest and most effective dose, thus preventing significant adverse events.

---

*with permission From Yin & Miata, Throm Res, 120 (1), 2007*
Cancer Genetics

There are emerging examples of the successful use of genetic information in cancer therapeutics. Perhaps the best example is the use of trastuzumab (Herceptin), a monoclonal antibody directed against the extracellular domain of HER-2, for breast cancers with amplification of HER-2[4]. There is promising data emerging for similar generic markers that may have direct therapeutic implications in cancer, for example EGFR mutations in lung cancer, and KRAS mutations in colorectal cancer.

Implications of genomic studies in common diseases

While the above examples represent successful approaches in selected situations, the role that genetic variation plays in influencing the individual expression and outcome of common diseases is unclear. Data from genome-wide association studies is just beginning to answer these questions. As mentioned above, the goal of personalized medicine is to tailor preventative and therapeutic interventions for an individual based on their genetic profile. This is as yet not possible for the most common diseases that we face (such as hypertension, diabetes, sporadic cancers etc). Most researchers agree that common, complex diseases have both environmental and genetic risk factors. The interaction between these risk factors is not well understood, and just how much of a role a single risk factor plays in the development of disease in an individual is not known.

Each small circle above the magnified chromosome (labeled 5’ to 3’) represents one SNP with its two allelic possibilities. At the intersection between any two of these SNPs, the associations between their variants are shown in various shades from white to red, with the deepest red indicating the strongest association. Patterns of triangular blocks of strong association are separated by short nodes with very little association. One SNP (called a tagging SNP) represented above a deepest-red block - block 1 (3t) or block 2 (8t) — can serve as a surrogate for any variant within its block. Testing for one SNP might provide almost complete genetic information for that block. (with permission from Christensen & Murray, NEJM 356:11, 2007)

Genome-wide association studies (GWAS) are now making it possible for us to better understand the role of genetic variation in the pathogenesis of these common diseases. The principle on which these studies work is that the human genome contains significant variation within the species, with the most common example being single nucleotide polymorphisms (SNPs) that occur at roughly every 300 base pairs of DNA. If SNPs lie
in close proximity to each other, they are more likely to be inherited "en bloc" and travel together down generations. This concept of linkage disequilibrium allows one SNP to act as a surrogate marker for other SNPs or mutations that may be inherited together and contribute to disease pathophysiology (Figure 2).

The occurrence of such genetic variants that are inherited en bloc on a chromosome is called a haplotype. With the International HapMap Project delineating the location of certain informative SNPs called "tagging SNPs", it has become possible to identify disease associated SNPs without having to go through the laborious and expensive process of identifying every SNP in the DNA sample under study (Figure 3).

In this figure, invariant nucleotide bases (gray circles) are interspersed with SNPs (orange circles). SNPs lying in close proximity in genome regions that tend to be unaffected by genomic shuffling during meiosis are usually inherited together. The inheritance pattern of SNPs 3 and 4 suggests that they are tightly linked to each other (box) — G travels with C and T travels with T — as well as to SNPs 1 and 2 in Figure 1. One tagging SNP may therefore be used as a surrogate for other SNPs in genome-wide analyses. (with permission from Christensen & Murray, NEJM 356:11, 2007).

If an adequate number of cases and controls (usually thousands) are studied, one may then be able to statistically discern which SNPs are more likely to be present in cases vs. controls. If a few SNPs do stand out, the genes on which they occur, or other genes in close proximity may be studied further to explore their role in the pathogenesis of that disorder. It also becomes statistically possible to obtain an odds ratio for the occurrence of a certain SNP in cases vs. controls, leading people to use this information in a predictive fashion in asymptomatic individuals. The "hypothesis generating" role of GWAS is well accepted, and many fruitful candidate genes have been explored and confirmed to have causal relationship with disease, e.g. TCF7L2 in T2DM (5). The "disease prediction" role of GWAS is more controversial and less well accepted. This is mainly because common complex diseases by their very nature result from the combined effects of multiple genetic and environmental factors, with each individual risk factor having only a modest effect on disease occurrence. Thus prediction models generated from such data will typically involve a large number of SNPs or risk genotypes, with the risk from each individual genotype being quite small (Figure 4).

With a large number of genotypes being studied, one will find that each individual genotype may occur frequently in the control population, thus the risk attributed to a particular genotype may be only slightly higher or lower in cases vs. controls. It thus becomes extremely problematic to interpret a profile that may contain both "risk increasing" as well as "protective" genotypes, as the interaction between these individual genetic factors is currently unknown. How much more this type of risk genotyping will
add to the information more cheaply gathered from traditional clinical risk factors questions the current role of GWAS in personalized medicine today. With the exception of five susceptibility variants for age-related macular degeneration (AMD) (6, 7) and seven variants in hypertriglyceridemia (8), the predictive value of data from GWAS is in question. Simulation models have been used to compare the predictive value of data from GWAS from traditional clinical risk factors like age, sex, family history and serum markers. Data from these studies indicates that genomic profiling did not substantially improve the prediction of T2DM (9, 10), cardiovascular disease (11) or prostate cancer (12). Thus it seems clear that current prediction models from GWAS have been rather simplistic, identifying a few susceptibility markers that do not explain the complex nature of common diseases.

CONCLUSION

We conclude that although genomic studies are playing an immense role in identifying novel disease pathways and biomarkers, their role in realizing the dream of individualized medicine is still in its infancy. The predictive data from these studies needs intense scrutiny and review, and is currently not ready for implementation in every day clinical practice or to drive healthcare policy. The urgency in starting to use genomic information for predictive purposes in medicine is understandable and there are several laboratories that offer direct-to-consumer products. However, one needs to be aware of the complexities in interpretation of test results and possible errors in the process that can lead to significant consequences for an individual. So until we are better informed in the future it is prudent to remember, primum non nocere.
REFERENCES


CLINICAL SIGNIFICANCE OF THE KRAS MUTATION

SEAD BEGANOVIĆ

Central Indiana Cancer Centers, Indianapolis, USA

* Corresponding author

ABSTRACT

The challenge of translational medicine is to translate very complex scientific data into the clinical setting so that medical management can be better guided towards the ultimate goal of better patient outcome. Physicians now have the opportunity to use specific biomarkers to personalize therapeutic options in various settings. Recent research has demonstrated that presence of Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation may directly influence medical decisions in patients with colon and lung cancer. Use of KRAS oncogene as a selection marker for specific treatment is a good example of individualized medicine approach to cancer treatment.

KEY WORDS: KRAS mutation, prognostic biomarker, selection marker

INTRODUCTION

One KRAS (Kirsten rat sarcoma viral oncogene homolog) mutation is present in up to 25% of all human tumors, and this is one of the most frequently activated oncogenes(1). Recent research has demonstrated that presence of KRAS mutation may directly influence medical decisions in patients with colon and lung cancer. This review article will briefly discuss the following concepts about Kras oncogene that may be significant for practicing physicians:

1. RAS oncogene and Carcinogenesis as a multistep process
2. KRAS MUTATION AS A PROGNOSTIC BIOMARKER IN NON SMALL CELL LUNG CANCEER
3. KRAS as a selection marker for EGFR inhibitor treatment in colon cancer.
4. KRAS mutation and resistance to erlotinib
5. KRAS mutation and response to bevacizumab
6. KRAS mutation and Personalized Medicine
KRAS oncogene and Carcinogenesis as a multistep process

Alterations in oncogenes, tumor-suppressor genes, and micro-RNA genes are important in pathogenesis of cancer (2). These alterations are a sequential multistep process that in the end results in neoplastic transformation. The accumulation of multiple genetic mutations occurs over significant period of time. For example, time required for transformation of colon adenoma to colon carcinoma may be up to 10 years. Generally for this process mutational activation of oncogenes and the inactivation of tumor suppressor genes are both necessary (3). Somatic mutations in at least four or five genes of a cell are crucial for a malignant transformation. Oncogenes are normal genes with an important role in the process of stimulation of controlled cellular proliferation. Mutations in these genes result in uncontrolled proliferation and development of cancer. RAS genes are expressed in normal cells, and are involved in controlled cell growth. Three distinct mutations of RAS have been identified: H-ras, N-ras, and K-ras. In general, colon, pancreas and lung carcinomas have mutations of KRAS, bladder tumors have HRAS mutations, and hematopoietic neoplasms are associated with NRAS mutations. RAS mutations are infrequent in breast cancer. It is important to emphasize that activation of RAS oncogene is only one component in the ‘genetic cascade’ of events that finally results in malignant transformation (4). Given the development of cancer is a multistage process theoretically it is not likely that understanding the role of one mutation will have a direct impact on therapeutic decision. However, recent research showed that analysis of a single mutation may have a direct influence on a treatment selection.

KRAS mutation as a prognostic biomarker in non-small cell lung cancer

KRAS mutation in a non-small cell lung cancer is associated with smoking. Lung cancers with K-ras point mutations have worse prognosis and a tendency to be smaller and less differentiated than those without mutations. (5) In one study 63% of patients with K-ras mutation and completely resected adenocarcinoma of the lung died during the follow-up period as compared with 32% of patients with no mutation in the K-ras oncogene (P = 0.002) (5). The protein product of the Ras oncogene is called p21. Immunohistochemical staining on paraffin sec-
study skin toxicity was not sufficient to predict outcome in patients treated with cetuximab and KRAS mutation status provided supplementary information. EGFR expression based on Immunohistochemistry (IHC) is not clinically useful to predict response to cetuximab. There is a large number of growth factor-dependent and -independent mechanisms for activating the EGF receptor and it can be activated by receptor over-expression as it is the case in colorectal cancer. Monoclonal antibodies that bind and block EGFR signaling may be important in therapy of metastatic colorectal cancer. However, mutations of the K-RAS protein result in increased cancer proliferation and metastasis even in the presence of EGFR inhibition. Cetuximab or panitumumab are active in wild-type KRAS colorectal cancers. These monoclonal antibodies inhibit binding of the ligands of EGF (epidermal growth factor) and TGF alpha (transforming growth factor) to EGFR. Therefore, signaling of the RAS pathway is inhibited. Therefore Cetuximab or panitumumab are effective and should be used in colon cancer patients with wild-type KRAS. In contrast, K-RAS mutation promotes downstream signaling in the presence of EGFR inhibition. This process will stimulate cancer proliferation, angiogenesis and metastasis. Consequently mutations of the K-RAS protein result in increased cancer progression even in the presence of EGFR inhibition. In this clinical situation, if K-RAS mutation is present in patients with colon cancer, oncologist should not use Cetuximab or panitumumab. This is a good example of personalized or individualized medicine.

**KRAS mutation and resistance to erlotinib**

EGFR and KRAS mutations are considered to be mutually exclusive (9). Non-Small Lung Cancer patients with KRAS mutations have primary resistance to erlotinib (9). Again this may be an example of a individualized treatment decision on the basis of biomarkers. Patients with an EGFR mutation but not a KRAS mutation have a high probability of response to erlotinib. Those tumor cells that are positive for a KRAS mutation and negative for the EGFR mutation are resistant to erlotinib; thus, this costly treatment in this group of patients should be not used.

**KRAS mutation and response to bevacizumab**

Can KRAS mutation predict response to bevacizumab? In a study of 230 patients treated with irinotecan, fluorouracil, and leucovorin (IFL) in combination with either bevacizumab or placebo, KRAS status was assessed (10). The median progression-free survival (PFS) in patients with wild-type of KRAS was 13.5 months for group treated with irinotecan, fluorouracil, leucovorin and bevacizumab (IFLB) versus 7.4 months for the group treated with irinotecan, fluorouracil, leucovorin and placebo (IFLP) (hazard ratio 0.44, p < .0001). Metastatic colon cancer patients with KRAS mutations treated with irinotecan, fluorouracil, leucovorin and bevacizumab (IFLB) had progression-free survival (PFS) of 9.3 months versus 5.5 months (hazard ratio 0.41, p = 0.0008) for the group treated with irinotecan, fluorouracil, and leucovorin without bevacizumab. Despite of the fact that patients with KRAS mutations had inferior progression-free survival (PFS) than patients with wild-type of KRAS, addition of bevacizumab to IFL still provided a significant clinical benefit to the KRAS mutations group. This suggests that action of bevacizumab may be independent of alterations in the Ras/Raf/Mek/Erk pathway (10).

**KRAS mutation and Personalized Medicine**

The challenge of clinical medicine is to translate very complex scientific data into the clinical setting so that medical management can be better guided (11). Therefore, a concept of personalized medicine becomes very important in clinical oncology. Our general goal is to individualize treatment depending on both cancer and patient characteristics. This personalized or tailored therapy may improve outcomes (12). Physicians now have the opportunity to use biomarkers to personalize therapeutic options. For example, for patients with metastatic colorectal cancer who have progressed after cytotoxic therapy, the goal of treatment is to stabilize disease with minimal toxicity. Thus, one can select patients with a wild-type KRAS tumor and treat them with Cetuximab or panitumumab. In contrast, there is no benefit of Cetuximab or panitumumab therapy in colon cancer with KRAS mutation and this costly treatment should not be used in this group of patients. KRAS mutation in non-small Lung Cancer is also associated with resistance to erlotinib. Hence, a physician should not use this very expensive drug in the treatment of Non Small Lung Cancer with a KRAS mutation.
CONCLUSION

KRAS mutation is selection biomarker that can directly influence medical decision making in patients with colon cancer. Clinical use of information provided by testing for KRAS mutation may serve as an example of personalized medicine.

REFERENCES

ABSTRACT

The past two decades have witnessed increased scrutiny regarding efficacy and risk of the once unquestioned therapy of red blood cell (RBC) transfusion. Simultaneously, a variety of changes have been identified within the RBC and storage media during RBC preservation that are correlated with reduced tissue oxygenation and transfusion-associated adverse effects. These alterations are collectively termed the storage lesion and include extensive biochemical, biomechanical, and immunologic changes involving cells of diverse origin. Time-dependent falls in 2,3-diphosphoglycerate, intracellular RBC adenosine triphosphate, and nitric oxide have been shown to impact RBC deformability and delivery of oxygen to the end-organ. The accumulation of biologic response modifiers such as soluble CD40 ligand (sCD40L), lysophosphatidylcholine (lyso-PC), and Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES) have been associated with altered recipient immune function as well. This review will address the alterations occurring within the RBC and storage media during RBC preservation and will address the potential clinical consequence thereof.

KEY WORDS: red blood cell transfusion, storage lesion, transfusion efficacy, transfusion risks.

INTRODUCTION

Since the first successful attempt at blood storage almost a century ago, advances in extracorporeal red blood cell (RBC) preservation have incrementally prolonged the viability of stored RBCs. Persistent difficulties evaluating the efficacy of RBC transfusion has resulted in the exclusive reliance on post-transfusion 24-hour RBC survival when defining the acceptable RBC storage duration. Acceptable 24-hour RBC survival has been defined as 75%(1) and with contemporary preservative solutions, the storage duration for RBCs has been extended to 42 days.(2) Over the past two decades, there has been increased interest in the time-dependent changes in RBC quantity and quality during the storage period. The various changes that occur within both the RBC and storage media during ex vivo preservation have been collectively termed the RBC “storage lesion” (Figure 1). These alterations can be extensive and are primarily classified into three broad categories: biochemical, biomechanical, and immunologic. Importantly, the
alterations that occur during this storage process are believed responsible for many of the increasingly recognized adverse effects associated with RBC transfusion. In the present review, we will address the characteristic changes observed during the storage process. We will also address their potential clinical impact.

Biochemical Changes During RBC Storage

The biochemical changes within stored RBCs are principally related to alterations in energy metabolism with 2,3-diphosphoglycerate (DPG) and adenosine triphosphate (ATP) depletion. Our improved understanding of the role of the RBC in regional hypoxic vasodilation has also raised interest in the impact of RBC storage on nitric oxide (NO) metabolism. Additional time-dependent biochemical changes of potential significance include the accumulation of oxidized lipid and protein species and loss of chemokine scavenging capacity.

2,3-DPG

One of the most notable changes during RBC storage is the rapid fall in 2,3-DPG. 2,3-DPG is an allosteric modifier of hemoglobin which plays a critical role in the release of oxygen at the end-organ. Levels of 2,3-DPG have been shown to fall quickly during the storage of RBC, becoming undetectable within a week. This observation has raised concern that despite improved oxygen delivery with transfusion, stored RBCs may not release sufficient oxygen to the tissues. While biologically plausible, there appears to be little clinical consequence from this dramatic fall in 2,3-DPG as multiple authors have failed to find a meaningful effect from the transfusion of RBCs deplete in 2,3-DPG. In part, this lack of effect may result from the quick recovery of 2,3-DPG following transfusion. Normalization of 2,3-DPG levels begins within hours of transfusion and is completely restored within 48 to 72 hours.

ATP

A second well-described biochemical change of potential significance is a time-dependent reduction in intracellular RBC ATP. Due to its central role in cellular metabolism, adequate levels of ATP are essential for innumerable cellular processes. Examples include the maintenance of Na⁺-K⁺ ATPase activity, RBC membrane stability, glucose transport, oxidative stress defense mechanisms, membrane phospholipid distribution, and regional vasodilation under hypoxic conditions. Importantly, these levels normalize quickly after RBC transfusion. Additionally, more gradual reductions in ATP levels appear to correlate with morphologic changes seen with prolonged RBC storage (see below), these morphologic changes are readily reversed with normalization of ATP levels. Importantly, these levels normalize quickly after RBC transfusion. Additionally, more gradual reductions in intracellular ATP levels do not appear to correlate well with these morphologic changes. The impact of RBC ATP depletion on the vasodilatory response to regional hypoxemia is an area of interest that has been inadequately explored and will require additional study.
Nitric Oxide

Nitric Oxide (NO) plays a critical role in vascular reactivity due to its potent vasodilatory effects (8,15). The critical role for RBCs in the oxygen-dependent regulation of blood flow has recently been described (7,16). This oxygen-sensitive vasodilatory effect of RBCs is believed largely mediated by hemoglobin (Hb), which releases the vasodilator S-nitrosothiol (SNO) in proportion to the extent of regional hypoxemia (7,8). S-nitrosohemoglobin (SNO-Hb) forms within RBCs when a NO equivalent binds to the β3 Cys thiol residue of Hb (7). The RBC then releases SNO at the tissue level in proportion to Hb oxygen desaturation, matching regional perfusion and oxygen delivery to metabolic demand (17). The effect of RBC storage on this response has recently been characterized (7,8). Specifically, SNO bioactivity within RBCs has been shown to fall rapidly with storage (within 6 hours ex vivo). It has been suggested that this may result in altered oxygen delivery within the microcirculation and adverse clinical outcomes even after “fresh” RBC transfusions (7, 8, 18). The rapidity of the effect obscures the impact of prolonged RBC storage on SNO-mediated hypoxic vasodilation. As with ATP-mediated hypoxic vasodilation, this too will require additional study for further characterization.

Biomechanical Changes During RBC Storage

As capillary diameter ranges from 3 to 8 μM, subtle alterations in the deformability of an 8-μM RBC can have substantial impact on its ability to traverse the microcirculation. RBC deformability has been shown to rely greatly on surface area-to-volume ratio, membrane elasticity, and intracellular viscosity (19). Notably, the biomechanical changes seen in RBCs during the storage process include: alterations in corpuscle shape, deformability, osmotic fragility, aggregability, and intracellular viscosity (11). These changes have been shown to affect RBC transit through the microcirculation with a resultant counterintuitive decrement in tissue oxygenation (20,21). Specific changes in RBC morphology include a transition from a deformable biconcave disc to poorly deformable echinocytes with protrusions, and ultimately non-deformable spherocytinocytes (22,23). The proposed biochemical alterations in stored RBCs which result in these morphologic changes include: a depletion of ATP (5,6) and 2-3 DPG (3,4) loss of membrane phospholipid with associated vesiculation (14,23), protein rearrangement (9,22) and lipid oxidation (24). Additionally, Brunauer (25) and others (26) have described the internalization of membrane phospholipids in the setting of an oxidative load. The resultant loss of phospholipid asymmetry is believed to affect RBC deformability and survival in vivo as well. Recently, Karon et al. demonstrated that there may be irreversible morphological changes with loss of RBC function which occur early during storage, at day 12 (27). Using a more sensitive spectroscopic technique (TPA, or Time-resolved Phosphorescence Anisotropy), the authors found that Band 3 reorganized within intact RBC membranes before the loss of Band 3 from the RBC membrane and the appearance of Band 3 vesicles, both of which are known to occur later in storage (30 days and beyond). Additional studies are ongoing in the attempt to better characterize the morphologic changes which occur in the RBC membrane during cold storage (28,29).

Immunologic Changes During RBC Storage

The association between transfusion therapy and alterations in recipient immune function had not been recognized until 1973, when Opelz et al. (30) reported an intriguing observation that recipients of allogeneic blood transfusions had improved renal allograft survival compared to similar patients who did not receive a blood transfusion. Specifically, this work demonstrated the presence of an immunosuppressive or immunomodulatory effect of RBC transfusion on the recipient (later referred to as “TRIM”, or Transfusion Related Immunodulation) (31-34). Subsequent observations have noted the potential for multiple adverse effects (e.g. nosocomial infections, transfusion-related acute lung injury, multiorgan failure) resulting from these immunomodulatory effects.

Leukocyte Contamination

Though profound immunologic changes have been noted during RBC storage, it remains unclear which substances play a primary role in the immune modulating process. Historically, emphasis has been placed on the role of leukocyte contamination in the RBC product (35). Though leukoreduction has mitigated the occurrence of specific adverse effects such as febrile non-hemolytic transfusion reactions, it appears to have had little effect on other adverse consequences such as transfusion-related acute lung injury (TRA-LI) (36) or nosocomial infections in trauma patients (37). Recent evidence has also failed to find a beneficial effect of leukoreduction on mortality (37,38).
Soluble biologic response modifiers

An alternative explanation for the immunomodulatory effects of RBC transfusion relates to the presence of a variety of non-leukocyte derived biologic response modifiers. In a prospective evaluation of 22 units of leukocyte-reduced stored RBCs (LR-RBC), we recently characterized the time dependent changes of a variety of these substances. Progressive elevations in multiple proinflammatory mediators (e.g. cytokines, immunologically active phospholipids, CD-40 ligand) from diverse cellular origin were noted (Figure 1). Soluble CD40 ligand (sCD40L) and lysophosphatidylcholines (lyso-PCs) were two examples that may be of particular importance.

sCD40L is a platelet-derived, pro-inflammatory mediator which binds rapidly to CD40 expressed on neutrophils that adhere to the endothelium. In preclinical models, sCD40L induces neutrophil-mediated increases in pulmonary capillary permeability (39). We continue to explore the potential role of sCD40L in the adverse effects associated with RBC transfusions.

Lyso-PCs are the most abundant lysophospholipids in plasma and tissues and their levels increase in the setting of ischemia and inflammation. Lyso-PC shares a structural similarity to platelet activating factor. It is capable of priming and activating neutrophils and induces various proinflammatory actions in leukocytes, endothelial cells and smooth muscle cells. Unsaturated LysoPC can induce long-lasting superoxide production in neutrophils (40,41) and has been shown to increase alveolar-capillary permeability and pulmonary arterial pressure in pre-clinical models (42,43). Increased levels of this lipid have been found in patients after TRALI reactions and in the blood products associated with TRALI reactions as well (44). LysoPC-mediated neutrophil priming activity develops by the second week of routine RBC storage, with maximal priming activity by product outdate (42 days) (45).

Finally, although current pre-storage leukoreduction methods greatly diminish the concentration of leukocyte-derived products, our preliminary data suggest that some pro-inflammatory molecules may still accumulate in clinically relevant concentrations. For example, RANTES, or Regulated on Activation, Normal T-cell Expressed and Secreted, is a chemotactic cytokine, or chemokine, released from white blood cells (46). This cytokine functions as a pro-inflammation mediator by actively recruiting T-cells, eosinophils, basophils, and monocytes to sites of inflammation. In addition, RANTES also induces the proliferation and activation of natural killer cells (NK cells) (46). We recently noted a progressive increase in RANTES levels during LR-RBC storage. The clinical significance of this finding remains under investigation.

Clinical Implications of RBC Storage Duration

Over the past decade, we have witnessed an extensive re-evaluation of transfusion strategies. Pre-clinical and clinical studies have begun to question the efficacy of RBC administration and increasingly expose the potential risk. Specific concerns associated with allogeneic RBC transfusions include an increased risk of infection, pulmonary complications such as TRALI, multiorgan failure, and mortality. Importantly, the duration of RBC storage is believed to impact both transfusion efficacy and the associated risks.

Regarding efficacy, it should be noted that few studies outside the setting of acute hemorrhage have shown meaningful clinical benefit with RBC transfusion (47). Indeed, a landmark multicenter randomized controlled trial failed to find benefit with a more aggressive RBC transfusion strategy (48). Despite the intention to increase end-organ oxygen utilization, multiple evaluations have failed to identify an increase in oxygen utilization with the administration of allogeneic RBCs (20,49,50). To the contrary, loss of RBC membrane integrity and reduced red cell deformability, as occurs with RBC storage, has raised concern over the potential for microcirculatory occlusion and resultant tissue ischemia. In support of this theory, Murphy et al. (38) noted a substantially higher rate of ischemic events with RBC administration in their risk-adjusted analysis of cardiac surgery patients receiving RBC transfusion. Marik and colleagues (20) also reported a fall in gastric mucosal pH, an indicator of splanchnic hypoxia, after transfusion of RBCs stored for more than 15 days. Preclinical studies have suggested the possibility of reduced microcirculatory oxygenation in the setting of RBC transfusion as well (21). In contrast, Walsh and colleagues’ recent randomized controlled trial failed to confirm this finding (50). Though conflicting data exist, available evidence provides remarkably little support for the once unquestioned benefit of RBC transfusion.
Risks associated with RBC transfusion

Concern over the potential transmission of blood-borne pathogens such as human immunodeficiency virus (HIV) has led to a heightened awareness of the risks associated with allogeneic RBC transfusion. Although advances in blood banking strategies have markedly reduced the incidence of transfusion-transmitted infections, increased scrutiny of transfusion practices has identified several additional adverse outcomes associated with RBC administration. Chief among these concerns is the mounting evidence correlating RBC transfusion with risk-adjusted mortality (38,47,51,52). Importantly, multiple studies have suggested this association becomes stronger with increasing duration of RBC storage (53). Multiple additional adverse effects of RBC transfusion are believed influenced by the RBC storage lesion as well.

In 1999, the Transfusion Requirements in Critical Care investigators published results from their randomized controlled trial of restrictive versus liberal transfusion strategies in critically ill patients (48). A trend towards higher mortality was noted in the liberal transfusion group. More recently, Koch and colleagues performed a large, single-center, retrospective review of RBC transfusion in patients undergoing cardiac surgery (52). When compared to those who received fresh blood (≤ 14 days old), patients who received older blood (> 14 days old) had a higher rate of in-hospital mortality (1.7% vs. 2.8%, p = 0.004). Concerns over the unequal distribution of patients who received massive transfusion tempered the results of this trial and while multiple additional studies have suggested the presence of higher mortality with increasing RBC storage age, (54,55) findings to the contrary exist as well (56). At present, the conflicting data prevent definitive statements on the effect of an RBC storage lesion on mortality.

As noted, allogeneic RBC administration can have profound affects on recipient immune function. While some aspects of the immunomodulatory process appear short lived, others appear to have long term or potentially permanent impact (57). Mounting evidence associates these immunomodulatory effects with an increased risk for nosocomial infections (38,47,58). This association has been noted in multiple surgical populations (38,58) in addition to those who are critically ill (31,47). This risk of infection has also been associated with RBC storage duration (52,59,60). While it has been suggested that the causative immunosuppressive factors arise from leukocyte contamination, (35) the impact of leukoreduction has been inconsistent (37,38,61). Though leukocytes and leukocyte-derived products (e.g. RANTES) likely have a role, additional non-leukocyte derived products such as the above mentioned CD-40 ligand and lyso-PC may be involved as well.

Conceptually, the lungs are particularly susceptible to the adverse effects of stored RBCs as the pulmonary microcirculation is the first exposed to the mediators of a storage lesion. Transfusion-related pulmonary complications, and in particular TRALI, have emerged as the most important group of complications resulting from transfusion (62). In addition to plasma transfusion from alloimmunized donors, biologic response modifiers that accumulate during storage of cellular blood products (e.g. sCD40L and Lyso-PC) are implicated in the pathogenesis of this syndrome (39,63). In contrast to febrile reactions, donor white blood cells are not believed instrumental in mediating the pulmonary vascular permeability seen in TRALI (36). In a recent experimental study, plasma from stored LR-RBCs induced a disruption of pulmonary endothelium and resulted in increased capillary permeability (64). This finding was abrogated by pre-transfusion washing, suggesting a soluble nature of biologic response modifiers. Notably, in our recent prospective study in critically ill medical patients, both the presence of alloantibodies in multiparous female donors and a higher LysoPC concentration (odds ratio 1.5 for each 10 µL, p<0.01), but not RBC storage age per se were associated with development of TRALI.

In addition to the adverse effects described above, RBC transfusion has also been associated with the development of multi-organ failure (MOF) (53,65). Zallen and colleagues evaluated RBC transfusions in trauma patients and demonstrated that the mean duration of storage of RBCs, the number of RBC units stored for longer than 14 days, and the number of RBC units stored for more than 21 days were all independent risk factors for MOF (53). In a more recent single-center retrospective evaluation of patients undergoing re-operative cardiac surgery, similar findings were reported (65). In addition to an association between RBC storage duration and mortality, a particularly strong correlation was noted between mean duration of RBC storage and postoperative acute kidney injury. While intriguing and hypothesis generating, this data must be interpreted with caution due to its retrospective nature and potential for multiple uncontrolled confounding variables.
CONCLUSION

The past two decades have witnessed an extensive re-evaluation of the risks and benefits of RBC transfusion. Accumulating evidence questions the efficacy of RBC administration while simultaneously exposing previously unrecognized risks. Multiple investigations have identified an array of biochemical, biomechanical, and immunologic changes which occur within RBCs and the associated storage media during the storage process. These alterations are collectively termed the "RBC storage lesion." Mounting evidence suggests a potential relationship of RBC storage lesion with transfusion-associated complications such as nosocomial infection, multiorgan failure, and mortality. Unfortunately, available data are conflicting and likely confounded. Prospective trials will need to confirm this relationship before strategies aimed at preventing or avoiding the RBC storage lesion are pursued.

REFERENCES

(12) d’Almeida M.S., Gray D., Martin C., Ellis C.G., Chin-Yee I.H. Effect of prophylactic transfusion of stored RBCs on oxygen reserve in response to acute ischemic hemorrhage in a rodent model. Transfusion 2001;41:930-936.
(64) Rao R.S., Howard C.A., Teague T.K. Pulmonary endothelial permeability is increased by fluid from packed red blood cell units but not by fluid from clinically-available washed units. J. Trauma 2006;60:851-858.
THIGH COMPARTMENT SYNDROME, PRESENTATION AND COMPLICATIONS

ERIC G. VERWIEBE¹, ENES M. KANLIC¹*, JEREMY SALLER², AMR ABDELGAWAD¹

¹ Department of Orthopaedic Surgery and Rehabilitation at Texas Tech University HSC in El Paso, 4801 Alberta Ave. El Paso, TX
² Department of Orthopaedic Surgery and Rehabilitation at Texas Tech University HSC in Lubbock, 3601 4th Street – STOP 9436, Lubbock, TX

* Corresponding author

ABSTRACT

To describe the patient population, etiology, and complications associated with thigh compartment syndrome (TCS). TCS is a rare (0.3% of trauma patients) condition of elevated pressure within a constrained space that may cause necrosis of all tissues within the compartment resulting in severe local (infection, amputation) and systemic complications (renal insufficiency, even death). Retrospective cohort This study examines the course of treatment of nine consecutive patients with thigh compartment syndrome sustained during an eight-year period at our Level 1 trauma centre, admitting more than 2,000 trauma patients yearly. Patients developing TCS were young (average 34.8 years) and likely to have a vascular injury on presentation (55.5%). A tense and edematous thigh was the most consistent clinical exam finding prompting the compartment release (77.8%). Average time from admission to the operating room was 19.8 ± 6 hours and 3/9 (33%) were noted to have ischemic muscle changes upon compartment releases. Complications ranging from infection to amputation developed in 4/9 (44.4%) patients.

TCS is associated with high energy trauma and it is difficult to diagnose in non-cooperative - obtunded and polytrauma patients. Vascular injuries are a common underlying cause and require prompt recognition and team work including surgical intensive care, interventional radiology, vascular and orthopaedic surgery in order to avoid severe medical and legal consequences.

KEY WORDS: thigh injuries, compartment syndrome, amputation, renal insufficiency
INTRODUCTION

Compartment syndrome of the thigh is a serious condition resulting from increased pressures and muscle damage within any of the three thigh fascial compartments. The most common aetiologies include blunt trauma, with or without fracture, vascular injuries with ischemia reperfusion, or frank bleeding into the myofascial spaces (1,2,3). While the mechanism of compartment syndrome has been well described in the literature, the outcomes of those affected by thigh compartment syndrome have not. A review of the English literature reveals only two series, aside from isolated case reports, which document the outcomes of this condition. Schwartz et al. reported on their results of 17 patients and Mithöfer et al. on 28 patients with thigh compartment syndrome (4,5). In some patients this syndrome leads to significant morbidity and mortality with others experiencing complete recovery. The disparity in outcomes may result from different mechanisms of injury, severity of soft tissue trauma, fracture, and/or the timing of treatment. Once thigh compartment syndrome is identified, immediate and complete compartment releases are required to prevent further ischemic insult to the tissues. This may not be the case when the diagnosis is delayed more than twelve hours, as the complication rate increases precipitously. There are many reasons the diagnosis or intervention may be delayed including prolonged extrication, transfer time to definitive treatment facility, or other emergent medical or surgical life threatening injuries. The obtunded and/or intubated patient, if the treating physician is not vigilant, is the most likely to experience a delay in diagnosis and subsequently the clinical outcome for this group is poor. Sheridan et al. showed that when the fasciotomy is performed more than twelve hours after diagnosis, complication rate increased from 4.5% to 54% with 1 in 5 patients requiring amputation (6). To further elucidate the timing of optimal intervention and better understand the impact of injury mechanism on outcomes, we present our cohort of nine patients with thigh compartment syndrome.

MATERIALS AND METHODS

We performed a retrospective review of trauma registry at Thomason Hospital, the only Level 1 Trauma Centre in El Paso, Texas. Approximately 2,000 severely injured patients are admitted to our centre yearly, and we looked specifically for those patients diagnosed with thigh compartment diagnosis during the period of September 1999 to March of 2007. The Institutional Review Board approved the study protocol. Nine patients with thigh compartment syndrome were identified. The data collected included time and mechanism of injury, time to surgical decompression, associated injuries, vital signs and GCS (Glasgow Coma Score) on presentation, compartment pressure measurements, muscle appearance at the time of surgery, subsequent surgical interventions, hospital length of stay, and ultimate outcome following definitive closure to include infections, nerve damage, chronic pain, and amputation. In the awake and alert patient, the diagnosis of compartment syndrome was made most often using clinical criteria to include pain out of proportion to injury, pain with passive stretch (can be complicated by the presence of fractures), palpation of compartment tension (anterior – quadriceps, posterior – hamstrings and medial - adductors compartments - muscles), and hypoesthesia or changes in motor function in the distribution of the nerves traversing the compartments in question (femoral, sciatic and obturator nerves) (7). The presence or absence of distal pulses was noted but not used as a sole criterion for compartment release as several patients had vascular injuries below the level of Hunters canal. The changes in distal pulses may result from a late compartment syndrome or an acute vascular injury. For non-cooperative, obtunded and polytrauma patients intubated prior to examination, both compartment pressure measurements and clinical exam finding of palpably tense compartments were used in the decision making process. Absolute compartment pressures greater than thirty millimetres of mercury were considered diagnostic, especially in the critically patient where blood pressure fluctuations may alter tissue perfusion pressures acutely (8). In those patients not at risk for development of hemorrhagic shock, a delta pressure (Δp) of less than 30 mm Hg was used as an indication for fasciotomies (9). The compartments of the thigh were released through a single, long, lateral incision to access the anterior compartment directly and posterior compartment through the lateral intermuscular septum (10). After these compartments were released, a repeat evaluation of the medial (adductor) compartment was performed. If pressures remained elevated, the medial compartment was released through a separate incision. Assessment of muscle viability was made at the time of surgical decompression using the bovie for electrical stimulation in conjunction with contractility when grasping muscle tissue with forceps. If muscle twitch was not noted following stimulation with electro-cautery, then appropriate debridement was carried out until bleeding and contractile muscle was encountered. Most incisions
following fasciotomy were left open and treated with either non-adhesive dressings or a vacuum assisted device. Split-thickness skin grafting or delayed primary closure was performed after subsidence of swelling, usually in timeframe of five to seven days. If necrotic muscle was encountered, a thorough debridement was carried out, a drain placed, and primary closure easily performed (without tension) to prevent contamination or infection.

**RESULTS**

The average patient age was 34.8 years. The primary mechanism for development of thigh compartment syndrome was motor vehicle collision in 4/9 (44.4%), blunt injuries to the thigh including those with pelvic fractures 3/9 (33%), isolated gunshot wound to the thigh 1/9 (11.1%), and intramuscular injection of drugs 1/9 (11.1%). A vascular injury which may have contributed to development of compartment syndrome was present in 8/9 (88.9%). This includes patients with injury to the femoral arteries (Figures 1 - 5), external iliac vessels and retroperitoneal vessels that may have contributed to abdominal compartment syndrome and thus decreased venous return from the lower extremity. Tense compartments were noted in 11/9 patients (11.1%). The anterior compartment had the highest pressures. Average time from admission to compartment releases in the operating room was 19.8 ± 6 hours. Nonviable muscle was noted in 3/9 patients (33.3%) and follow-up information was available on all nine patients. Of these, 1 patient required an above knee amputation for complications relating to infection, closed femur fracture, open fracture of the ipsilateral tibia, and compartment syndrome of the leg. Three minor complications were also reported to include hematoma formation, superficial infection, and local tissue necrosis treated with limited debridement. Ipsilateral femur fractures were noted in 4/9 patients (44.4%), three closed and one open. Three fractures were treated with intramedullary fixation at time of thigh compartment released and one with external fixation. There were no fatalities in this series. Wound closure data was available on 8/9 thighs. Primary closure of the fasciotomy sites was performed in 5/9 (55.6%) thighs, delayed primary closure in 1/9 (11.1%), split thickness skin grafting in 3/9 (33%), full thickness skin grafting in 1/9 (11.1%), above knee amputation with split thickness skin grafting in 1/9 (11.1%).

**DISCUSSION**

Thigh compartment syndrome remains a rare clinical entity with only two complete series reported in the English literature comprised of 45 patients (4,5). The variability in patient outcomes following treatment of TCS is not only a function of injury mechanism.
but also the timely and accurate diagnosis of reversible muscular ischemia and immediate surgical intervention. In a canine model, Matava et al. showed that eight hours of increased intracompartmental pressures to within 20 mm Hg of the diastolic blood pressure (Δp) was the critical threshold for ischemic muscle necrosis (11). In an earlier study, Heppenstall et al. also showed that ischemic changes may be present in a four to six hour time frame when the Δp approached 50 mm Hg. They also suggest that periods of hypotension may result in muscle damage at even lower compartment pressures (12). These studies highlight the need for increased emphasis to be placed on compartment pressure monitoring or serial examinations in those patients who are at risk for developing TCS as the window for successful treatment may be very narrow.

Whereas fracture is the leading cause of compartment syndrome in the leg, thigh compartment syndrome is more commonly associated with blunt trauma or vascular injury (7,8,44). Hope et al. reported on 184 cases of acute compartment syndromes, including both upper and lower extremities, noting that only 40% of those developing compartment syndromes of thigh could be attributed to a fracture (14). This contrasts sharply with the 77.8% of his patients whose compartment syndromes of the leg were attributed to tibia fractures. In addition, compartment syndrome of the leg was diagnosed in 59.6% of this cohort while thigh compartment syndrome was present in only 6.6%. This makes selection of those who are at risk for developing TCS more difficult as the sentinel event may be more obscure than a displaced femoral shaft fracture and the frequency at which this is seen is considerably lower than that of the leg. Case reports of thigh compartment syndrome highlight the diverse mechanisms of injury to include exercise induced, quadriceps tendon rupture (1), drug popping, crush injury, thigh contusion, aggressive resuscitation in the trauma setting, positional ischemia, aneurysm, following joint replacement, deep venous thrombosis, vascular injury, and of course fracture (2, 5,10, 27, 29, 31, 33). In our study, the vast majority of TCS resulted from blunt trauma to the pelvis or lower extremities in 6/9 (66.7%) thighs. Of these patients, 4/9 (44.4%) had fractures of the ipsilateral femur. Vascular injury was the most common mechanism in our cohort. Those were present in the ipsilateral extremity in 5/9 (55.6%) cases, making this diagnosis likely in the face of a developing TCS, though only 3/9 (33%) involved the superficial femoral, iliac, or deep femoral vessels. This rate of vascular injuries is higher than that previously published by Mithöfer et al. 7/52 patients (47%) and Schwartz et al. with 7/41 patients (17.1%) (7.8). The most consistent objective exam finding leading to diagnosis of TCS was a tense and oedematous thigh noted in 7/9 (77.8%) compartment syndromes. Pain and paresthesias to the effected extremity have also been well supported in the literature as an indication for impending compartment syndrome. This was documented in only 6/9 (66.7%) of thighs lending to the high energy mechanisms and multiple systems involved in these patients. These findings will only be useful in the awake and alert patient. Two of 9 (22.2%) patients were intubated either on scene or upon arrival to our trauma centre due decreased GCS. The difficulty in managing patients who are at risk for developing TCS is early recognition, especially in
the poly-trauma patient who is intubated and sedated. While TCS may be obvious on initial exam in the trauma bay, it also may develop insidiously over the next 24-48 hours as seen in two patients in our series. It is critical to identify at what time intracompartmen-ental pressures have reached the critical, tissue “suffocating” level. Our average arrival to the operating room for compartment releases was 19.8 ± 6 hours from the time of admission to our facility (clearly documented). This wide range resulted from two patients who developed thigh compartment syndrome after 30 and 45 hours respectively. They were closely monitored during their hospital course and were both noted to have viable compartments at time of decompression, resulting in excellent outcomes. At surgical decompression 3/9 (33%) of our patients had nonviable or dusky muscle noted and one of those patients required an amputation. The other two patients with dusky musculature did not develop a wound infection. The overall complication rate was high (44.4%): 1 hematoma requiring second procedure and evacuation, 1 deep wound infection, and 1 amputation. Of patients who experienced complications, 75% sustained a vascular injury. Mithöfer et al. reported similar duration (measured from time of injury) of 11.1 ± 3 hours for all patients and 14.5 ± 5.8 hours in those patients presenting without fractures, though they reported a much lower complication rate of 18% (5). Schwartz et al. did not report the time from injury to fasciotomy but the time of diagnosis averaging 4 hours. They reported a much higher wound complication rate of 66% though there were no reports of amputations (4). Wound closure data was available in 8/9 of our patients. Definitive treatment of the fasciotomy sites often (50% of patients) required skin grafting for closure which is comparable to the Schwartz et al. cohort (41%) and significantly higher than the Mithöfer cohort (12%). Delayed or primary closure of the incision sites was possible in 3/8 (37.5%) thighs. We had no fatalities in this series, though previous series have shown mortality rates to be between 11% - 47% depending on the study (4.5).

**Conclusion**

The key to successful treatment of compartment syndrome in any location depends on a prompt diagnosis of pending muscle and nerve ischemia and expedient compartment releases. While these large surgical wounds will often require secondary procedures for definitive closure, the benefits of early release surely outweigh the risks, evidenced by the poor results in those who had necrotic muscle at the time of compartment release. One out of three such patients in our study required an amputation. A careful clinical exam at the time of admission and diligence with serial examinations of the extremity at risk may identify the majority of TCS in the awake and alert patient, but other objective measures need to be employed in the obtunded or multiply injured patient. The side port needle used with the Stryker system remains a mainstay in the measurement of compartment pressures at our institution. Though it provides only a single data point regarding a condition that is both continuous and dynamic, its accuracy and simplicity often help to confirm compartment syndrome in patients with a confusing exam or in those who are unresponsive. Continuous monitoring of extremities at risk using an arterial line manometer as described by Matsen et al. should be considered when a more comprehensive set of data is required (8). Newer technologies include infrared imaging of the extremities in the trauma setting, using temperature differences between the proximal and distal skin surfaces in order to make the diagnosis (31). This technology is promising though requires additional equipment in the emergency room setting, software, and personnel for data interpretation.

Regardless of the technology employed, strong consideration for early compartment releases should be given to those patients sustaining high energy injury mechanisms to the thigh, with or without fractures. The treating physician needs to be well versed in detecting the signs and symptoms of TCS and strongly consider continuous intracompartmen-tal monitoring in the uncooperative or sedated patients. For the cooperative patient, a clinical diagnosis is sufficient to move forward with urgent compartment releases. For patients in whom the diagnosis has been delayed for more than twelve hours (or even 6 hours in the face of high intracompartmen-tal pressures), strong consideration should be given to avoid exposing these damaged tissues to the environment due to increased infection risk (32). In this subset of patients, aggressive management of medical issues to prevent renal damage may better serve these patients, allowing for preservation of limb, life, and late reconstructions (33).
MEDICAL INFORMATICS: AN ESSENTIAL TOOL FOR HEALTH SCIENCES RESEARCH IN ACUTE CARE

MAN LI¹, BRIAN W. PICKERING¹, VERNON D. SMITH¹, MIRSAD HADZIKADIC², OGNJEN GAJIC¹, VITALY HERASEVICH*¹

¹ Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) Mayo Clinic, Rochester, MN USA

² College of Information Technology, University of North Carolina, Charlotte, NC USA

* Corresponding author

ABSTRACT

Medical Informatics has become an important tool in modern health care practice and research. In the present article we outline the challenges and opportunities associated with the implementation of electronic medical records (EMR) in complex environments such as intensive care units (ICU). We share our initial experience in the design, maintenance and application of a customized critical care, Microsoft SQL based, research warehouse, ICU DataMart. ICU DataMart integrates clinical and administrative data from heterogeneous sources within the EMR to support research and practice improvement in the ICUs. Examples of intelligent alarms – “sniffers”; administrative reports, decision support and clinical research applications are presented.

KEY WORDS: ICU, EMR, DataMart, alarm, dashboard, modeling
INTRODUCTION

The practice of medicine and biomedical research are information-based sciences which involve gathering, synthesizing, and acting on information. As early as the 19th century, mechanical computers have been applied in the medical field. Herman Hollerith’s “punched-card data-processing system,” originally used for the US census, was subsequently developed to support surveys in public health and epidemiology (1). Medical informatics is the applied science of patient data management for the purpose of improving understanding of health and bioscience. It is, by its nature, a multidisciplinary science with interactions across a number of fields. Medical informatics was static until the invention of the first generation of digital computers in the 1940s. Since then it has played an increasingly important role in health care and as a novel academic discipline acts as a bridge between medical and information sciences (2).

Health information technology, an example of which is the electronic medical record (EMR), consists of: the clinical data repository, clinical decision support tools, controlled medical vocabulary, computerized provider order entry, pharmacy, and clinical documentation applications. It supports in- and out-patient’s EMRs, and is used by care providers to document, monitor, and manage service delivery within health care organizations. EMR has being broadly advanced by governments, healthcare providers, large employers, hospitals, and organized medicine (3, 4). The adoption of EMR brings an unprecedented opportunity for providers, but ill considered implementation can lead to information overload (5) and an increase in the very errors they are expected to reduce (6). Central to this opportunity is a means of organizing and analyzing large quantities of digital information, the principal task of medical informatics.

The relevance of ICU care to public health in the United States is reflected in annual figures of 4.4 million ICU admissions, 500,000 deaths, 13.3% of hospital costs, 4.2% of national health, and 0.56% of the gross domestic product expenditures (7, 8). The demand for ICU services is expected to increase as the US population ages; patients older than 65 years currently account for more than 55% of all ICU days (9, 10). Unmeasured burdens include a high degree of disability and associated loss of productivity for both ICU survivors and their caregivers (11-13).

Clinical and translational research benefits from the availability of a comprehensive medical record. Extracting information from the clinical record has always presented a challenge. The current generation of EMRs were not developed to support clinical research activities and do not routinely support systematic data access and queries. This significantly impedes the development of complex real-time alerts or reports for clinical practice, administrative and research purposes. Most data continues to be retrieved manually from the EMR and entered back into a research database. This process is time consuming, and error prone (14). A better solution would be to transfer data automatically, efficiently, and accurately between the EMR and research database (15). The medical records of all new patients coming to Mayo Clinic, Rochester, Minnesota, are in an electronic form since early 2005 (16, 17). Using this resource we have developed a customized near-real time open schema ICU data warehouse, “ICU DataMart”. ICU DataMart accommodates 3 major strategic objectives: 1) practice monitoring, reporting and feedback, 2) intelligent alert systems and 3) education, research and decision support (18). In this article we share our initial experience in the design, maintenance and application of ICU DataMart to achieve those objectives.

Hospital Overview

Mayo Clinic, Rochester campus is an academic medical center with two hospitals. There are approximately 1900 beds and 135,000 hospital admissions per year (2006). The combined ICU capacity is 201 beds with 14,800 admissions per year (2007). As a national tertiary/quaternary referral centre Mayo Clinic, Rochester also provides primary and secondary care to all the residents of Olmsted County. Remarkably only Mayo Clinic provides ICU services to the county population. Access to a geographically defined cohort of patients allows us to conduct population-based studies. All ICUs are equipped with multiple Dell workstations, with password protected EMR and clinical database access, with 24/7/365 institutional IT support.

ICU DataMart Overview

The ICU DataMart project was approved by the institutional Critical Care Committee as a quality improvement project. All research projects require Institutional Review Board approval. The main platform is a Microsoft SQL based database which integrates a near real time copy of clinical and administrative data from the heterogeneous and distributed EMR. Data points are extracted and copied within 15 minutes (physiological monitors) to 4 hours (clinical notes) from entry into the EMR.
Data from external sources (Minnesota death registry) are updated once per quarter. The components of METRIC DataMart are schematically outlined in Figure 1.

Data Security and Confidentiality

Patient oriented research projects guarantee patients’ confidentiality and security in accordance with institutional policy and Health Insurance Portability and Accountability Act (HIPAA). Providers require an institutional, single log on, password and must have successfully completed a review of HIPAA in order to access patient data.

User Interface

For end users, who are not technical “gurus” the most important requirement when designing a database is the availability of a simple, intuitive user interface (UI) which does not require specialized programming knowledge. As the UI for research purposes we have adopted the JMP statistical software (SAS Institute, Cary, NC), a standard statistical analysis tool available at each workstation within the institution. JMP’s advanced intuitive query builder (Figure 2.) not only allows easy access to data but also provides a means for advanced statistical analysis. The institution provides JMP user education classes and extensive online support materials.

Database Management

For database development and administration we have used the EMS SQL Manager 2008 for SQL Server (EMS, New York, NY), which is a flexible, high performance tool for Microsoft SQL Server database administration. The versatile array of tools available include; Visual Database Designer which supports the creation of SQL Server database in few clicks; Visual Query Builder and advanced SQL editor which allow the user to build complex SQL Server queries. SQL Manager has an intuitive graphical user interface.

Data Validation and Integrity

It is the fundamental goal of any medical informatics project to provide secure, accurate and reliable data storage. The main challenge for the support team is the provision of effective outage detection and repair responses such that data and application integrity are always maintained. A customized monitor application runs every 2 hours and checks the status of each table within the database. If a table is out of range for
MAN LI ET AL.: MEDICAL INFORMATICS: AN ESSENTIAL TOOL FOR HEALTH SCIENCES RESEARCH IN ACUTE CARE

updating, an alert message is issued to the ICU DataMart administration team via pager and/or email with specific detailed information (table, time of outage etc.). In this way the team can find and repair the problem and fill any resulting data gap in a timely fashion. A web based dashboard continuously displays the status of the database including the latest time each table had been updated. Descriptive statistical data analyses are run at monthly intervals to discover any unusual data patterns. As part of the quality control process we perform regular historical data auditing in which we randomly compare selected data sets from ICU DataMart to source data from the original EMR.

**Sniffers: Intelligent Alert System for Decision Support and Research**

The availability of large quantities of data within the EMR can cause information overload (19) and the impact this has on clinical judgment is of genuine concern. Neither EMR nor modern Clinical Information Systems provide effective solution to these problems. On the other hand, the availability of data in an electronic format provides an opportunity for automated solutions, including electronic patient surveillance. Early detection of critical care syndromes such as sepsis, shock and acute lung injury (ALI) can improve outcome and decrease the cost of medical care (20). Bedside ICU monitors are not designed to recognize complex physiologic syndromes. Most generated alarms are clinically insignificant, and serve only to distract bedside providers (21). While syndrome surveillance technology has been widely used in public health, of the availability of an EMR facilitates the expansion of these techniques into the areas of clinical medicine, quality improvement, patient safety and research. By using patients’ data from ICU DataMart we have designed, tested and implemented syndrome surveillance in the ICU. “Sniffers” are custom built, JAVA computer programs which facilitate syndrome surveillance and allow rule based query building. These rules are easily modified with a limited need for additional coding with each new query (22, 23). Sniffers run at pre-specified intervals and when they detect that a patient’s condition has met some predefined criteria they trigger a system response. This response is initiated through an alert message directed to the appropriate person(s) via email and/or pager. From a technical prospective, sniffers utilize object-oriented design, and are implemented through open source technologies such as Java. This renders them platform and data source independent. Sniffers can be deployed across multiple databases with simi-
lar characteristics. The growing list of applications in the host institution includes: decision support for ICU discharge decisions; personalized mechanical ventilation orders; detection of transfusion complications; acute lung injury prevention; and enrollment into time sensitive clinical research studies.

Practice Reporting

Quality of care is usually estimated in structure, process, and outcome. The metrics describing those domains are often poorly defined and difficult to measure. However, the measurement and analysis of processes of care are essential components of quality improvement initiatives. Administrative reports should be readily available to a management team tracking service utilization, costs, quality and billing. Unfortunately, most of the high level administrative reporting is meaningless as it is based on flawed data; most elements known to be important indicators of processes of care are either not captured, or are captured with insufficient accuracy to be useful. The EMR, on the other hand, is a rich source of pertinent information. The current generation of clinical information systems do not routinely support the generation of practice management reports.

Statistical process control (SPC) is an effective method of monitoring a process through the use of visual charts. This approach is increasingly common in the analysis of health care processes. Using the SPC approach we have developed and implemented the SAS (SAS Institute, Cary, NC) based administrative Clinical Reporting Tool (CRT) and Score Calculation Tool (SCT). CRT is a web-based reporting tool which generates customized reports of the main ICU processes of care and resource utilization. A total of 47 variables were selected for inclusion by the institutional Critical Care Committee. The leadership teams in individual ICUs can choose to report any combination of these variables, for example, length of ICU and hospital stay, ventilator free days, admission source and service code, etc. The output can be represented either in chart or table formats (Figure 3). Add-hoc reports are available on request.

One of the first quality improvement projects supported by ICU DataMart focused on reducing ICU readmissions. Unintended readmission to the medical intensive care unit (MICU) is associated with worse outcome and the provider’s ability to predict which patients are likely to deteriorate after ICU dismissal is limited. Our group has developed and implemented an automated tool which identifies discharged patients at high risk for ICU readmission. The tool calculates each patient’s Stability and Workload Index for Transfer (SWIFT) score, a calculation based on ICU admission source, ICU length of stay, and day of discharge neurologic (Glasgow Coma Scale) and respiratory (arterial blood gas) dysfunction. Results are displayed on a web-based dashboard and are used daily for ICU discharge decision making by clinical providers.

Clinical Research

ICU DataMart has been extensively used in observational research projects and facilitates screening of patients who may be eligible for enrollment into clinical trials. Automated alerts notify study coordinators via e-mail or pager when patient characteristics fulfill study specific enrollment criteria, thus greatly improving the
efficiency of clinical research in the acute setting. Novel research applications supported by ICU DataMart include simulation modelling of sepsis resuscitation, physiologic modelling of acute lung injury development and complex adaptive system modelling of critical illness and life support interventions in the community.

CONCLUSION

The reduction of error and waste is one of the key strategic goals of modern hospitals. The availability of data in electronic format facilitates the development of novel medical informatics approaches in support of quality improvement and research in complex hospital environments, such as the ICU.

REFERENCES


(23) Oppenheim M.I. et al., Design of a clinical alert system to facilitate development, testing, maintenance, and user-specific notification. Proc AMIA Symp. 2000; p. 630-634.


EXTRAMEDULLARY INTRADURAL SPINAL TUMORS: A REVIEW OF MODERN DIAGNOSTIC AND TREATMENT OPTIONS AND A REPORT OF A SERIES

KENAN ARNAUTOVIC*, ASKA ARNAUTOVIC

Semmes-Murphey Clinic and Department of Neurosurgery, University ofTennessee, Memphis, TN, USA

* Corresponding author

ABSTRACT

Extramedullary intradural spinal tumors are rare. Less than 15% of all central nervous system (CNS) tumors are spinal. Ninety percent of these patients are older than 20 years. Most of spinal tumors are extradural (50-55%) whereas 40-45% are intradural. Furthermore, 5% are intramedullary and 40% are extramedullary. Most common are Schwannomas (29%), followed by meningiomas (25%) and gliomas (22%). These tumors produce pain syndroms, a variety of neurological symptoms - motor, sensory, sphincter or a combination of thereof. All spinal levels may be involved. The diagnostics includes magnetic resonance imaging (MRI) including contrast enhancement, computerizing tomography (CT) scanning (bone windows with reconstruction) and possibly CT myelograms. Preferred treatment is the microsurgical radical resection. Perioperative mortality is very low as is serious morbidity.

We herein discuss various aspects of presenting symptomatology, diagnostics, preoperative planning and tactics, surgical treatment and complications. In addition, we include our own retrospective experience with 14 patients treated over the 5.5 years time interval.

KEY WORDS: spine; spinal cord; tumors; intradural; extramedullary; meningiomas; Schwannomas; ependymomas
INTRODUCTION

Spinal tumors comprise 15% of all CNS tumors. Their annual incidence is 2-10 per 100,000. Ninety percent of these patients are older than 20 years. Most common spinal tumor location is extradural (55-60%), where cancer metastasis to spine leads the way. Primary vertebral bone tumors are less frequent extradural spinal tumors (1-4%). Extramedullary, intradural spinal tumors (EISTs) are rare. They comprise about 40-45% of all spinal tumors. They are distinguished from intramedullary tumors by their extra-axial location. First recorded resection of EIST has been done by Sir Victor Alexander Haden Horsley (1888) in a 42 year old patient. The lesion has been originally classified as fibromyxoma, but was probably a degenerated Schwannoma (5). The mean age of patients with EISTs is 46 years and 54-57% of them are male. Their annual incidence is 0.4 per 100,000 population. An average neurosurgeon may see 1-2 EISTs patients per year, a neurologist 1 patient every 8-9 years, whereas every third general practitioner will see a case during their carrier (5, 6).

Presenting signs and symptoms

Median time to diagnosis is 12 months and cauda equina location is not presenting earlier than other spinal locations. The symptoms are lesion nonspecific and do not differ between intramedullary and extramedullary locations. Most common initial symptom is pain, which may be local and nocturnal or radiating to arm and/or leg. Sphincter dysfunction, paraparesis and erectile dysfunction occur in 50%, 15% and 2% of patients respectively (3, 6, 7).

Diagnostics

Primary diagnostic modality for EISTs is magnetic resonance imaging (MRI) without and with contrast enhancement. Diagnostics also include plain X-ray imaging in anterior-posterior, lateral and dynamic (flexion, extension) projections. Furthermore, computerized tomography (CT) scan, thin cuts with reconstructions (“bone windows”) are important to evaluate bony anatomy. In patients who could not undergo MRI scanning, CT myelography is an alternative. Most common tumors within the EISTs group are meningiomas, nerve sheath tumors, and filum terminale ependymomas, making up to 85% of this group (3). Dumbbell appearance accounts for 18% of EISTs, with cervical location being most common. Most common tumors with dumbbell appearance are Schwannomas (60%), followed by neurofibromas (12%). Least common dumbbell appearance have meningiomas (5%) (8).

Meningiomas

Meningiomas arise from arachnoid cap cells embedded in dura near the spinal nerve root sleeve. They are second most common EISTs. Their predominant spinal canal location is lateral. Other cells of origin may be fibroblasts associated with the dura or pia. In this case the tumor has a ventral dural origin. Frequently the attachment to dura is broad based. Most common patients' age interval is between fifty and seventy years although any age group may be involved. They are more common in women (75-85%) and in the thoracic location (80%). In 75% of meningiomas, calcifications were registered. Most commonly they are solitary although 1-2% may be multifocal, particularly in neurofibromatosis type I (NF I) patients. Majority of spinal meningiomas are intradural, although 10% may involve extradural location. Spinal meningiomas are iso- or hypointense on T1 weighted images and slightly hyperintense or hypointense on T2 weighted MRI. Upon contrast application they enhance vividly (except for a calcified part) and frequently display a “dural tail” sign. Only 5% of meningiomas may present in a dumbbell shape (1-4, 9-14).

Nerve sheath tumors

Spinal nerve sheath tumors (SNSTs) include Schwannomas (neuromas, neurinoma, neurilemmomas) and neurofibromas. They are most frequent EISTs. Schwannomas are composed of Schwann cells with fibrous tissue. These tumors may show cystic degeneration and hemorrhage. They usually displace nerve roots. If they are multiple, they may be associated with NF II patients. Neurofibromas are composed of Schwann cells, fibroblasts, and nerve fibers in a matrix of mucopolysaccharides, fluid and fibrous material. Typically SNSTs are found on the dorsal sensory roots which they encase. There is no gender predilection. Most commonly they are seen in cervical and lumbar regions; less frequently in the thoracic spinal segment. Predominantly they have an intradural location but 25% are completely extradural and 15% are intra/extradural. Their peak incidence is fourth decade of life. Ninety % of these tumors are benign. Multiple tumors are typical for NF I patients. SNSTs are isointense on T1 weighted MRIs and have hyperintense signal on T2 weighted...
images. Upon contrast application enhancement is variable. SNST may present in a dumbbell shape. If they do, there is a 80% chance that a tumor is a SNST. If they reach a large size, they may remodel intravertebral foramen or even erode or cause scalloping of the posterior aspect of the vertebral body (1-3, 7-14, 17).

Filum terminale ependymomas

Fifty percent of all ependymomas are spinal. Within spinal ependymomas, 50% are intramedullary and another 50% are located within terminal filum. Despite the neuroectodermal origin of filum terminale, from anatomical and a surgical perspective it is appropriate to group them with IESTs. Filum terminale ependymomas arise from ependymal rests in filum terminale and are of myxopapillary histologic variant. They can occur at any age but most commonly between 3rd and 5th decades. These tumors are well circumscribed and seldom infiltrate the dura. After radical resection recurrence is generally rare although subarachnoid seeding is possible. On T1 weighted images they are hypo- or isointense and are hyperintense on T2 weighted MRIs. Homogenous or heterogenous enhancement is seen upon contrast application (3, 9, 11, 12).

Preoperative planning and treatment

EISTs can significantly compress and displace the spinal cord, the nerve roots or even the surrounding structures (e.g. the vertebral artery). This can impact preoperative neurologic presentation and operative morbidity. Gross total tumor resection while preserving and improving neurologic function is the usual goal of surgery. This can be achieved in great majority of cases. Intraoperative monitoring - somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP) may be utilized. Intraoperative ultrasound may at times be useful to evaluate intra-operative extent of lesion and radicality of surgery. After a detailed clinical, neurologic and neuroradiologic evaluation, the operative approach is planned. Approaches are based upon location of the tumor, its extension, its size and other parameters. The goal is to provide maximal intra-operative exposure of the tumor, while minimizing damage to the surrounding structures. Excessive removal of bony structures and ligaments may result in spinal instability (4, 5, 14, 15, 17). A normal spine remains stable as long as two out of the three columns remain undisturbed. The anterior column consists of the anterior half of the vertebral body, the anterior half of the intervertebral disk and the anterior longitudinal ligament. The middle column consists of the posterior half of the vertebral body, the posterior half of the intervertebral disk and the posterior longitudinal ligament. The posterior column includes paired facets, the transverse and spinous processes and the paired laminae (16). For most EISTs resections, the posterior approach with midline incision is sufficient. The patient in prone position and neck and spinal alignment should remain as neutral as possible. Certain cases may require awake, fiberoptic intubation to avoid hyperextension. The extent of incision and exposure is guided with topographic anatomy and intraoperative C-arm x-ray navigation in lateral and anterior-posterior projections. While performing laminectomies, care should be taken to preserve facets, its capsules and intertransverse ligaments to avoid postoperative kyphosis and instability. Otherwise, instrument stabilization may be required. Sometimes only hemilaminectomies may suffice for tumor resection. Posterolateral approaches with removal of pedicle and/or costotransversectomy may be necessary for certain ventral thoracic EISTs locations or extraforaminal tumor extensions. Anterior approaches are sometimes needed for ventral cervical locations whereas anterolateral approaches for ventral thoracic EIST locations. Subsequent instrumented fusion is then necessary. (4, 5, 14, 15, 17-20). The results of surgery of EISTs are usually excellent. Even long lasting preoperative neurologic deficit may be improved and reversed postoperatively. Most common complications include CSF leak, pseudomeningocele formation and wound infections. Less common is postoperative spinal instability and neurologic deficit (3-5, 7.

5 Schwannomas
- C2-C3 (41y, M)
- T9-T10 (50y, F)
- L2 (84y, F)
- L4-L5 (32y, F)
- S1-S2 (48y, M)

7 meningiomas
- C1-C3 (75y, F)
- C5-C7 (24y, F)
- T1-T2 (88y, F)
- T5-T6 (62y, F)
- T10 (49y, M)
- T10 (72y, F)
- L2 (69y, F)

2 myxopapillary ependymomas (filum terminale)
- L3 (46y, F)
- L4 (47y, F)

TABLE 1. Overview of the EISTs tumor types, the ages, the gender and locations in our series (y-years, M-male, F-female, C-cervical, T-thoracic, L-lumbar, S-sacral)
Recurrence for radically resected SNST was reported to be 10 and 28% after 5 and 15 years respectively (18, 19). In case with residual tumor and/or recurrence, radiation treatment or radiosurgery may be utilized (22, 23). Chemotherapy may be used in malignant EISTs (3).

**Our Series**

Over the period of 5 and one half years (September, 03-March, 09) the senior author has operated on 14 cases of EISTs. There were 3 men and 11 women. Their age range was 24-84 years with a mean of 56 years. Two patients were septuagenerians and two octogenerians. Most common were meningiomas (7 cases- 50%), 5 were Schwannomas, and 2- filum terminale myxopapillary ependymomas. Follow up range was 1-67 months with a mean of 28 months. The overview of tumor types, ages, gender and locations are presented on Table 1. Four representative cases are demonstrated in Figures 1-4.
Postoperative lateral C-spine x-ray showing good spinal alignment and instrumentation in position. Except for 4 patients with Schwannomas who presented with pain and numbness at their appropriate levels and nerve distributions, all other patients presented with a quadriparesis or paraparesis with the corresponding sensory level and sphincter involvement.

All patients were treated in a prone position, with microsurgical technique. For the cervical spinal EISTs locations, the head of the patient was secured in a 3 point head fixation. Radical tumor resection was confirmed on postoperative MRI scans in all patients. No tumor recurrence was noted during a mean follow up of well over 2 years (48 months). All patients completely recovered their neurologic deficit after the surgery during the follow up period. One patient with sacral Schwannoma developed pseudomeningocele 2 weeks after the surgery and was treated with surgical revision and external lumbar CSF drainage and resolved completely. There were neither perioperative nor follow up mortalities.

Utilizing microscope and microsurgical technique provides the magnification, the illumination, the stereotactic vision, the communication with the remaining surgical team and the education of trainees. A cavitron ultrasonic aspirator (CUSA) may be used for debulking of the tumor. Dural opening should extend beyond the tumor limits proximally and distally and may be midline or off midline. First, proximal dural opening with the release of CSF should be done. This is to avoid cauda equina nerves herniation in dorsal direction. Section of one or more dentate ligaments frequently aids resection. A watertight dural closure is very important to prevent pseudomeningocele formation or cerebrospinal fluid (CSF) leak with resulting meningitis and infection. We have utilized harvest of 5-10 cc of abdominal fat graft via a small, 1 inch incision at the beginning of surgery. This fat tissue was used at closure to obliterate the epidural "dead space." We postulate that resulted in the absence of CSF leaks or pseudomeningocele formation in our series (except the case of sacral Schwannoma where we did not utilize this maneuver).

Frequently, for resection of nerve sheet tumors, sacrifice of the parent nerve may be necessary. Fortunately, this is frequently a sensory branch and ventral, motor

FIGURE 3. 47 y/o F with L3 flum terminale myxopapillary ependymoma presenting with paraparesis, bowel incontinence and L2 sensory level
a) Preoperative sagittal T-1 weighted MRI showing the isointense ependymoma (asterix) compressing the cauda equine nerves.
b) Preoperative postcontrast axial T-1 weighted MRI showing the enhanced ependymoma occupying about 90% of the spinal canal.
c) Postoperative axial T-2 weighted MRI showing the radical tumor resection.
Postoperative sagittal T-2 weighted MRI showing the radical tumor resection
branch may be preserved with a gentle microsurgical dissection. In meningiomas, early interruption of broad based tumor attachment to the dura provides bloodless surgery. Preserving arachnoid planes while dissecting the tumor minimizes risk of postoperative neurologic deficit. In myxopapillary ependymomas, after the tumor dissection, proximal division of filum terminale is recommended first. This is to avoid sudden tumor retraction proximally beyond the dural opening, should the division of the filum terminale is done distally first.

**CONCLUSION**

EISTs can be radically resected with no mortality and minimal perioperative morbidity. Thorough perioperative planning, meticulous microsurgical techniques and early mobilization and rehabilitaion are essential for good clinical outcomes.

CSF leak and pseudomeningocele formation could be prevented with meticulous dural closure, fat grafting for obliteration of the dead space and 72 hours postoperative bed rest. Patients tend to completely recover their preoperative neurologic deficits even in the case of longstanding preoperative neurological deficit. Advanced age does not seem to preclude eligibility for surgery.

**References**


CURRENT PROPHYLACTIC PERIOPERATIVE ANTIBIOTIC GUIDELINES IN TRAUMA: A REVIEW OF THE LITERATURE AND OUTCOME DATA

Lejla Hadzikadic*
Department of Trauma Surgery, Boston University Medical Center 88 E. Newton Street Boston, MA, USA
* Corresponding author

ABSTRACT

A comprehensive review of prophylactic use of perioperative antibiotics in trauma from the 1970s to the present was performed. Evidence based guidelines were used to analyze the data from the past 32 years and define standards of care in the field. Recommendations and suggestions are provided to offer guidelines for prophylactic antibiotic use in trauma. Highlighted topics include general trauma surgery, with focus placed on abdominal and thoracic surgery in trauma, and non-trauma surgery, including subspecialties, for comparison.

KEY WORDS: guidelines, prophylactic antibiotic use in trauma, data from the past 32 years, define standards of care.

INTRODUCTION

Management of surgical site infections has remained an important topic over the years, and use of prophylactic perioperative antibiotics continues to ignite controversy. While there is no doubt that antisepsis has changed the face of surgery, there exists a wide spectrum of beliefs on duration and use of perioperative antibiotics. Practices based on limited experience have been replaced with scientific evidence of the benefits and perils of antibiotics. Despite the decreased morbidity and mortality ascribed to antisepsis, there are complications associated with overuse. The history of this topic dates back more than thirty years and the need for guidelines for antibiotic use is more necessary today than ever before. This review highlights the historical aspects of antisepsis in surgery and focuses on the current use in general trauma, including abdominal and thoracic surgery, as well as in non-traumatic general and subspecialty surgery.
The studies cited in support of the current recommendations have been selected using a Medline search since 1977. The historical background provided comes from a wide variety of sources in the surgical literature. Most citations supporting the current recommendations are prospective, randomized studies with retrospective data used in cases where prospective data is unavailable.

**Historical Background**

As an English surgeon promoting the idea of sterile surgery in the 1860s, Joseph Lister used phenols to sterilize surgical instruments and clean wounds. Expanding on Louis Pasteur’s concepts of eradicating micro-organisms in wounds, Lister introduced antisepsis to surgery and made surgeons wash their hands and wear clean gloves, a novel concept at the time. Before his principles were accepted into use, surgery commonly resulted in post-operative fevers and infection, which often lead to sepsis and death. Lister was surrounded by contemporaries that echoed his sentiments of antisepsis. Ignaz Semmelweis, a Hungarian physician in the 1860s, discovered that puerperal fever could be decreased if physicians washed their hands in a chlorinated lime solution. He had many followers such as American born Oliver Wendell Holmes Sr, who advocated for medical reform in Cambridge, Massachusetts. Semmelweis’ ideas, however, did not gain wide acceptance until after his death, when Louis Pasteur developed the germ theory of disease in the late 1860s, thus providing a theoretical explanation for the initiative. Florence Nightingale, a British nurse who brought these similar pioneering principles to the Crimean War in the 1850s, revolutionized the perception of infection by introducing the concept that cleanliness and sterility were barriers to infectious disease. Since the introduction of antiseptic technique, surgery has continued to evolve into a process that cures disease and prolongs life (1). US Surgery data states that there were approximately 28.5 million surgical procedures performed in 2004. This number is estimated to reach more than 38 million by 2012 (2). From the most recent available data from the National Nosocomial Infections Surveillance (NNIS), there were 274,100 surgical site infections (SSI) in the US in 2002, roughly 2 infections per 100 procedures (3). Surgical site infections cause significant morbidity for patients and are costly for hospitals, thus making prevention an important topic. Various methods of decreasing SSI include recommendations for preoperative, intraoperative, and postoperative practices. Preoperative techniques include proper scrubbing of hands prior to surgery and appropriate patient selection as well as patient preparation prior to surgery. Intraoperative techniques include proper sterile procedure with avoidance of unnecessary tissue destruction along with optimizing the operating room environment to decrease the chance of infection by monitoring patient aspects such as temperature and the sterile environment. Postoperative patient care is important to maintain the integrity of the surgical wound. The use of perioperative antibiotics should only be seen as an adjunct to careful technique and proper procedure. Perioperative antibiotics are thought to decrease surgical site infections and, as such, have become an important topic of discussion for the surgeon. The use of prophylactic antibiotics in general surgery is well established and the evidence supporting this practice is overwhelming. Trauma surgery, however, has not been studied as extensively with regard to antibiotic usage. Surgery for traumatic wounds presents a unique perspective as the patients are often mechanically contaminated by foreign debris in the wound. Yet another detractor is the multi-service approach to caring for the trauma victim resulting in input from a variety of specialties, most of which have differing viewpoints on antibiotic prophylaxis and duration of therapy. More and more literature has emerged in an attempt to provide guidelines for prophylactic antibiotic use in trauma patients undergoing surgery.

**The Perils of Antibiotic Overuse**

Although perioperative antibiotic use has gained wide acceptance as a measure to decrease surgical site infections in general surgery and has become a mainstay of our daily practice, it is not without risk. The overuse and misuse of antibiotics has been linked to organism resistance that leaves physicians with limited tools to use against these bacteria. Complications such as ventilator associated pneumonia (VAP), candidal infections, catheter-associated infections such as urinary tract infections and central line infections, and clostridium difficile colitis have been linked with antibiotic overuse as well (4). There has been increased interest in prevention protocols for these complications such as interventions studied to decrease catheter related infections in the intensive care unit (5). Hoth looked at the effect that prolonged antibiotics (greater than 48h) had on trauma patients and the formation of VAP. Patients who received prolonged prophylactic antibiotics before the diagnosis of VAP had the pneumonia diagnosed later than usual, by an organism that was more resistant, with an incidence
of antibiotic complications twice that of patients who did not receive prolonged prophylactic antibiotics. The prophylactic prolonged antibiotics shifted the pattern from early to late-onset nosocomial VAP with different organisms, which are more virulent and harder to eradicate, therefore increasing the morbidity and mortality caused by VAP in these patients. In this study, the primary reasons for greater than 48 hours of antibiotics perioperatively were open fractures and external ventricular drains. However, often prophylaxis is not stopped appropriately due to oversight of physicians, residents, or the logistics of the computerized ordering systems, therefore contributing to the cost and complications associated with antibiotic usage (6).

Lansford looked at the efficacy of a pneumonia prevention protocol in the reduction of VAP in trauma patients. Their VAP protocol included keeping the head of the bed > 30 degrees, twice a day chlorhexidine oral swabs, daily vent weaning by respiratory therapists, and trading nasogastric tubes for orogastric tubes when able. The conclusion was that VAP protocols may decrease VAP incidence in trauma patients. Pneumonia is the second most common nosocomial infection in the intensive care unit and the CDC has documented that trauma patients have among the highest incidence of VAP with 15.1 cases/1000 vent days, thus making prevention of VAP both cost-effective for the hospital and beneficial for our trauma patient population (7).

At our institution, we adopted the current Institute for Healthcare Improvement (IHI) guidelines for the creation of a VAP bundle protocol in our trauma intensive care unit. The recommended bundle consists of five elements: maintaining the patient’s head of the bed above 30-45 degrees, daily sedation breaks, daily assessment for extubation, peptic ulcer prophylaxis, and deep venous thrombosis prophylaxis (4). Implementation of this bundle (See Table 1) for a period of eighteen months allowed us to decrease our VAP rate by 23.1% (unpublished data).

Many studies have shown that alterations in antibiotic choice are associated with a decrease in antibiotic resistance patterns. Raymond performed an outcome analysis in which they showed a statistically significant reduction in the incidence of antibiotic resistant gram-positive infections, antibiotic resistant gram-negative rod infections, and mortality associated with infection during quarterly rotation of empiric antibiotic schedules. Their patient population included intensive care units (ICUs) consisting of general, transplant or trauma surgery patients who developed pneumonia, peritonitis, or sepsis of unknown origin. They further showed that age, Apache II scores, solid organ transplant, and malignancy were independent predictors of mortality and that antibiotic rotation was an independent predictor of survival in this patient population (8).

<table>
<thead>
<tr>
<th>TABLE 1. Institute for Healthcare Improvement Guidelines for VAP Bundle Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Head of bed above 30-45 degrees</strong></td>
</tr>
<tr>
<td><strong>2. Daily sedation breaks</strong></td>
</tr>
<tr>
<td><strong>3. Daily assessment for extubation</strong></td>
</tr>
<tr>
<td><strong>4. Peptic ulcer prophylaxis</strong></td>
</tr>
<tr>
<td><strong>5. Deep venous thrombosis prophylaxis</strong></td>
</tr>
</tbody>
</table>

Most institutions implement departmental guidelines on antibiotic usage based on evidence-based medicine. It is interesting, however, that much variety exists from one center to another when it comes to prophylactic antibiotic usage prior to surgical procedures. At our level one academic trauma center, the trauma surgery department has been working closely with several subspecialty surgical departments to implement protocols to limit the duration of prophylactic perioperative antibiotics and to establish a perioperative time frame that terminates usage, at most, 24 hours after surgery. We recently collaborated with the oral-maxillofacial surgery department to prospectively examine our experience of antibiotic use in the setting of facial fractures to determine whether the application of a 24-hour protocol of perioperative antibiotics affects the rate of osteomyelitis or superficial wound infection. Our conclusion was that treating patients with exclusively perioperative antibiotics in facial fractures repaired within 72 hours has shown no increase in infection rates at our institution. Standardizing antibiotic usage with our protocol has increased the number of patients that receive only prophylactic antibiotics, potentially decreasing health care costs and decreasing complications associated with antibiotic resistance (unpublished data presented at the American Association for the Surgery of Trauma-AAST in 2008 with manuscript in preparation).

It remains our goal to perform similar prospective studies with our neurosurgical, otolaryngology, and orthopaedic departments so that we may standardize our perioperative prophylactic antibiotic use as an institution. This is regarded as a highly important matter as these departments work closely to care for the trauma patient. Thus it would be prudent and cost-effective for an institution to have a uniform system of guidelines in place that is followed by all of the integral services that provide surgical care to that trauma patient. Our goal is to standardize antibiotic use while allowing for occasional exceptions, as clinically indicated.


**Literature Review for Prophylactic Antibiotics in General Trauma Surgery**

Trauma is the leading cause of death between the ages of 1 and 37 and is the fourth leading cause of death in the United States. It is well known that infection plays a large role in the morbidity and mortality of trauma patients. Injured patients represent a unique population of surgical patients that are more prone to infection. Some predisposing factors include an amplified host defense mechanism and activation of the complement cascade that characterizes tissue damage in severe injury. Similarly, decreased tissue perfusion is an important predisposing factor to infections. Unique to trauma is the extrinsic factor of mechanical contamination of the wound with foreign material. Prior to evaluating the literature, it would be beneficial to review the classification of surgical wounds. Guidelines from the Centers of Disease Control and Prevention and the stratification of surgical wounds are as follows: A Class I (clean) wound is one in which the respiratory, alimentary, genital, and urinary tracts are not entered as part of the surgical procedure. Conditions under which a patient undergoing a Class I, clean, procedure should receive prophylactic antibiotics include those in which prosthetic material is used or the procedure enters a joint such as a total hip arthroplasty. Class II (clean-contaminated) wounds are ones in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions. Class III (contaminated) wounds are those that are open wounds or incisions made as part of the operation where major breaks in sterile technique or gross spillage of gastrointestinal contents has occurred. Class IV (dirty) wounds are those that include old traumatic wounds or involve existing clinical infection or perforated visceras. Patients undergoing Class IV, dirty operations should not receive prophylactic antibiotics; rather, they should receive therapeutic antibiotics directed at anticipated organisms based on anatomic location and mechanism of injury. It is held in common agreement that patients undergoing procedures that involve entry into a hollow viscous under controlled conditions should undergo antibacterial prophylaxis (9, 10). See Table 2.

Alexander examined clinical trials of prophylactic antibiotics in trauma and found that in abdominal trauma, preoperative antibiotics decrease the infection rate when compared to intraoperative or postoperative administration of antibiotics. Duration of these prophylactic antibiotics is not well established in trauma. Antibiotics were not favored in burn trauma or superficial lacerations; prophylactic antibiotics in fractures were found to decrease infection rates, yet there was no consensus on duration. There was no evidence that greater than 48 hours of antibiotics has any benefit in trauma. On the contrary, they may be harmful. Noting that continued contamination is the primary reason for antibiotic ineffectiveness, when choosing prophylactic antibiotics in trauma, more rapidly penetrating ones such as ampicillin, penicillin, cephalosporins or tetracycline are good options (11). Thus antibiotics should only be used as an adjunct to aggressive irrigation and debridement of contaminated wounds. Cushing echoes this sentiment of immunosuppression of the injured patient and claims that not much has changed in terms of prophylactic antibiotic usage since 1977. In penetrating trauma to the chest, infection depends on the severity and contamination of the wound as well as the condition of the patient. Penetrating trauma to the abdomen is often associated with bowel perforation which is in turn associated with infections of mixed bowel flora. Preoperative antibiotics in this scenario decrease the incidence and severity of wound and deep tissue infections. However, proper surgical aseptic technique is the best way to ward off infection and constantly being aware of the organism that you are treating is the

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Clean</td>
</tr>
<tr>
<td>II</td>
<td>Clean-Contaminated</td>
</tr>
<tr>
<td>III</td>
<td>Contaminated</td>
</tr>
<tr>
<td>IV</td>
<td>Dirty</td>
</tr>
</tbody>
</table>

**TABLE 2. Classification of Surgical Wounds**
Abdominal trauma is a particularly important focus as it comprises a large portion of commonly found injuries. Contamination is frequently present, so antibiotic prophylaxis is truly a euphemism for therapeutic treatment. Ericsson looked at the hazards of underdosing prophylactic antibiotics in abdominal trauma surgery. There was no difference between infection rates in 72 hours of coverage with prophylactic amikacin and clindamycin versus 24 hours of coverage in trauma laparotomy patients. They recommended that higher initial doses were more effective than long courses in laparotomy patients. The patient population included high-risk trauma patients, thus suggesting that prophylactic antibiotics are useful in patients at high risk for infection, such as increased estimated blood loss or spillage of colonic contents. They recommend covering aerobic and anaerobic organisms and also saw no difference seen in the interval at which the antibiotics were given, 46 hours or 72 hours. They further tested their theory that antibiotic pharmacokinetic profiles were altered in trauma patients and that this was related to resuscitative fluid administration therefore accounting for the increase in antibiotic requirements. They show that the volume of distribution is increased in all of their included trauma patients secondary to increased fluid resuscitation therefore diluting the administered drug. They maintain their original recommendation of using a higher initial dose of prophylactic antibiotics, instead of a prolonged course, in patients with abdominal trauma.

Sawyer reviewed a large number of consecutive surgical infections in order to identify the demographics and characteristics of infections in surgical patients to clarify the areas that needed emphasis. The most common sites of infection were the colon, lung, and the surgical wound; staphylococcus epidermidis, staphylococcus aureus, and candida albicans were the most common organisms isolated. The most frequently used antibiotics were ciprofloxacin, vancomycin and metronidazole. Overall the death rate was 13%, ranging from 5% of community-acquired infection to 25% of nosocomial infections in the ICU. His conclusions were that surgeons deal mainly with nosocomial infections resulting in increased morbidity and mortality so an emphasis should be placed on preventing infections acquired in the hospital.

Velmahos compared prophylactic antibiotic duration after severe trauma and showed that there was no difference in using one antibiotic for 24 hours when compared to multiple antibiotics for longer than 24 hours, thus concluding that a single agent for 24 hours of prophylaxis is effective. The surgical infection society (SIS) recommends a short duration of prophylactic (less than 24 hours) antibiotics with a spectrum appropriate to the operative site. Good data is available supporting short-term single agent antibiotic prophylaxis in low-risk patients, but has been indeterminate in high-risk patients so this study was designed to evaluate high-risk trauma patients. The SIS recommendations for low-risk patients seem to apply for high-risk as well.

**Literature Focus on Abdominal Surgery in Trauma**

Abdominal trauma is a particularly important focus as it comprises a large portion of commonly found injuries. Contamination is frequently present, so antibiotic prophylaxis is truly a euphemism for therapeutic treatment. Ericsson looked at the hazards of underdosing prophylactic antibiotics in abdominal trauma surgery. There was no difference between infection rates in 72 hours of coverage with prophylactic amikacin and clindamycin versus 24 hours of coverage in trauma laparotomy patients. They recommended that higher initial doses were more effective than long courses in laparotomy patients. The patient population included high-risk trauma patients, thus suggesting that prophylactic antibiotics are useful in patients at high risk for infection, such as increased estimated blood loss or spillage of colonic contents. They recommend covering aerobic and anaerobic organisms and also saw no difference seen in the interval at which the antibiotics were given, 46 hours or 72 hours. They further tested their theory that antibiotic pharmacokinetic profiles were altered in trauma patients and that this was related to resuscitative fluid administration therefore accounting for the increase in antibiotic requirements. They show that the volume of distribution is increased in all of their included trauma patients secondary to increased fluid resuscitation therefore diluting the administered drug. They maintain their original recommendation of using a higher initial dose of prophylactic antibiotics, instead of a prolonged course, in patients with abdominal trauma.

Fabian looked at prophylactic antibiotic use in penetrating abdominal trauma and concluded that antibiotics should be discontinued after the operation is over in penetrating abdominal trauma. In this series, shotgun wounds carried the greatest risk for postoperative infection, followed by rectal injuries and colon injuries and cefotaxime was considered a drug with adequate properties for such prophylaxis.

Hofstetter compared a triple drug regimen of an aminoglycoside, ampicillin, and clindamycin to cefoxitin alone for 24 hour prophylaxis in laparotomy for trauma in 119 patients. Excluding remote site infections, the abdominal wound and intraperitoneal infection rate was 13.0% for the cefoxitin group and 12.0% for the triple-drug group. He concluded that a 24 hour course of cefoxitin, a second-generation cephalosporin, was a safe prophylactic regimen in abdominal trauma.

Sarmiento also found no difference in infections among low-risk patients with abdominal trauma given prophylactic intraoperative antibiotics, which were suspended at the end of surgery, when compared to those given prophylactic intraoperative antibiotics that were prolonged until 48 hours. Low-risk patients were identified as ones with an abdominal trauma index (ATI) less than 25. They reasoned that for patients with an ATI greater than 25, such as colonic wounds, antibiotics should be continued for 48 hours as a colonic wound was one of the strongest indicators for postoperative administration of antibiotics. However, for low-risk wounds with an ATI less than 25, 24 hours of perioperative antibiotics was sufficient for prophylaxis.

Weigelt compared penetrating abdominal trauma patients who were given a prophylactic regimen of ampicillin/sulbactam to those given cefoxitin. There was an increased incidence of enterococcal infection in the cefoxitin group resulting in the conclusion that a single, broad-spectrum antibiotic for prophylaxis (including improved enterococcal and bacteroides coverage) for 24 hours perioperatively effectively controls surgical infections.
wound infections. Their findings join others in suggesting that a perioperative antibiotic for abdominal trauma should include anaerobic and aerobic coverage (20). Maxwell and Fabian offer a comprehensive review of colon trauma from World War I to 2003. They recommend that prophylactic antibiotics are appropriate for most types of gastrointestinal surgery associated with trauma. They support the use of the least expensive, most commonly available agent such as a second-generation cephalosporin and advocate use that defines 12 to 24 hours of antibiotic coverage instead of more lengthy courses of therapy (21). The conclusion of these multiple studies is that in penetrating abdominal trauma, 24 hours of a second-generation cephalosporin is adequate perioperative antibiotic prophylaxis with some surgeons preferring to add enterococcal and bacteroides coverage to this regimen.

**Literature Focus on Thoracic Surgery in Trauma**

Eren looked at the risk factors and management of traumatic empyema and noted that posttraumatic empyema increases morbidity and mortality, length of stay, and cost. In this series, duration of chest tubes over six days, length of stay in the ICU greater than 2 days, lung contusion, retained hemothorax, and an exploratory laparotomy are shown to be independent predictors of posttraumatic empyema and the use of prophylactic antibiotics is recommended for those patients. The relative risk of posttraumatic empyema is increased if the injury is from penetrating trauma, the patient has associated injuries, or there is fracture of more than two ribs. Other than these scenarios, the criteria for antibiotic prophylaxis are emergent/urgent thoracotomy, soft-tissue destruction of the chest wall by shot-gun injury, and associated open long bone fracture (22). Holzheimer commented on a meta-analysis done on randomized controlled trials on prophylactic antibiotics in chest trauma that showed inconsistent data and maintains that the ultimate decision is up to the surgeon, and that one should look at the patient’s risk factors, mechanism of trauma, extent of trauma, and transfusion requirements before deciding on prophylactic antibiotics (23). Mandal compared prophylactic antibiotics to no antibiotics in penetrating chest trauma and found no difference in outcome, concluding that routine antibiotic prophylaxis is not recommended in penetrating chest trauma. Unless there is an esophageal tear, the risk of microbial contamination of the mediastinum and pleural cavity is negligible because of the sterile nature of the tracheobronchial tree (24). They also examined the 24-year experience at their trauma center with posttraumatic empyema and found that of 5,474 patients, 1.6% developed empyema after no use of prophylactic chest tube antibiotics. They found that of those empyemas, 91% were cured with chest tube placement and did not require thoracotomy, so they concluded that no routine use of antibiotic prophylaxis is necessary for all trauma patients with chest tubes (25). It is prudent, however, to mention that the Eastern Association for the Surgery of Trauma (EAST) practice guidelines for prophylactic antibiotic use in tube thoracostomy for traumatic hemopneumothorax presents level III recommendations, of Class I and II data, that a first-generation cephalosporin should be used for no longer than 24 hours. They suggest that there may be a reduction in pneumonia, but not empyema, in trauma patients receiving prophylactic antibiotics when a tube thoracostomy is placed (26).

**Literature on Non-Trauma and Subspecialty Surgery Antibiotic Protocols for Prophylaxis**

A plethora of literature exists in non-trauma surgery favoring prophylactic perioperative antibiotic usage to reduce postoperative infection. This has been well established in general surgery, general non-trauma thoracic surgery, and subspecialty otolaryngology (ENT) surgery. For example, pre-operative bowel preparations, body temperature control, and perioperative antibiotic use has had a great impact on decreasing infections after abdominal surgery. The principle of decreasing surgical site infection applies in non-trauma surgery and results in increased hospital stay, morbidity and mortality. This, once again, highlights the importance of prevention. Allen echoes the sentiments of many others in stating that meticulous technique and proper procedure is the number one way to decrease surgical site infections, and that perioperative antibiotics should only be viewed as an adjunct to careful surgical procedure. He focused on pneumonia and empyema following general thoracic surgery and, after reviewing 14 studies in the thoracic literature, concluded that prophylactic antibiotics decrease wound infection and that a short course is more effective than a longer course (1). The otolaryngology surgical literature provides convincing evidence that perioperative antibiotics decrease wound infections in head and neck surgery patients. As in most surgeries, wound contamination is the biggest reason for post-operative infection and in the ENT literature, aerobes are most commonly found in surgi-
cal wound specimens. Clayman obtained specimens of pus or draining fluids from the wounds of 43 surgical patients who received perioperative antibiotics, and then analyzed the bacteriologic profile of these surgical infections after antibiotic prophylaxis. He found polymicrobial infection in 30%, with 82% of the isolates from aerobic organisms and 18% anaerobic. He concluded that “wound colonization following dental extraction procedures in clean contaminated head and neck surgery increases the risk of anaerobic infections, and that the use of a therapeutic dose and possibly longer duration of perioperative antibiotics may be warranted.” Anesthesiology literature has emerged as another source of information for the use of perioperative antibiotics. Current anesthetic practice has an important influence on the prevention of surgical site infections and infectious risk. Keegan and Brown reviewed concepts involved in prophylaxis of SSI and discussed perioperative care provided by the anesthetic team that may alter the risk of infection, thus influencing patient outcomes. Increased surgical site infections occur more often when associated with older age, poor nutrition, obesity, smoking, diabetes, immunosuppression, preoperative hospital stay, and colonization coexistent with infection, thus each patient should be reviewed on a case by case basis for prophylaxis. They also review procedure-specific current recommendations for antimicrobial prophylaxis and provide a composite list. Prosthetic joint replacements require cefazolin for 24 hours. Ophthalmic surgery guidelines indicate only antimicrobial eye drops for surgery involving the globe for prevention of postoperative endophthalmitis. Obstetric/gynecologic recommendations include prophylaxis for 24 hours as well as otolaryngology surgeries excluding endoscopic sinus procedures. Neurosurgical guidelines include prophylactic 24 hour antibiotics for patients undergoing craniotomy as well as after penetrating cranial trauma. Thoracic vascular/cardiac guidelines recommend antimicrobial prophylaxis for 24 hours with ancef with the exception of chest tube placement. Current urologic guidelines recommend prophylactic antibiotics if the patient has an indwelling catheter or bacteriuria. Colorectal procedures have guidelines supported by literature that reports positive results for single dose or short term use of a first-generation cephalosporin for antimicrobial prophylaxis. Some advocate the addition of metronidazole to cefazolin or the use of agents with extended gram-negative coverage.

Keegan and Brown also highlight the importance of knowing the dosing/timing of antibiotic administration and not underestimating re-dosing principles of antibiotics depending on the EBL, half life of the agent, the volume distribution, or drug elimination properties. Simple operating room procedure has also been shown to decrease infection risk such as limiting the number of people in the operating room, proper scrub technique, antibiotic coated catheters and sterile technique of location and placement of intravascular devices by anesthesia personnel, temperature regulation to maintain normothermia, and glucose control.

CONCLUSION

The general principles of antisepsis that were introduced by Lister in the 1860s revolutionized the role that surgery had in curing disease and prolonging a patient’s life. We have come a long way in decreasing patient morbidity and mortality with proper scrub practice, sterile operating room environment and equipment, and meticulous surgical technique. These facets of surgery, along with proper patient selection and procedure selection, as well as protocols of pre-operative bowel preps in abdominal surgery, remain the basic tenets of surgical site infection prevention. Antimicrobial prophylaxis was introduced as an adjunct to these tenets and remains as such today. There has been sufficient general surgery literature to support the use of single agent and short term prophylactic perioperative antibiotics to decrease the rate of surgical site infections. The topic remains an important one as surgical site infections remain a significant burden to the health care system by increasing costs of hospitals with increasing hospital stay and length of intensive care unit stay, as well as negatively impacting a patient’s recovery and even mortality.

Trauma surgery cares for patients who frequently arrive to the hospital with imbedded foreign material such as bullets, metal, or debris from the scene of the injury. This patient population also represents those who enter surgery with an existing stressed metabolic state, one where proinflammatory mediators are abundant. This is most similar to general surgery patients who undergo emergent surgery. Thus there has existed a debate about the best way to utilize perioperative antibiotics in this patient population.

A review of the past thirty years of trauma surgery literature on the role of perioperative prophylactic antibiotic use is presented in this paper. Recommendations for perioperative antibiotic use in general trauma surgery mimics the data.
for general surgery, which is the use of a single agent for a short 24-hour course perioperatively. A focus on abdominal trauma surgery revealed strong support for the same guidelines.

Thoracic trauma surgery literature also supports the use of prophylactic perioperative short course antibiotics when there is contamination of the sterile cavities of the chest and thorax, however rare this event may be. Though the EAST guidelines support the use of 24 hours of a first generation cephalosporin in the management of tube thoracostomy for traumatic hemopneumothorax, popular belief is that there is no benefit; thus Class I and II studies need to be performed. Differences exist within subspecialty departments such as otolaryngology, orthopaedics, oral and maxillofacial surgery, neurosurgery, and urology, to name a few, who are integrally involved in trauma patient care. There are wide differences in their respective literatures and many protocols are center-specific. A more uniform stand should be taken by the respective national academies of each group to provide more specific guidelines. As presented in our own institution, the implementation of a protocol to standardize prophylactic perioperative antibiotic use in trauma patients managed by the trauma surgery and oral and maxillofacial surgery departments resulted in more patients receiving only perioperative antibiotics without increasing our rate of infections. It should be a collaborative approach between multiple subspecialties to undertake the goals of defining protocols that will benefit the patient and assist caregivers.

This review article aimed to establish a pattern of recommendations supported by evidence based literature in trauma surgery. The long-term goal is that this can be used to establish center-specific protocols that may assist with patient care from a quality improvement perspective.

References

WHEN LESS IS MORE IN THE INTENSIVE CARE UNIT; LESSONS LEARNED

EMIR FESTICI*, OGNJEN GAJIC2

1 Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL, USA
2 Mayo Clinic Rochester, MN 55905, USA
* Corresponding author

ABSTRACT

In parallel to technological advances in late twentieth century, medical diagnostics and therapeutic options greatly improved. A surge of evidence-based research in intensive care medicine provided additional opportunities and the “best” medical practice has been changing rapidly. However, the primary focus of Hippocrates: “Primum non nocere” (first do no harm) is often neglected at the bedside. It became apparent that lesser intervention in the ICU may actually mean more for the patient. Multiple examples of the concept “when less is more in the ICU” are described here in an ABC format. Critical care providers have an obligation to keenly and closely follow the results of new investigative studies and to carefully incorporate those into our practice. However, they have to be sensitive to individual circumstances, patient and family preferences, and avoidance of harm.

KEY WORDS: Intensive care, evidence-based, first do no harm
INTRODUCTION

The past several decades have been marked by great technological advances, which resulted in significant improvements in the way we diagnose and treat different disease states. In the United States, we have literally become a “death-denying society”, and death in the hospital and in the intensive care unit (ICU) often represented “a failure”. This focus shift, from the comfort to cure, often lead us away from the primary focus of Hippocrates: “Primum non nocere” (first do no harm). Rather than a primary guiding principle of medical practice, this important concept became a historical phrase. What we mean by this is not that we, medical practitioners, actually ignore potential harms, but in our desire to achieve the cure, by all means, sometimes we neglect Hippocrates’ first guiding principle. While we routinely try to weigh benefits and risks of proposed treatments, the decisions to treat despite significant (and prohibitive) risks are employed more and more commonly.

The last decade of the 20th century was marked by a rising concept of evidence-based medicine, and what followed in the first decade of this century was unparalleled surge in good-quality research, especially in the field of intensive care medicine. The results of controlled trials provided opportunities to save more lives, by adhering our practice to the published protocols. However, the focus of research has mainly been improvement in mortality, by all means. The domino effect-protocols spread rapidly from the bench to the academia and community, sometimes, prematurely so (1) (2). Therefore, our intention with this writing is to point out most common occurrences in the intensive care medicine when less could actually mean more for the patient. The following is not all-inclusive illustration and is supposed to motivate the readers to search for moderation and individualization in their medical practice in the complex critical care environment.

When less is more...

As fellows in critical care medicine at Mayo Clinic in early 2000s, due to abundance of new data being published, we sought and found an easy way to organize our medical reasoning and application of best available data at the bed side. A concept of ABCs of evidence-based critical care medicine (3) was created, where each letter from A to G reminded a provider of the certain step in the care for critically ill patient. This tool has been taught to subsequent generations of trainees at Mayo Clinic, as it is simple to remember and use. The tool is not all-inclusive by any means but represents most common used interventions in the ICU. With each letter and corresponding intervention, it will be easy to appreciate how less may actually mean more for the patient.

A – Acute Respiratory Distress Syndrome (ARDS)
Mechanical ventilation saves lives and it is a therapeutic support of choice for the patients with ARDS. Traditional teaching and practice of mechanical ventilation (MV), until recently, utilized relatively large tidal volumes (TV), 10-15ml/kg of actual body weight, with the goal of normalizing partial pressure of oxygen (O2), carbon dioxide (CO2) and pH on the arterial blood gas analysis. However, several studies including a landmark ARDS-Net trial (4) showed that ventilation with smaller TV (6ml/kg of predicted body weight, PBW) and accepting abnormal blood gas values actually improves survival, by decreasing potential for volutrauma and ventilator induced lung injury. Patients ventilated with smaller TV had a higher CO2 and a lower pH, which did not adversely affect the survival, hence the term “permissive hypercapnia”. The small TV group was ventilated with moderately high (8-10 cm H2O) positive end-expiratory pressure (PEEP), aiming to reduce atelectasis and “atelectrauma”. Subsequent studies of MV with higher levels of PEEP failed to show further survival improvement (5-6).

B – Blood transfusion
While actual blood transfusion practices varied a lot, the traditional teaching in the ICU suggested transfusing patient additional blood volume if hemoglobin (Hb) level fell below 10g/dl. This cutoff was based on early in vitro studies of blood viscosity and O2-carrying capacity, where it was found that this relation is adversely affected if Hb level drops below 10g/dl. These preclinical studies, however did not take into consideration potential for side effects associated with blood transfusion. A Canadian Critical Care Network study showed that restrictive blood transfusion strategy with a cutoff Hb level at 7g/dl was associated with improved morbidity and trend towards improved mortality when compared with liberal transfusion practices (Hb threshold of 10 mg/dL)(7). Critically ill patients seem to benefit from restrictive transfusion strategy except perhaps in cases of active bleeding, early shock and acute coronary syndrome. Given the frequency of transfusion complications including transfusion related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) (8-9), less transfusion of blood products indeed may mean “more” for the critically ill patient.
A French study published in JAMA in 2002 suggested that hydrocortisone and fludrocortisone improved survival in patients with septic shock (10). Performance of an ACTH stimulation test with cosyntropin was important part of the protocol where “nonresponders” (the cortisol increased by <9 on the cosyntropin test) treated with hydrocortisone and fludrocortisone benefited the most, number needed to treat (NNT) for 1 life saved was 7. Use of steroids then became standard of care in non-selected patients with septic shock. The mortality benefit observed in the French study has not been replicated in the most recent large international multicenter double-blind placebo-controlled study of 499 patients with septic shock randomized to hydrocortisone or placebo. Moreover, cosyntropin test was not shown to be useful to determine the presence or absence of adrenal insufficiency (11). Accordingly, steroids should be reserved for treatment of the most severe cases of septic shock, not responsive to fluid resuscitation and vasopressor medications.

D – Drotrecogin alpha
Drotrecogin alpha, or activated protein C (APC) marked early 2000s as the “hottest” drug in sepsis. The study by Bernard et al. showed significant reduction in mortality, a relative risk reduction (RRR) of death by 20% and an absolute risk reduction (ARR) of death by 6% if septic patients received APC 24mcg/kg/hr x 96 hours (1). However, there was higher incidence of serious bleeding in the APC group (3.5% vs. 2%). What followed was a rapid increase in use of this very expensive medication and infiltration of the industry (manufacturer of APC) in all pores of academia and community. Subsequent studies showed more risk than benefit with APC use among non-selected populations. APC did not benefit patients at low risk of death, patients with baseline bleeding risk and pediatric patients (12-15). Systematic review of Cochrane database in 2008 found no evidence suggesting that APC should be used in severe sepsis or septic shock; “APC seemed to be associated with a higher risk of bleeding and unless additional RCTs provided evidence of a treatment effect, policy-makers, clinicians and academics should not promote the use of APC”.

E – EGDT, early goal directed therapy
Dr. Rivers randomized septic patients to standard or EGDT (16). Per this study protocol, patients in EGDT group were started on treatment with intravenous fluids in the emergency room. In addition, those with apparent sepsis were treated with vasopressors and or inotropes to maintain a MAP >65. The average amount of fluid given in the first 6 hours was 5 liters. This included more blood transfusions if Hb was less than 10 and more inotropes (dobutamine) then in the control group. Although the evidence that either transfusion of blood to keep Hb above 10g/dl or dobutamine, improve outcome of septic patients is lacking, these steps were part of the protocol that resulted in significantly reduced hospital mortality (46% to 30%), and the protocol was widely accepted. As mentioned earlier, restrictive blood transfusion practices appear to be safer for critically ill patients (7). Also, dobutamine has arrhythmogenic potential and may increase an already elevated heart rate in septic patients. The key component of EGDT was early adequate fluid resuscitation (in the emergency room); potentially this alone would have made a crucial impact and difference in outcomes (17). One should probably exercise caution before transfusing septic patients with Hb less than 10g/dl and dobutamine use should be avoided in the absence of myocardial dysfunction, particularly in the presence of tachycardia.

F – Fluids
While aggressive fluid resuscitation is beneficial early in the course of sepsis, especially first 6 hours and possibly first 24 hours, liberal fluid administration later in the course of critical illness may have a deleterious effect. Hemodynamic monitoring of critically ill is sub-optimal, and frequently fluid challenges are used in order to determine patient’s fluid responsiveness. This often results in giving more fluid than necessary with consequences ranging from hypoxemia to increased incidence of pressure ulcers. The negative impact of fluid over-administration was best demonstrated in the study that compared liberal versus conservative fluid management in ARDS (18). The group with conservative fluid administration showed trend towards lower mortality, spent less time on mechanical ventilator and in the ICU, with no adverse effects on renal function. Another important issue with fluid resuscitation is related to “the great fluid debate”, i.e. crystalloids versus colloids. Crystalloids have been a mainstay of fluid therapy for decades; they are inexpensive and widely available. However as we have witnessed earlier, there has always been a push towards newer, fancier and more expensive therapeutics. Multiple studies over last several years, including systematic review of Cochrane database in 2007 and large meta-analysis have shown no overall advantages of albumin, plasma protein fraction, dextran, hydroxyethylstarch or gelatin over simple crystalloid solutions. These compounds frequently increased...
complications and morbidity rates, depending on the solution used or patient population studied (19-22).

G – Glucose control

In a one of most cited medical publication of this decade, Van den Bergh et al. showed relative risk reduction in ICU mortality of 50% among postoperative, mostly cardiac surgery patients by adhering them to intensive insulin therapy (IIT) and tight glucose control between 80 and 110 mg/dl (2). There was also an overall reduction in hospital mortality by 34%, bloodstream infections by 41%, transfusions by 50% and acute renal failure by 41%. Needless to say that IIT swept the medical world and shortly became standard of care in most ICUs. Fortunately, practitioners and experts most often adopted more modest goals of glucose control (<150 mg/dL). The results of this study could not be largely replicated, and series of studies and publications including meta-analysis, showed no significant reduction in hospital mortality with IIT and an increased risk of hypoglycemia (22-27). A recently completed large international NICE SUGAR trial (28) included over 6000 patients, demonstrated an increased risk to benefit ratio of IIT (target glucose between 89-110 mg/dL) compared to more conservative approach (target glucose between 140-180 mg/dL). Early in critical illness hyperglycemia may simply be an adaptive response, providing glucose for the brain, red cells, and wound healing. Potentially more important factor than simple serum glucose concentration seems to be standard deviation of glucose measurements or glucose variation (29-30). A target glucose control should therefore be maintained between 140 and 180mg/dl for majority of patients, with avoidance of excessive glucose variability.

DISCUSSION

Above examples are not all inclusive. Any therapeutic approach, intervention or medication has its’ risks and careful consideration of risk/benefit ratio, taking into account patient preference should always be sought. Even oxygen therapy or antibiotics, which we often order without thinking twice, may exhibit adverse effects, pose toxicity to the cells or induce drug resistance. So, where do we go from here? The answer is not simple nor there a single one. As critical care providers we do have obligations to keenly and closely follow the results of new investigative studies and carefully incorporate those into our practice. However, we need to pay attention to the very details and tailor these results and their application to each and every patient individually. We have to carefully weigh the risks and harms of such treatments with their proposed benefits, and to communicate them readily to patients and their families. The ultimate goal is to improve not only “quantity” but also the quality of life, and we ought to think first not to cause more harm. Good knowledge of research results and protocols, taking into consideration individual circumstances and patient and family preferences and applied in moderation seems to be the most sensitive way for a responsible and truly evidence-based medical practice. That’s when less actually may mean more for our patients.

REFERENCES


Abstract

Acute lung injury and its more severe form acute respiratory distress syndrome (ARDS) are characterized by diffuse impairment of alveolocapillary membrane in the settings of different predisposing conditions such as sepsis, trauma and shock. Many intrahospital exposures, including aspiration, delayed resuscitation, high tidal volume mechanical ventilation and non critical use of transfusions may contribute or worsen ARDS. Therapy is targeted to treatment of predisposing condition, life supportive measures and prevention of nosocomial complications. Rigorous adherence to lung-protective mechanical ventilation is critical to prevent ventilator induced lung injury and decrease mortality. Although survival of ARDS patients has improved in the last decades ARDS mortality rates are still high and survivors encounter significant physical and psychological impairments.

Key Words: Respiratory distress syndrome, adult; mechanical ventilation; pulmonary edema
INTRODUCTION

More than 40 years ago Ashbaugh et al. first described acute respiratory distress syndrome (ARDS), a life threatening condition in patients with precipitating factors and mortality that ranged from 50 to 70%. In recent years many basic and clinical studies have improved our understanding of ARDS but the clinical impact has been limited to advances in supportive treatment. ARDS affects 200,000 people in the US every year, and is associated with 75,000 deaths, 3.5 million hospital days and mortality of approximately 40% (1,2).

History

In 1967 Ashbaugh et al. described 12 patients with acute respiratory failure, oxygen refractory cyanosis and diffuse alveolar infiltrates on chest X-ray (3). The syndrome was first named adult respiratory distress syndrome (4), but soon after it was noted in children it was renamed to acute respiratory distress syndrome. Due to lack of clear definition in 1988 an attempt was made to quantify respiratory impairment in terms of lung injury score (LIS) based on four parameters: radiographic changes, level of hypoxia (PaO2/FiO2), lung compliance and positive end expiratory pressure (PEEP). Factors causing direct and indirect lung injury were defined, and the role of multiorgan failure (MOF) was emphasized in terms of prognosis (5). The lack of specificity and inability to differentiate between ARDS and heart failure resulted in current definition by American-European Consensus Conference Committee in 1992 (Table 1) (6).

Definition

Acute respiratory distress syndrome is a syndrome of acute respiratory failure with radiological feature of acute pulmonary edema in the absence of clinical evidence of left heart failure as a principal explanation of pulmonary edema. The condition is characterized by abrupt injury in alveolocapillary membrane resulting in alveolar flooding, inflammation and change in surfactant properties that cause severe impairment of oxygenation and respiratory failure requiring mechanical ventilation (7). The definition takes into account the degree of respiratory impairment and distinguishes acute lung injury (ALI) and a more severe form acute respiratory distress syndrome. Although early recognition of these patients facilitates enrollment into clinical trials, previous studies found no correlation between PaO2/FiO2 and survival (8, 9). The majority of patients who present with ALI progress to ARDS within first three days (10). Arterial oxygen saturation measured by pulse oximetry is useful in estimating level of respiratory impairment in both pediatric patients and adults (SaO2/FiO2 of 315 and 263 correspond to PaO2/FiO2=300, SaO2/FiO2=235 and 201 corresponds to PaO2/FiO2=200 in adults and children, respectively) (11, 12).

Etiology

The diagnosis of ALI is usually made in the ICU but the biological process begins much earlier. ALI/ARDS is rarely present at the time of hospital admission and usually develops in first hours to days after hospital admission in patients with predisposing conditions that can cause direct (pneumonia, aspiration, im-

---

TABLE 1. American-European Consensus Conference Committee Definition of Acute Respiratory Distress Syndrome; PCWP—Pulmonary Artery Wedge Pressure

<table>
<thead>
<tr>
<th>Description</th>
<th>PaO2/FiO2</th>
<th>PCWP ≤ 18 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute onset</td>
<td>≥300</td>
<td></td>
</tr>
<tr>
<td>Bilateral chest radiographic infiltrates consistent with edema</td>
<td>≥200</td>
<td></td>
</tr>
<tr>
<td>The absence of clinical evidence of left atrial hypertension as the principal explanation for pulmonary edema</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

FIGURE 1. Diffuse alveolar damage with hyaline membranes
FIGURE 2. Radiogram of patient with ARDS
FIGURE 3. CT findings in ARDS
Risk factors

Sepsis, and in particular pulmonary sepsis, has been recognized as the most common cause of ARDS. But only a small proportion of patients with pneumonia (10%), aspiration (16%), extrapulmonary sepsis (6%) and acute pancreatitis (1%) develop ALI/ARDS.14 Previous research identified various factors that model the development of ALI (‘multiple hit hypothesis’). Primary patients’ characteristics (‘first hit’) such as local and systemic inflammation, oxidative stress, epithelial cell injury caused by acid or inhalation toxins, smoking, alcoholism, chronic lung disease (interstitial diseases and COPD), acidosis and certain genetic polymorphism with additional exposures (‘second hit’) to high tidal volumes, high oxygenation fraction, certain drugs (amiodarone, cytostatics) and transfusion of alloimmunized donors lead to development and progression of ARDS (15). Massive transfusions (>15 units) have been previously associated with ARDS (16). It has now been widely recognized that any transfusion of fresh frozen plasma, thrombocytes and erythrocytes can cause lung injury inside 9 hours after transfusion (17). This, transfusion related lung injury-TRALI is caused by immune reaction of donor antibodies (sensibilization in previous pregnancies or during previous transfusions) and

<table>
<thead>
<tr>
<th>TABLE 2. Causes of ALI/ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct (pulmonary) causes</td>
</tr>
<tr>
<td>Epithelial injury</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Indirect (extrapulmonary) causes</td>
</tr>
<tr>
<td>Endothelial injury</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Increased capillary transmural pressure</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3. Risk factors for the development of ALI/ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
</tr>
<tr>
<td>Treatment of infection and resuscitation</td>
</tr>
<tr>
<td>Delayed antibiotic administration (&gt;3 hours)</td>
</tr>
<tr>
<td>Delayed early goal directed resuscitation</td>
</tr>
<tr>
<td>Respiratory support</td>
</tr>
<tr>
<td>Inspired oxygen concentration -FiO2 (%)</td>
</tr>
<tr>
<td>Anesthesia (hours)</td>
</tr>
<tr>
<td>Tidal volume (mL/kg predicted weight)</td>
</tr>
<tr>
<td>Peak airway pressure (cm H2O)</td>
</tr>
<tr>
<td>Peak Airway Pressure &gt; 30 cm H2O yes/no</td>
</tr>
<tr>
<td>PEEP (cm H2O) &gt;5 cm H2O yes/no</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Chemotherapy, yes/no</td>
</tr>
<tr>
<td>Blood transfusion</td>
</tr>
<tr>
<td>Blood product transfusion, yes/no</td>
</tr>
<tr>
<td>Red blood cells,</td>
</tr>
<tr>
<td>Fresh frozen plasma, yes/no ICU patients (2004-2005)</td>
</tr>
<tr>
<td>Platelet transfusion</td>
</tr>
<tr>
<td>Number of pregnancies among donors</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Aspiration, yes/no</td>
</tr>
<tr>
<td>Medical or surgical misadventures (ICD-9 codes E870-E879.9), yes/no</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoking, current &gt;20 cigarettes a day</td>
</tr>
<tr>
<td>Chronic alcohol abuse</td>
</tr>
</tbody>
</table>

*unadjusted
Acute lung injury is characterized by damage and increased vascular permeability of alveolocapillary membrane that result in protein rich pulmonary edema (increased permeability edema as opposed to hydrostatic edema in cardiogenic shock) (7). Injury to alveolocapillary membrane can be physical (increased pulmonary pressure), chemical or due to an activation of immune response. These affect both alveolar epithelium and capillary endothelium. Alveolar epithelium consists mainly (90%) of alveolar epithelial cells type I that are responsible for gas exchange and prevent extravasation of fluid into alveoli. Cubic, alveolar epithelial cells type II are less prone to injury and have a role in reabsorption of the fluid and surfactant production. Proliferation of alveolar cells type II and their differentiation to alveolar epithelial cells type I allows healing of alveolocapillary membrane (30). Injury of alveolar epithelial cells type II causes dysregulation in surfactant production and results in severe derangements of respiratory mechanics and decrease in pulmonary compliance. Endothelial cells edema and widening of intercellular gaps causes increase in vascular permeability (‘capillary leak syndrome’) (31). Both inadequate and hyperimmune response can cause injury of the alveolocapillary membrane. Dysregulation of inflammation in immune response is the common cause of acute lung injury (32). After initial stimuli activate macrophages to secrete tumor necrosis factor TNF-α and IL-1 neutrophils migrate into intraalveolar space. Activated neutrophils, endothelial and epithelial cells induce a cascade of cytokines that amplify immune response. Products of neutrophils such as oxygen radicals and proteases can result in damage of the membrane (‘collateral damage’) (7). Epithelial cells are also found to have an active role in inflammation. In pulmonary infections activated macrophages directly (IL-1, TNF-α) or indirectly (T-cells) stimulate nuclear factor κB (NF-κB) pathway of epithelial cells that consequently leads to increased production of chemokines, colony stimulating factors and adhesion molecules. Experimental studies have shown that inhibition of inflammatory molecules may have a protective role in ARDS (32). Some but not all studies indicated correlation between increased plasma or bronchoalveolar TNF-α and development of or mortality in ARDS (33, 34, 35). Recent genomic studies of cytokines and their receptors have shown that polymorphism in the genes for TNF-α is associated with increased mortality of ARDS, as well as ARDS susceptibility in some subgroups of patients according to the site of injury (36). Damage to epithelial and endothelial cells and production of inflammatory cytokines can lead to increased expression of tissue factor and stimulation of inhibitors of plasminogen activators. In addition levels of activated protein C (APC), antithrombin (AT) and tissue factor pathway inhibitor (TFPI) are found to be lower in sepsis due to decreased production and increased degradation (37) thus leading to increased fibrin production and microvascular thrombosis early in the course of ARDS (7).

Pathophysiology

Acute lung injury is characterized by damage and increased vascular permeability of alveolocapillary membrane that result in protein rich pulmonary edema (increased permeability edema as opposed to hydrostatic edema in cardiogenic shock) (7). Injury to alveolocapillary membrane can be physical (increased pulmonary pressure), chemical or due to an activation of immune response. These affect both alveolar epithelium and capillary endothelium. Alveolar epithelium consists mainly (90%) of alveolar epithelial cells type I that are responsible for gas exchange and prevent extravasation of fluid into alveoli. Cubic, alveolar epithelial cells type II are less prone to injury and have a role in reabsorption of the fluid and surfactant production. Proliferation of alveolar cells type II and their differentiation to alveolar epithelial cells type I allows healing of alveolocapillary membrane (30). Injury of alveolar epithelial cells type II causes dysregulation in surfactant production and results in severe derangements of respiratory mechanics and decrease in pulmonary compliance. Endothelial cells edema and widening of intercellular gaps causes increase in vascular permeability (‘capillary leak syndrome’) (31). Both inadequate and hyperimmune response can cause injury of the alveolocapillary membrane. Dysregulation of inflammation in immune response is the common cause of acute lung injury (32). After initial stimuli activate macrophages to secrete tumor necrosis factor TNF-α and IL-1 neutrophils migrate into intraalveolar space. Activated neutrophils, endothelial and epithelial cells induce a cascade of cytokines that amplify immune response. Products of neutrophils such as oxygen radicals and proteases can result in damage of the membrane (‘collateral damage’) (7). Epithelial cells are also found to have an active role in inflammation. In pulmonary infections activated macrophages directly (IL-1, TNF-α) or indirectly (T-cells) stimulate nuclear factor κB (NF-κB) pathway of epithelial cells that consequently leads to increased production of chemokines, colony stimulating factors and adhesion molecules. Experimental studies have shown that inhibition of inflammatory molecules may have a protective role in ARDS (32). Some but not all studies indicated correlation between increased plasma or bronchoalveolar TNF-α and development of or mortality in ARDS (33, 34, 35). Recent genomic studies of cytokines and their receptors have shown that polymorphism in the genes for TNF-α is associated with increased mortality of ARDS, as well as ARDS susceptibility in some subgroups of patients according to the site of injury (36). Damage to epithelial and endothelial cells and production of inflammatory cytokines can lead to increased expression of tissue factor and stimulation of inhibitors of plasminogen activators. In addition levels of activated protein C (APC), antithrombin (AT) and tissue factor pathway inhibitor (TFPI) are found to be lower in sepsis due to decreased production and increased degradation (37) thus leading to increased fibrin production and microvascular thrombosis early in the course of ARDS (7).

Histology

Pathohistological changes in ARDS correspond to diffuse alveolar damage-DAD. Acute, exudative phase develops within first week and is characterized by interstitial and intraalveolar edema, capillary congestion, neutrophilic infiltrate, macrophages, erythrocytes and presence of hyaline membranes- eosinophilic structures which consist of cellular debris and proteins (albumin, fibrinogen and immunoglobulins). Elements of vascular microthrombosis are also present. Late, proliferative phase develops in first two weeks after insult. Proliferation of cuboid cells, fibroblasts, and myofibroblasts are seen with rare cellular infiltrate and interstitial deposition of collagen (38). DAD results in loss of the integrity of the alveolar-capillary barrier, exudation of protein-rich fluid across the barrier, pulmonary edema, and hypoxemia. Although described in 1976 by Katzeinstein (39) and considered to be a pathological substrate of ALI/ARDS presence of DAD was never included as one of the criteria in previous definitions since lung tissue is rarely available for pathological diagnosis. Furthermore, in patients with positive clinical criteria histological conformation of DAD is found in only about 50% on post mortem analysis (40, 41). Clinical and pathohistological definition correlates better in patients with extrapulmonary ARDS (40).

Diagnosis

Diagnosis of ALI is largely based on interpretation of chest radiograph that is consistent with pulmonary edema. Interpretation of chest X ray in critically ill may be difficult due to differences in quality, influence of mechanical ventilation as well as subjectivity of the interpreter. The interobserver agreement in applying radiographic criterion of ACCP definition was found to be moderate (kappa 0.55) (42). Cardiothoracic ratio
and vascular pedicular width could be useful in differentiating cardiogenic from non-cardiogenic pulmonary edema (43). CT findings in ARDS correspond to ground glass opacity and zone dependent heterogeneous consolidations (44). Patients with extrapulmonary causes of ARDS present more often with symmetric evenly distributed ground glass opacification in contrast to ARDS associated with pulmonary risk factors where the infiltrates tend to be asymmetric with a mix of dorso-caudal consolidation and ground glass opacification (45). In recent years there has been an increasing use of ultrasound techniques in the ICU which are valuable in assessing cardiac function as well as presence of lung edema by lung ultrasonography (‘comet tail sign’) (46). Preserved systolic function does not rule out cardiogenic edema since diastolic dysfunction (E/E’ >15) is the common cause of cardiogenic edema. Echocardiography also allows evaluation of pulmonary hypertension and functional status of the right ventricle. Excessive stretching of the ventricles induces secretion of Brain natriuretic peptide- BNP by myocytes. Values of 250 pg/mL are highly specific for diagnosis of non cardiogenic pulmonary edema while values of 950 pg/dl and higher are suggestive of heart failure (Table 4). Right heart failure which is often observed in ARDS can cause increased values of BNP (300-600pg/dl) (47). In differential diagnosis there are conditions that can present as ARDS but require specific treatment (Table 5). In the case of unclear etiology of ARDS surgical biopsy may have a crucial role in establishing diagnosis and initiation of appropriate therapy, especially in immunocompromised patients (table 5)(50). In previous studies, open lung biopsy in ARDS cases of unclear etiology led to alteration of treatment in majority of cases (60-89%) and was not associated with increased morbidity (51-53).

Treatment is focused on identification and management of predisposing condition such as adequate infection source control and supportive therapy. With the exception of low tidal volume strategy no other medical intervention or pharmacology treatment has been proven to reduce mortality in ARDS patients.

**Mechanical ventilation**

Lung protective ventilation using low tidal volumes 6ml/kg predicted body weight according to US National Institutes of Health Network for the Acute Respiratory Distress Syndrome (NIH ARDS Network) has led to a reduction of overall mortality from 39.8 to 31.0% in ARDS patients (8). Years of experimental studies indicated that using traditional tidal volumes of 10-15ml/kg can cause or worsen lung injury by direct mechanical stress, overdistension of healthy part of the lungs (volutrauma) (54-58), cyclic opening and closing of alveoli (atelectrauma)(59,60) and increasing production of proinflammatory cytokines (biotrauma) (61-64). Lung protection strategy is aimed at achieving SaO2 88-95% or PaO2 55-80mmHg and P plateau <5-30 mm Hg, with the lowest FiO2–PEEP values that often leads to retention of CO2 and acidosis. Positive end expiratory pressure

<table>
<thead>
<tr>
<th>Protein in alveolar edema fluid/plasma protein</th>
<th>Cardiogenic edema</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.65</td>
<td>&gt;0.65</td>
<td>Generally not available (30)</td>
</tr>
</tbody>
</table>

### Table 4. Differential diagnosis of cardiogenic and non-cardiogenic pulmonary edema

<table>
<thead>
<tr>
<th>Pulmonary capillary wedge pressure (PCWP)</th>
<th>Cardiogenic edema</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP &lt;18mmHg</td>
<td>PCWP &gt;18mmHg</td>
<td>Limited use of pulmonary artery catheter</td>
</tr>
</tbody>
</table>

In diastolic pulmonary edema may be normal if not measured during ischemic episode (“flash pulmonary edema”)

Values above 18 mm Hg can be found in ARDS patients due to volume overload or coexisting cardiac failure (48).

### Table 5. Differential diagnosis of ARDS

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>Cardiogenic edema</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF&lt;45% E/E’&gt;15</td>
<td>EF&gt;45% E/E’&lt;15</td>
<td>Exam might be limited in critically ill patients</td>
</tr>
</tbody>
</table>

Chest X-ray

<table>
<thead>
<tr>
<th>Brain natriuretic peptide (BNP)</th>
<th>Cardiogenic edema</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250 pg/mL</td>
<td>&gt;950 pg/mL</td>
<td>May be in elevated in renal failure</td>
</tr>
</tbody>
</table>

Lower values in obese patients (49).

Response to treatment

<table>
<thead>
<tr>
<th>Cardiogenic edema</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;24h, rapid improvement following treatment with positive pressure, venodilators and diuretics</td>
<td>Generally not available (30)</td>
</tr>
</tbody>
</table>

### Table 4. Differential diagnosis of cardiogenic and non-cardiogenic pulmonary edema

Abbreviations: EF-Ejection fraction; VPW-vascular pedicular width; CTR-Cardiothoracic ratio

### Table 5. Differential diagnosis of ARDS

Abbreviations: CBC-complete blood count; BAL-bronchoalveolar lavage

**Diffuse alveolar hemorrhage**

Decreased hemoglobin level in CBC and hemorrhagic BAL

**Acute interstitial pneumonia** (Hamman Rich)

Subacute presentation in previously healthy individuals

**Idiopathic acute eosinophilic pneumonia**

Elevated eosinophil levels in BAL (40%) and blood

Rapid response to corticosteroid treatment (48h)

**Lymphangitis carcinomatosa**

Table 5. Differential diagnosis of ARDS; CBC complete blood count, BAL-bronchoalveolar lavage

Abbreviations: CBC-complete blood count; BAL- bronchoalveolar lavage
Adult Respiratory Failure - CESAR TRIAL

Pulse (PEEP) opens atelectatic alveoli, decreases fraction of intrapulmonary shunt and improves oxygenation. On the other hand PEEP may cause distension of healthy part of the lungs and increase dead space fraction, decrease ventricular preload and cause hypotension. There is no evidence in difference in survival using high and low PEEP values [65]. Use of low tidal volumes is shown to decrease concentration of inflammation markers and frequency of extrapulmonary organ failures compared to traditional ventilation modes [66]. In case of inadequate oxygenation unconventional mechanical ventilation may be indicated. High frequency oscillation HFO uses rapid delivery (180 to 600 breaths in minutes, Fr 3-10Hz) of low tidal volumes (often below the values of anatomical dead-space). The concept of HFO is similar to low tidal volume ventilation. Experimental studies have shown lower level of lung injury and inflammation in HFO compared to conventional ventilation [63, 67]. Small volumes prevent overdistension of alveoli while high mean pressure in airways prevents its collapse. Downsides of using HFO are risk of pneumothorax and hemodynamic instability due to decreased stroke volume. Preliminary studies failed to show benefit of survival in patients who were ventilated with HFO that could be due to a late initiation of HFO. Future studies should be focused on identifying patients who could benefit from unconventional mechanical ventilation and timing of initiation of HFO in these patients [68]. In the cases of severe refractory hypoxemia extracorporeal membrane oxygenation (ECMO) could be initiated. The benefit of ECMO remained to be confirmed in controlled clinical trials (Conventional ventilation or ECMO for Severe Adult Respiratory Failure -CESAR TRIAL) [69]. Lung recruitment and prone position can improve oxygenation but effect is often transient, and there is no evidence of improved survival [7].

Noninvasive mechanical ventilation

Non invasive mechanical ventilation (NIV) may be used in early stages of ALI in patients without multorgan failure and in whom there is no expectation of prolonged mechanical ventilation. Presence of shock and acidosis are associated with failure of NIV. All noninvasively ventilated ALI patients should be closely monitored to prevent potential delay in intubation [70, 71].

Fluid management

Due to an increased vascular permeability reduced fluid intake is beneficial to a gas exchange. On the other hand reduction of circulatory volume can impair tissue oxygenation. Conservative fluid strategy reduces days on mechanical ventilation and ICU length of stay but does not affect overall mortality or development of acute renal failure. Similarly, use of pulmonary arterial catheter was not found to be superior to central venous catheter [72]. After initial fluid resuscitation fluid administration should be closely monitored and CVP should be maintained at 4 mmHg if shock is not present. Negative cumulative fluid balance at day 4 is associated with reduced mortality in acute lung injury [73].

Corticosteroids

Inflammatory changes in ALI as well as possible hyperimmune response and pathohistological changes in late ARDS give rationale for the use of corticosteroids in both early and late stages of ARDS. In the eighties high dose of corticosteroids were used for the treatment of ARDS but after reports of increased mortality related to their use, corticosteroids were used more cautiously. Corticosteroids have an indication in following clinical conditions that may present as ARDS: vasculitis (diffuse alveolar hemorrhage), acute eosinophilic pneumonia, acute interstitial pneumonia and acute bronchiolitis obliterans with organizing pneumonia. SARS experience has shown positive effect of corticosteroids on some infectious forms of ARDS. There is evidence that in early ARDS (inside first 72 h) use of corticosteroids may decrease days of mechanical ventilation, ICU length of stay and hospital mortality but this data needs to be confirmed in larger clinical trials [74].

National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network study did not show difference in survival of patients with persistent ARDS (at least seven days) who did and did not receive corticosteroids, although there were evidence of improved gas exchange, respiratory compliance and ventilator free days [75]. For those enrolled at least 14 days after the onset of ARDS the mortality rates in corticosteroid group were higher. Based on these results current guidelines do not recommend routine administration of corticosteroids in ARDS. Although previously associated with critical illness neuromyopathy and increased infection rates two recent meta-analysis found no relationship between use of corticosteroids and infection, neuromyopathy, or any major complications in ARDS patients [76, 77].

Pulmonary vasodilators

Use of semi-selective (nitric oxide, prostacyclin, prostaglandin E1) and non-selective (nitropruss-
side, hydralazine) vasodilators can improve oxygenation and reduce pulmonary hypertension in severe refractory forms of hypoxia by reducing pulmonary vascular resistance and improving perfusion of well ventilated parts of lungs. In spite of obvious physiological effects clinical studies failed to confirm its effect on reducing overall mortality rates (7).

**Surfactant replacement**

Although in ARDS metabolism of surfactant is severely impaired use of surfactant did not improve survival in adults. There is evidence that some subgroups of ARDS patients such as those with pneumonia and aspiration could benefit from treatment with surfactant (78). Possible additional therapeutic targets include use of antioxidants, β adrenergic receptor agonists, ACE inhibitors and nutritional modifications as well as use of GM-CSF and activated protein C (44, 50). Other supportive measures include adequate nutrition, stress ulcer, DVT and decubital prophylaxis. Recent data show that intensive insulin therapy reduces the duration of mechanical ventilation, duration of ICU stay and 180-day mortality in ICU patients but there are no exclusive data on subpopulation of ALI patients. There is evidence that intensive insulin therapy reduces the incidence of critical illness polyneuro-and/or myopathy (77).

**Prognosis**

Severe impairment of alveolar epithelia and failure to improve in first week are associated with adverse outcome (79). Older patients with sepsis, liver diseases and MOF carry worse prognosis (80). Although severe impairment of pulmonary function is a hallmark of ARDS only two pulmonary features, oxygenation index and increased dead space fraction ventilation are shown to be of predictive value (81). The main cause of death is withdrawal of treatment due to irreversible MOF (82) and low quality of life in older patients (83) and patients with significant comorbidities. About 10% of patients will be mechanically ventilated for more than a month (44). In some patients acute phase may be complicated with fibrosing alveolitis and persisting hypoxemia, increased dead space ventilation and reduced compliance. First fibrotic changes may appear after 5-7 days (7). Obliteration of pulmonary capillaries and refractory hypoxia can cause severe pulmonary hypertension with right heart failure. In those who recover radiologic changes withdraw gradually and pulmonary function test recovers completely, sometimes with mild restriction, obstruction or decreased diffusion capacity that are usually asymptomatic (84). Histological resolution in ARDS survivors is not well known. Prospective studies have indicated that ARDS survivors have impaired quality of life at one year follow up. Main problems that ARDS survivors are facing are weight loss, deconditioning, cognitive and psychological problems as well as neuromuscular weakness (85).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>In hospital OR (95% CI)</th>
<th>Six month OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per decade (86)</td>
<td>1.96 (1.50–2.53)*</td>
<td></td>
</tr>
<tr>
<td>Acute Physiology and Chronic Health Evaluation III score, per 25 point increase (86)</td>
<td>1.78 (1.16–2.73)*</td>
<td></td>
</tr>
<tr>
<td>Arterial pH &lt;7.22 (86)</td>
<td>2.32 (1.02–5.25)*</td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity score, for each point increase (87)</td>
<td>2.08 (1.34, 3.33) 3.11 (2.01-5.05)</td>
<td></td>
</tr>
<tr>
<td>Day 3 cardiovascular failure (87)</td>
<td>4.46 (1.66, 12.73) 3.30 (1.19-9.92)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary dead space fraction (81)</td>
<td>4.15 (1.15 to 1.83)</td>
<td></td>
</tr>
<tr>
<td>Oxygenation index (88)</td>
<td>1.84 (CI 1.13 to 2.99)</td>
<td></td>
</tr>
<tr>
<td>N-terminal probrain natriuretic peptide (NT-proBNP) levels&gt;6813 ng/L (89)</td>
<td>2.36 (1.11-4.99)*</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 4. Predictors of mortality in ARDS

*60-day mortality

**CONCLUSION**

Although survival of ARDS patients has been significantly improved in the last decades ARDS mortality rates are still high and survivors encounter significant physical and psychological impairments. Early treatment of predisposing conditions and the prevention of “second hit” in-hospital exposures are critical for prevention and treatment of this important complication of critical illness. Since ARDS patients represent etiologically and pathophysiologically a heterogeneous group of patients future studies should be focused on better defining subgroups of patients that could benefit from specific target therapies.
References


FROM MECHANICAL VENTILATION TO INTENSIVE CARE MEDICINE: A CHALLENGE FOR BOSNIA AND HERZEGOVINA

Guillaume Thiéry1,2,3*, Pedja Kovačević2,4, Slavenka Štraus5, Jadranka Vidović2, Amer Iglica1, Emir Festić6, Ognjen Gajić7

1 Medical Intensive Care Unit, Clinical Centre University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
2 Medical Intensive Care Unit, Clinical Center Banja Luka, 78000 Banja Luka, Bosnia and Herzegovina
3 Medical Intensive Care Unit, St Louis Hospital, University Denis Diderot, 1 avenue Claude Vellefaux, 75010 Paris, France
4 Faculty of Medicine, University of Banja Luka, 78000 Banja Luka, Bosnia and Herzegovina
5 Heart Center, Clinical Centre University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
6 Department of Critical Care Medicine, Mayo Clinic, Jacksonville, FL, USA
7 Division of Pulmonary and Critical Care, Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) Mayo Clinic, Rochester, MN, United States
* Corresponding author

ABSTRACT

Intensive care medicine is a relatively new specialty, which was created in the 1950’s, after invent of mechanical ventilation, which allowed caring for critically ill patients who otherwise would have died. First created for treating mechanically ventilated patients, ICUs extended their scope and care to all patients with life threatening conditions. Over the years, intensive care medicine developed further and became a truly multidisciplinary speciality, encompassing patients from various fields of medicine and involving specialists from a range of base specialities, with additional (subspeciality) training in intensive care medicine. In Bosnia and Herzegovina, the founding of the society of intensive care medicine in 2006, the introduction of non invasive ventilation in 2007, and opening of a multidisciplinary ICUs in Banja Luka and Sarajevo heralded a new age of intensive care medicine. The number of admissions, high severity scores and needs for mechanical ventilation during the first several months in the medical ICU in Banja Luka confirmed the need of these kinds of units in the country. In spite of still suboptimal personnel training, creation of ICUs in Bosnia and Herzegovina may serve as example for other developing countries in the region. However, in order to achieve modern ICU standards and follow European trends toward harmonisation of medicine, Bosnia and Herzegovina needs to take up this challenge by recognizing intensive care medicine as a distinctive speciality, by implementing a specific training program and by setting up multidisciplinary ICUs in acute care hospitals.

KEY WORDS: intensive care, mechanical ventilation, critical care, non invasive ventilation, developing countries.
INTRODUCTION

From the first attempts of resuscitation to modern and sophisticated intensive care medicine, many centuries have passed. However, the major development occurred from the 1950’s. Over the last 60 years, mechanical ventilation and other life sustaining interventions dramatically improved, and intensive care units (ICUs) became able to treat patients presenting with more and more critically ill conditions. In this review, we would like to describe the parallel history of mechanical ventilation and intensive care medicine, and to point out the current situation of intensive care medicine in Bosnia and Herzegovina, with special focus on the main requirements that are necessary in order to reach modern standards in intensive care medicine.

History of Mechanical Ventilation

The early ages

The first experiments of respiratory resuscitation have been reported in the middle of the 16th century, describing insufflations of air into the lungs through a pipe introduced into the trachea. Between the 16th and the 19th century, various attempts of mechanical insufflations were made, using a positive airway pressure. In the late 19th, the first ventilators were described, namely “tank respirators”: the patient was put into the ventilator and inspiration was provoked by a negative pressure applied in the ventilator. This system was subsequently developed as “iron lung”, which was commonly used in the first half of the 20th century. The emergence of mechanical ventilation in its modern sense began in Denmark in the 1950th, when an epidemics of poliomyelitis devastated northern Europe. In 1952, hundreds of patients were hospitalised in Copenhagen because of respiratory paralysis related to poliomyelitis and were put in iron lungs. Despite this treatment, almost all patients died. A young anaesthetist, named Dr Bjorn Ibsen, showed that the addition of an intermittent external positive airway pressure through tracheotomy would save lives, and described the first standardizes approach of treatment of respiratory failure, including tracheal intubation, tracheotomy, and artificial respiration by manual ventilation (1-3). During several months, hundreds of medical students, nurses and physiotherapists spent ours applying manual ventilation and provided the 24-hours coverage (1-3). That was the starting point of mechanical ventilation and modern intensive care medicine. Because of high requirements in human resources could not be easily filed, several types of machines were tried out during this period. The Engstrom respirator was then developed, widely used, and became the first respirator that could deliver a predetermined volume at a preset frequency. The efficiency of this respirator was subsequently confirmed in Stockholm Hospital in 1953, where 54 patients with poliomyelitis were ventilated with a 27% mortality rate (4). Meanwhile, major progress was made in understanding lung physiology and pathology. Several physiologists allowed a better understanding of respiration and gas exchanges. Measurements of PCO2, pH and oxygen saturation were developed (5). Similarly to Ibsen, Astrup gained great experience during the 1952’s epidemics in Denmark, and subsequently described the influence of artificial ventilation on modification of pH and PCO2. He even reported the risk of over-ventilation, which, 40 years later, became a major issue in mechanical ventilation. During the following two decades, improvements in laboratory measurements helped clinicians evaluate the effectiveness of ventilation and various physiological conditions such as circulatory collapse, renal function or fluid balance. In addition, new knowledge and modern equipment facilitated safer and more successful use of mechanical ventilation. From the 70’s, ventilators became more sophisticated, with new modes and the ability to continuously monitor various parameters such as pressures, volumes and flows that were actually delivered to the patients. Consequently, blood gas analysis, ventilator monitoring and other forms of physiologic monitoring were increasingly used to guide ventilator settings. Particularity of respiratory physiology of mechanically ventilated lungs was better understood thanks to both research works and daily use of monitoring system at the bedside. In 1967 the first description of Acute Respiratory Distress Syndrome (ARDS) was published (6), and simultaneously Positive End Expiratory Pressure (PEEP) was found to be an effective treatment for severe hypoxemia in ARDS (7). The number of patients successfully treated with mechanical ventilation dramatically increased, as did the number of beds dedicated to intensive care medicine.

Complications of mechanical ventilation

From the 80’s however, awareness of the complications of invasive mechanical ventilation led to interest in less aggressive, potentially less injurious ventilatory support, despite more and more higher acuity of critically ill patients. New ventilator modes were proposed, most of them aiming to improve synchronisation between patient and ventilator, or to increase patient’s participation in his ventilation, reducing aggressive-
ness of fully controlled ventilation. The most important deleterious effect of mechanical ventilation was described in 1988 by Didier Dreyfuss who showed that excessive volume insufflated could seriously damage the lung (8). This phenomenon was subsequently called Ventilator Induced Lung Injury (VILI) (9) and led to a complete reappraisal of ventilation strategies by the end of the 90’s (10), in which the reduction of the tidal volume and the airway pressure was a priority. Clinicians soon recognized that short term acceptance of abnormal blood gas analysis ("permissive hypercapnia") is tolerated by mechanically ventilated patients (10). However, despite improvement of respiratory care long term exposure to ventilatory support was shown to lead to various complications, such as ventilator associated pneumonia (VAP), poor nutrition, neuromyopathy, tracheal complications, etc... VAP became a major issue in patients on prolonged invasive mechanical ventilation, occurring in 20 to 60% of all ventilated patients. VAP is responsible for increased costs and prolonged length of stay, and maybe mortality. Several attempts were made in order to reduce the frequency of VAP, including patient positioning (11), more accurate diagnostic strategies (12), rational use of antibiotics and better use of enteral feeding. Paradoxically, although the effectiveness of invasive mechanical ventilation as a life-saving therapy was largely proven, it became obvious that its duration should be reduced, or even avoided, if possible. In addition to VAP, complications of artificial airway included the need for prolonged sedation and prolonged immobility. Considerable efforts were made to reduce the duration of sedation and ventilation, using sedation protocols (13, 14) or strategies of daily interruption (14), and to improve weaning process. In the early 90’s, a new strategy, so called non invasive ventilation (NIV) was promoted as an alternative to invasive ventilation in certain conditions. The potential benefit of continuous positive airway pressure using a face mask in patients with acute respiratory failure was recognized decades earlier (15,16), but the interest of NIV was renewed in more recent years, with the combination of pressure support and positive end-expiratory pressure delivered via a face mask or nasal mask. Endotracheal tube or tracheotomy was replaced by face mask, allowing mechanical ventilation without invasive airway device (18). Over the last 20 years, evidence has accumulated to support the use of NIV in exacerbations of chronic obstructive pulmonary disease, cardiogenic pulmonary edema, and acute respiratory failure in immunocompromised patients (19, 20, 21, 22). For these patients, there is a demonstrated benefit in terms of intubation rate, incidence of hospital acquired infection, duration of stay in the ICU and the hospital, and finally mortality (20-23). As a result, the use of NIV dramatically increased over the years, and has become the first line of treatment in these indications (24).

History of Intensive Care Medicine

By the end of the 1940’s, anaesthesia began to develop as an entire specialty. The Danish school of anaesthesia was one of the most famous, for both education and organisation of care. In 1950, Copenhagen hospital stated that anaesthetists should care for the patients during the operation and postoperatively "maintaining a sufficient circulation of blood...and infuse salt and water to restore the fluid balance and secure the best possible oxygen delivery by an energetic support of the respiratory function" (25). More importantly, the statement added that "these principles for supportive therapy should also be applied to patients with medical diseases and self-poisoning" (25). By 1952, newly created recovery rooms were exclusively dedicated to postoperative patients, but the 1952 poliomyelitis epidemic in Copenhagen led to high number of patients placed on artificial ventilation (1.2). Soon, it became obvious that mechanically ventilated patients should be observed and treated in special wards by physicians and nurses trained in restoring and/or maintaining the function of vital organs. Subsequently, this concept was extended to all critically ill patients (medical as well as surgical) by Dr Bjorn Ibsen who created the first ICU in 1953, which was dedicated to the treatment of respiratory and circulatory failure (26).

Definition and organization of ICUs

At the end of the 50’s, most of European and North American countries had started to implement ICUs. During the following decades, the importance of ICUs was recognized worldwide, and the number of ICU beds increased, but with important discrepancies between countries. At the end of the 90’s, the number of ICUs in Europe was estimated between 3000 and 4000. The a number of ICU beds is ranging from 3.3/100 000 (UK) to 20-25/100 000 population (USA, Germany, Belgium), and from 1.2% (UK) to 9% of all hospital beds (USA) (27). Not surprisingly, the volume of admission varies between countries (10-fold difference from least to greatest), as does the severity of patients, measured by physiological scores such as APACHE, SAPS, and mortality rate, which are higher in countries with low number of ICU beds (27).
During the first decades, each country has developed its own approach, regarding to organization of ICUs. Even definition of an ICU appeared to be different between countries. However, there is a now consensus among health care professionals to consider that ICUs are unit designed to provide care for patients presenting or susceptible to present with acute organ failures, directly threatening life and necessitating auxiliary support, mainly mechanical ventilation. Finally, the current definition emphasizes the overlap between intensive care medicine and mechanical ventilation from which it was born. Given the predominant involvement of anaesthesiologists in the early age of intensive care medicine, most of patients admitted to the ICUs were surgical patients. Other specialists however, such as pneumologists, cardiologists, neurologists..., recognized the need of critically care for their patients, and got involved in the ICUs. Consequently, the development of ICUs in hospitals has not followed a single pathway. In some countries, each specialty developed its own ICU, called “specialty ICUs”, while in others a distinction between surgical and medical ICUs was apparent, the later admitting all non surgical patients. Some other countries, such as Spain and Australia, chose immediately to disconnect ICUs from any other specialty, and implemented multidisciplinary and independent ICUs. At the end of the 90s, a consensus emerged that the problems presented by medical and surgical patients were similar, so that separate units should merge and mixed medical-surgical departments became the standard (29). European countries are now willing to harmonize the organization of ICUs, recognize intensive care medicine as a specialty, and help intensivists to set up common standards.

**Education**

When intensive care medicine began to develop it appeared that the management of such complex and multidisciplinary patients was no longer possible by doctors who did not have a specific knowledge. Nevertheless, education in intensive care developed heterogeneously from one country to another, leading to high diversity in access, structures, assessment, accreditation, and regulation of trainings between countries (30). Four main models can be described:

- **The single subspecialty model**, in which access to intensive care medicine is limited to trainees from anaesthesiology.
- **The multiple specialty model**: multiple base specialties each offer a programme of intensive care medicine training to their own trainees. Nationally, the content, duration and standards often vary between each base specialty.
- **The primary speciality model**, in which intensive care medicine is an independent primary specialty which can be accessed directly after undergraduate medical training.
- **The supraspeciality or subspeciality model** (such as proposed in Bosnia and Herzegovina), which permits multidisciplinary access from a range of base specialties (for example, internal medicine, anaesthesia, neurology...) to a common intensive care medicine training programme.

Over the time, it became obvious that an extra expertise (intensive care medicine) outside the domain of the primary speciality was required to provide high quality patient care by multidisciplinary input from doctors from various medical specialities. As a result, the supraspeciality model, based on multidisciplinarity, is being adopted by more and more countries. Moreover, there is currently a strong will of many countries in Europe to harmonize their training programme in order to provide similar level of education to intensivists. As part of this process, the European Society of Intensive Care Medicine is supporting a training programme called (CoBaTrICE) which "aim is to develop an internationally acceptable competency-based training programme in intensive care for Europe and other world regions, by using consensus techniques to develop minimum core competencies for specialists in intensive care medicine" (31).

**Current Development of Intensive Care Medicine in Bosnia and Herzegovina**

*First use of non invasive ventilation*

Until recently in Bosnia and Herzegovina, ICUs were almost exclusively surgical ICUs and only anaesthesiologists were involved in the care of critically ill patients. Although many non surgical clinics have their own semi-ICU, all patients requiring mechanical ventilation or presenting life threatening organ failures had to be transferred to the surgical ICU. Moreover, intensive care medicine was not defined as a specialty, but rather as part of anaesthesiology. As a result, access to intensive care medicine was not possible for non-anaesthesiologist trainees. Intensive care is however necessary in many non surgical situations, such as respiratory diseases, infectious diseases, neurological diseases, etc. In these cases, when patients suffered from acute respiratory failure,
providing appropriate care was uncertain because of inadequate access to invasive mechanical ventilation. The use of non invasive ventilation (NIV) in this setting was thus proposed, based on published recommendations that support its use in patients with chronic obstructive pulmonary disease (COPD) and patients with pulmonary edema (21, 22). The first aim was to use modern standards of care in these patients. The second aim was to supply the lack of invasive mechanical ventilation in some situations. Based on this, a multidisciplinary Society of Intensive Care Medicine was founded in November of 2006 (Udruzenje za Intenzivnu Medicinu Bosne i Hercegovine, UIMBIH). Only six months later, the Clinical Centre Banja Luka implemented NIV to nonsurgical critically ill patients. From 1st June 2007 to 1st March 2008, 36 patients with acute respiratory failure where placed on NIV (table 1 and 2). All patients underwent NIV in the semi-ICU pulmonary ward. All patients were ventilated in pressure support mode with face masks. In case of failure of NIV, patients were to be transferred to the surgical ICU and placed on invasive mechanical ventilation. In some cases however, transfer to the surgical ICU was denied, and this often resulted in the patient’s death. The main reasons for refusals were the lack of available beds and the general reluctance of anaesthesiologists to admit non surgical critically ill patients. The overall ICU-survival rate was 72%.

**Implementation of multidisciplinary ICUs**

Based on initial experience, the Clinical Centre in Banja Luka decided to set up a multidisciplinary ICU. In the same time, the Clinical Centre of University in Sarajevo started a similar project. Both projects were led simultaneously, with a help of American and French ICU specialists. The main aim was to extend access to intensive care to all patients, both surgical and non surgical, and to implement modern standards of care for critically ill patients. The Clinical Centre Banja Luka opened the multidisciplinary ICU on December 15th, 2008. It consists of 6 beds equipped for caring for mechanically ventilated patients. The medical staff consists of one anaesthesiologist, one pneumologist, and one French intensivist who spends a week per month in this ICU. Three young doctors in training were added to the medical staff. Night shifts are shared by ICU staff and non-ICU anaesthesiologists.

The nurse-to-patient ratio is 1:3. All nurses have at least at least 4 months of ICU experience, having worked previously in surgical ICU. Patients were admitted to the ICU if they presented with life threatening condition and/or with need for mechanical ventilation. The ICU functions as a closed-ICU; the decision to admit and all treatment decisions are done by intensivists. During the first 4 months, 90 patients were admitted, 52% of whom were ventilated. The overall ICU-survival rate was 65%, decreasing to 35% among ventilated patients (table 3).

**TABLE 3. Characteristics and outcomes of patients admitted in the ICU from December 15th to April 15th**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 (44-73)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>49.5 (30-65)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Origin of admitted patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>General ward, no. of patients (%)</td>
</tr>
<tr>
<td>Emergency Room, no. of patients (%)</td>
</tr>
<tr>
<td>Other hospital, no. of patients (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ventilated patients, no. of patients (%)</td>
</tr>
<tr>
<td>Number of patients ventilated &gt; 48h, no. of patients (%)</td>
</tr>
<tr>
<td>Median length of ventilation (days)</td>
</tr>
<tr>
<td>Extremes (days)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median length of ICU stay (days)</td>
</tr>
<tr>
<td>Extremes ICU (days)</td>
</tr>
<tr>
<td>ICU mortality, no. of patients (%)</td>
</tr>
<tr>
<td>ICU mortality in ventilated patients, no. of patients (%)</td>
</tr>
</tbody>
</table>

*SAPS II: Simplified Acute Physiological Score (28)
Values are median with interquartile range shown in parentheses

The Challenges of Intensive Care Medicine in Bosnia and Herzegovina

Developing countries need to use the lessons from the 50-year history of intensive care medicine in western countries and to avoid the mistakes already made. Moreover, many European countries
are now trying to harmonize their educational programs in intensive care medicine. Bosnia and Herzegovina, as a European country should therefore follow this process and move towards the same.

Lessons from 50-year history in developed countries

The first lesson is the position and state of ICU in acute care hospitals. Access to ICU must be given to all patients in need whether they come from surgical department, medical department or emergency room, provided they may benefit from admission to the ICU. The experience of Banja Luka’s new ICU, its activity and growth, highlights the strong need for such unit in this hospital. One can assume that same situation would apply to other acute care hospitals in the country. In other words, patients requiring ICU do exist everywhere. Artificial distinctions between surgical and medical ICUs or between ICUs connected with each different department or specialty are no longer relevant, but this organizational division remains to be present in many hospitals. In Western European countries, the majority of patients admitted to the ICU are non-surgical patients, and 75% of the ICUs are defined as mixed medical-surgical ICUs (29). The problems presented by surgical and medical patients, or by patients from various fields of medical specialties are similar, so that they all fall under the competence of intensivists and should be treated in centralized multidisciplinary units. This concept has been shown to be more cost-effective than separate units, by concentrating human resources and expensive medical equipment in one place, instead of disseminating expenditure in various locations, which is simply unsustainable for economic reasons. This model seems discrepant with the current process of developing multidisciplinary medical ICU in Clinical Centres in Sarajevo and Banja Luka. However, considering local conditions, the first step of setting up medial ICUs is essential to move towards modern standards of care, and to facilitate access to ICUs for non-surgical patients. For that matter, the experience of implementing NIV for patients with acute respiratory failure has been an essential starting point. Just as intensive care medicine was born from mechanical ventilation, we can assume that development of NIV may play a major role in the extension of intensive care to various types of patients.

The second lesson refers to internal organization of ICUs. There have been lots of debates about the issue of open or closed policy ICUs. In many places ICUs operate with an open policy: physicians from different specialties give orders after a patient is admitted to an ICU. On the contrary, most ICUs in Europe work with a closed policy: patients are screened for admission to the ICU by the intensivist, and the intensivist is solely responsible thereafter. Some investigators have reported that closed policy improves resources utilization and outcomes (32, 33). A prospective study has been conducted in Turkey, evaluating the effect of a closed policy on resources utilization and outcomes. Compared to open policy, the closed policy is associated with higher severity of illness among admitted patients, increased use of mechanical ventilation, and lower mortality (34). In addition, this study demonstrated that the appointment of a full time intensivist, with a 24h-coverage was associated with better quality of care (29). In 1992, 70% of all European ICUs had an intensivist present at night and during the weekend. Several authors reported better patient outcomes in units managed by a full time staff, and the 24h-coverage is now the rule. The challenge for Bosnia and Herzegovina is therefore to implement such closed units, managed by full time intensivists.

The third lesson refers to education issues. It is now recognized worldwide that intensive care medicine as a specialty requires it’s own training program. As previously stated, there are substantial variations in training programs in intensive care medicine across European Countries (30). Because of the European Union aim and objective for free movement of professionals and mutual recognition of qualifications, there is now a strong trend toward harmonization of curricula across European countries among health care professionals and especially intensivists (31). Therefore it is essential for Bosnia and Herzegovina, which is on the way to European integration, to timely move towards these harmonized standards of education. Moreover, this is also the best way to involve younger doctors in the specialty. The main parts of this process are:

- The recognition of intensive care medicine as a specialty
- The implementation of a training program based on subspecialty model, which permits multidisciplinary access from a range of base specialties to a common intensive care medicine training program.
- A training program in which trainees have to conduct practical work in the ICU and to complete several pre established learning objectives.

This form of training program in intensive care medicine has been proposed in early 2009 to ministries of Health in both entities in Bosnia and Herzegovina, and is currently being considered.
The fourth lesson is the need that all specialists in this field of intensive care medicine organize themselves in an efficient and recognized scientific society. The duties of such a society are:
1) to promote knowledge exchange within Bosnia and Herzegovina and in connection with other countries,
2) to be responsible for education,
3) to set up research projects,
4) to be the official representative of intensive care medicine in cooperation with administrative authorities.

Udruzenje za Intenzivnu Medicinu Bosne i Hercegovine (UIIMBIH) was founded in 2006 in this aim. There is however an urgent need for this society to grow and to develop partnership with similar societies in other countries. The French Society of intensive care medicine (Société de Réanimation de Langue Française, SRLF) and the American Society of Critical Care Medicine (SCCM) are already involved in Bosnia and Herzegovina. It is without doubt that the development of intensive care medicine in a country depends on such cooperation.

**CONCLUSION**

Born in the 1950’s, intensive care medicine is now a complex specialty that saves lives all over the world. Intensive care medicine can be defined as the active treatment and support of all life threatening conditions and mechanical ventilation and hemodynamic support remain its cornerstones. Because of the high diversity of patients requiring admission to the ICU, intensive care medicine is, above all, a multidisciplinary specialty. Various models exist in terms of organizations of ICUs and training programs. However, European countries are moving toward one common model. It is essential that Bosnia and Herzegovina timely takes part in this movement. With that in mind, we propose three major recommendations.

1. Bosnia and Herzegovina needs to set up multidisciplinary ICUs with closed policies, managed by full time intensivists, and which should admit both medical and surgical patients. Hospitals should avoid dispersion of human resources and medical equipment in numerous “semi-ICU” wards and should concentrate all these resources into multidisciplinary ICUs, which are more cost-effective and provide better outcomes.
2. Bosnia and Herzegovina needs to recognize intensive care medicine as a specialty, and to implement a specific training program based on subspecialty model, which permits multidisciplinary access.
3. Communication, share of knowledge and research must be encouraged, through an efficient scientific society, in order to benefit from major improvements in our specialty all over the world.

*List of Abbreviations*

- MV - mechanical ventilation
- NIV - non invasive ventilation
- ICU - intensive care unit
- ARDS - acute respiratory distress syndrome
- COPD - Chronic obstructive pulmonary disease
- VAP - Ventilator associated pneumonia
References

(3) Andersen E.W., Ibsen B. The anaesthetic management of patients with poliomyelitis and respiratory paralysis. B.M.J. 1954; 1: 786–788
EVALUATION OF THE INTRINSIC PROPERTIES OF PEDICLE SCREWS: DO DIAMETER, MANUFACTURING AND SCREW DESIGN AFFECT RESISTANCE AND/OR RESISTIVITY

Worawat Limthongkul¹, Jason Savage², Emmanuel K. Nenonene³, Eldin E. Karaikovic¹*

1 Department of Orthopaedic Surgery, North Shore University Health Systems (NUH), University of Chicago, IL, USA
2 Department of Orthopaedic Surgery, Northwestern University, Chicago, IL, USA
3 Department of Neurology, University of Chicago, Chicago, IL, USA

* Corresponding author

ABSTRACT

The pedicle screw diameter, composite and design are variables that can affect the threshold of intraoperative electromyographic monitoring. Even though we know that larger diameter objects tend to have less resistance, no study documented the effect that this variable could have on pedicle screw resistance. Using high quality equipment, resistance and resistivity of ten pedicle screws (from four manufacturers) were calculated based on known constant current and measured voltage. Voltage was measured three times for each screw to determine intraobserver measurement variability. Resistance of all screws ranged from 1.14 to 3.9 mΩ (mean = 2.69 ± 0.71 mΩ). The screw with largest diameter (7.75 mm) had lower resistance than screws with other diameters. Resistivity of screws ranged from 7.12 to 12.63 μΩ·m (mean = 9.91 ± 1.82 μΩ·m). Based on the screw design, one manufacturer’s pedicle screws (A) had significantly lower resistivity compared to three other manufacturers (p<0.01). Larger diameter screws (7.75 mm in diameter) had lower resistance. Screw design (polyaxial or monoaxial) had no effect on its resistance. Screws of one manufacturer (A) showed lower resistivity compared to those manufactured by other three companies.

KEY WORDS: pedicle screw, electrical resistance, electrical resistivity, intraoperative neuromonitoring
INTRODUCTION

In the past decade, pedicle screw systems have proven to provide the highest biomechanical stability in spinal instrumentation, which gives a surgeon greater flexibility to accommodate patient’s intrinsic anatomy. To achieve maximum fixation, the screw should be placed properly within the pedicle. Due to a high variability of pedicle geometry (1), the rates of pedicle cortical perforation have been reported to be between 5.4% and 40% (2-4). Clinically, this is relevant because an incorrect placement of a pedicle screw not only leads to suboptimal spinal stability and higher incidence of pseudoarthrosis (5), but also may lead to neurological irritation or nerve root injury.

An intraoperative electrical testing of pedicle screws is a widely accepted technique of minimizing intraoperative nerve root irritation or an injury during insertion of spinal instrumentation. A properly placed screw can be distinguished from those that perforate a pedicle wall by its minimum level (threshold) of the electrical current needed to elicit a compound muscle action potential (CMAP). On the other hand, stimulation thresholds have been shown to vary in several studies. The strong likelihood of a pedicle wall defect and a potential screw contact with a nerve root and/or the dura ranged from 7mA to 14mA (6-10).

Differences in CMAP threshold values may be attributed to a host of variables (screw, bone, nerve, muscle, subcutaneous fat tissue and skin). One variable that can affect the threshold is electrical conductivity of pedicle screws: their resistivity and resistance. Electrical resistivity (specific electrical resistance) is the property of an element that shows how strongly material opposes electrical current. High resistivity indicates that a material strongly opposes the movement of the electrical charge. Resistance is a material’s opposition to the flow of the current, which is affected by its length, diameter and resistivity. Resistance of a pedicle screw may vary with its length, diameter and resistivity of the material as well. This may affect electrical conduction during intraoperative neuromonitoring. To our knowledge, no earlier study evaluated effects of screw diameter, screw manufacturing and design on its intrinsic electrical properties.

MATERIALS AND METHODS

Ten titanium alloy (Ti-6Al-4V) pedicle screws from four different manufacturers (Table 1) commonly used in spine surgery were inserted into an aluminum block to provide a connection with the current source. A current meter (Keithley 195 system digits multimeter, Keithley Instruments, Inc., Cleveland, Ohio, USA) was attached to the aluminum block with a current wire on one side, and through a surgical monopolar probe (WR Medical Electronics Company, Stillwater, MN, USA) on the other. The probe was manually kept in contact with a pedicle screw in order to test its resistance based on screw design. This created an electrical circuit (Figure 1).

Two voltage wires that measured a current potential were attached 28 mm apart along the length of a screw (the X1 - X2 distance), using silver conductive epoxy (Chemtronics, Kennesaw, GA, USA) which has extremely low resistivity. A 100 mA current (I) was
passed through a screw via current wire. Generated voltage was recorded using a voltmeter (HP34401A digital multimeter, Hewlett-Packard Company Test and Measurement Organization, Santa Clara, CA, USA). The resistance was calculated based on Ohm’s law (R=V/I); where R is resistance of an object (measured in ohms; Ω), V is a potential difference across an object (measured in volts) and I is a current through an object (measured in amperes). Each screw was tested three times to minimize an intraobserver error. Each screw had several diameters (Table 1).

In order to test the difference in conductivity at different screw sites based on screw design (monoaxial versus polyaxial), we attached a contact with monopolar probe in three different locations on the screw surface; the screw top (the top of the screw crown surface), the inner surface (the inner site of the crown) and the screw shaft (a hexagonal screw base) (Figure 2). Resistivity of a screw was then calculated based on $\rho = \frac{R \cdot A}{\ell}$, where $\rho$ is resistivity of a material (measured in Ω•m), $R$ is resistance of an object (measured in ohms), $A$ is a cross sectional area (measured in m²), and $\ell$ is a length (measured in meters).

Statistical analysis was done by using SAS 9.2 (SAS Institute, Cary NC) software and ANOVA. In order to see difference between groups of screws of different diameters we used Tukey grouping as the statistic method to categorize the data. Mean values of screw resistance within the same Tukey group are not statistically different. As it is shown in Table 4, there are 7 different categories of screw sizes, which based on their means are grouped in four groups: Group I (5.5 and 6.5 millimeter screws with not statistically different means: 3.5 and 3.2965 respectively); Group II (6.5 and 6.2 mm screws had no statistically different means: 3.2965 and 2.9250 respectively); Group III (7.5, 7, and 6.25 mm screws had no statistically different means from each other, but they had statistically different means from everyone in groups I, II and IV); and Group IV (7.75 mm screws had a mean of 1.41, statistically different from all other groups).

<table>
<thead>
<tr>
<th>Screw manufacturer</th>
<th>Test trial</th>
<th>A</th>
<th>A</th>
<th>B</th>
<th>B</th>
<th>C</th>
<th>C</th>
<th>C</th>
<th>D</th>
<th>D</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td></td>
<td>6.25</td>
<td>7.75</td>
<td>6.2</td>
<td>7.0</td>
<td>5.5</td>
<td>6.5</td>
<td>7.0</td>
<td>5.5</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Measured voltage (mV)</td>
<td>1</td>
<td>0.2074</td>
<td>0.1401</td>
<td>0.2923</td>
<td>0.24</td>
<td>0.3922</td>
<td>0.3394</td>
<td>0.2134</td>
<td>0.3081</td>
<td>0.3203</td>
<td>0.2362</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.3083</td>
<td>0.1412</td>
<td>0.2927</td>
<td>0.2404</td>
<td>0.3926</td>
<td>0.3391</td>
<td>0.2135</td>
<td>0.3084</td>
<td>0.3201</td>
<td>0.2367</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.2068</td>
<td>0.1424</td>
<td>0.2925</td>
<td>0.2393</td>
<td>0.3932</td>
<td>0.3392</td>
<td>0.2132</td>
<td>0.3082</td>
<td>0.3198</td>
<td>0.2364</td>
</tr>
</tbody>
</table>

**TABLE 2. Measured screw voltage data**

**FIGURE 2.** Three different locations of a monopolar probe attachment on a polyaxial screw (a screw top, an inner screw and a screw base).
WORAWAT LIMTHONGKUL ET AL.: EVALUATION OF THE INTRINSIC PROPERTIES OF PEDICLE SCREWS: DO DIAMETER, MANUFACTURING AND SCREW DESIGN AFFECT RESISTANCE AND/OR RESISTIVITY

Results

The obtained voltages and calculated resistance values for each screw are summarized in Table 2 and Table 3. Resistance of all screws ranged from 1.4 to 3.9 mΩ (mean = 2.69±0.71 mΩ). There was a strong negative linear correlation (r = -0.76, p<0.001) between resistance and a screw diameter (Figure 3). By treating each screw diameter as a Tukey category (a screw size was treated as a categorical variable, and not as an ordinal or a scale), 7.75-mm-diameter screw (group IV in Table 4) had lower resistance than other diameter screws. A screw design (polyaxial versus monoaxial) and the location of a monopolar probe attachment had no effect on measured screw resistance (Figure 4).

Resistivity of screws also varied from 7.12 to 12.63 μΩ•m (mean = 9.9±1.82 μΩ•m). Resistivity values of each screw diameter and manufacturer were summarized in Table 5. Manufacturer A screws had a lower resistance than screws from other three manufacturers ANOVA, p<0.01 (Figure 5). We found no statistically significant differences in screw resistivity among three other manufacturers (B, C and D) regardless of a screw diameter.

Discussion

In regards to resistance, our study showed that larger diameter screws with the same manufacturing process had lower resistance and more current flowed through it. However, a manufacturing process might alter the results as the 6.5-mm diameter from one manufacturer (manufacturer A) showed as low resistance as the 7.0-mm or 7.5-mm diameter screws from other manufacturers (manufacturer B, C and D). (see group III in Table 5). Electrical resistivity of titanium is known to be 0.42 μΩ•m (11). In our study, resistivity of pedicle screws had higher ranges, from 7.12 to 12.63 μΩ•m (Table 5). Screws A showed a significantly lower resistivity when compared to screws of other three manufacturers (B, C and D). The difference in resistivity may be caused by difference in the process of anodization of screws (changing the voltage, electrolyte and temperature). Anodization of a titanium pedicle screw is a surface modification process that increases resistance.
WORAWAT LIMTHONGKUL ET AL.: EVALUATION OF THE INTRINSIC PROPERTIES OF PEDICLE SCREWS: DO DIAMETER, MANUFACTURING AND SCREW DESIGN AFFECT RESISTANCE AND/OR RESISTIVITY

It is known that this process increases thickness of a titanium oxide layer on its surface and causes changes in a color of a screw and therefore potentially changes resistivity. By measuring most of the same size screws, Anderson et al. demonstrated a resistance range from 10 to 36.4 Ω, both for titanium and stainless steel screws across all regions except the mobile crowns of polyaxial screws. Their higher resistance was explained by increased resistance across the mobile crown-shank connection (up to 36.4 Ω) or by high contact resistance between a screw and a measuring instrument. They also recommended placing the monopolar probe in contact with the hexagonal base of a screw shaft or directly on a screw shank below the crown in order to reduce a false-negative result. In our study, we found no difference between different probe locations (outer and inner mobile crown versus a screw’s shank stimulation) and voltage through a screw. A probable reason for that is that the equipment used in our study was more accurate. Furthermore, in our study, measured screw resistances were lower (1.4 to 3.9 mΩ) than in Anderson’s study. We believe that the reason for that is that the contact resistance between a screw and a voltage wire was reduced by using highly electrical conductive elements such as silver epoxy in our study. During testing, we observed that a negligible voltage decrease occurred regardless of current strength (for currents as high as 10 Ampers, the voltage drop was less than 0.1 Volt). Other parameters with higher resistance that can interfere with an intraoperative spinal cord monitoring in vivo are: pedicle cortical thickness, conditions of a recording nerve, conductivity of a muscle and thickness of a subcutaneous fat layer when using percutaneous compound muscle action potential recording. Figure 6, however, these factors were not examined in this study. More significant reduction in voltage will occur at the interface between a metal screw and a bone into which a screw is inserted. Bone and fat tissue (both perineural and subcutaneous) showed significantly higher resistance among other human tissues due to low water content (the mean of 160 Ω•m in cortical bone and 38.50 Ω•m in fat tissue). With an intact pedicle, more current (>10mA) is needed to pass through a bone in order to be recorded in a peripheral nerve. Other potential pitfalls in neuromonitoring may be caused by an actual condition of a nerve root. Using direct stimulation to a nerve root after decompression, Holland et al. showed that significantly higher stimulus intensities were required to evoke myogenic responses from chronically compressed nerve roots compared with normal nerve roots. It is possible that a channel with lower resistance such as fluid in the operative field or a blood vessel next to a nerve root may conduct the electrical current to the nerve as well. With prolong nerve root compression, a perineural fat tissue may diminish and may not play an important role in conduction.

Our study confirmed that resistance of pedicle screws with a larger diameter was lower, while resistivity varied depending on a screw manufacturer. By using a larger screw higher electrical current passes through it which might stimulate a nerve root earlier. Therefore, if higher threshold values are used intraoperatively (10 mA and above), there could be higher incidence of false positive measurements if larger diameter screws are used (7.75mm). A surgeon might accept even a lower threshold levels (below customary 10 mA) as a sign of an intact pedicle during spinal cord stimu-
The question of clinical relevance of our data remains open and further research on this is needed. Based on the combined results of an animal study and a prospective clinical series some authors (5) recommended that threshold stimulus intensity higher than 8.0 mA is to be considered an indicator that a pedicle screw was entirely within the pedicle, while intensity below that threshold was considered to be an indicator for a potential pedicle wall defect due to screw perforation and a possible contact of a screw with a nerve root. These values are not absolute so direct palpation of the inner pedicle wall, intra-operative radiographs and direct visualization should be considered as well. In our institution, we use 11 mA as a threshold as recommended by Clements et al. (10) Because of these considerations and the fact that these threshold values are not absolute, although the difference in resistivity of larger diameter pedicle screw was statistically significant in our study, the clinical relevance is not strongly evident since current technology can not successfully detect such small differences in resistivity (milli-Ampers). These differences are merely an indicator of the difference in the quality and resistivity of the different screws used for spinal fusion. Future research should look into other factors that might affect threshold stimulus intensity such as thickness and resistance of a pedicle cortex around a pedicle screw as well as a subjective interpretation of recordings by an interpreter. During the intraoperative pedicle screw stimulation, values are not definitive as a threshold is identified only when a clear and relatively robust CMAP is obtained 830 of the time. Nevertheless a very high threshold is a good indicator of an appropriate pedicle screw placement.

REFERENCES


Abstract

Multiple studies have examined the age of onset of major depression, indicating it is most frequent in adolescence and young adulthood. In this context, the offspring of depressed parents have a 2 to 4 time increased risk for depression compared with children of non-depressed parents.

Treatment for depression in adolescents can be divided into psychosocial, psychopharmacologic, somatic and combined psychosocial-psychopharmacologic, psychosocial-psychosomatic and psychopharmacologic-psychosomatic.

Depression in the children and adolescent population has been an area of research for over 20 years. Among novel therapeutic strategies, transcranial magnetic stimulation (TMS) has demonstrated the most favorable side effect profile. Until this time there are no published suicide attempts associated with this treatment and it may offer an option that is not associated with stigma of electroconvulsive therapy (ECT) or medications. Further research may provide more access to this therapy and hope to children, adolescents with depression and their families.

KEY WORDS: Depression, adolescents, novel treatment strategies.
**INTRODUCTION**

For many years depression was perceived as an adult disorder. The first reports describing youths with symptoms similar to depression, were described in the 17th century. The first time the National Institutes of Mental Health (NIMH) began to consider the issue in this age group was in 1975 when it organized a meeting to talk about the incidence and diagnosis of depression among children and adolescents. The results of this meeting clarified the diagnosis and the presence of depression in the child and adolescent population. (1). Since then, multiple studies have examined the age of onset of major depression, indicating it is most frequent in adolescence and young adulthood. While pre-pubescent onset is less common, it can occur. In this context, the offspring of depressed parents have a 2 to 4 times increased risk for depression compared with that of children of non-depressed parents. The most comprehensive epidemiologic data in adults comes from the National Comorbidity Survey (6), a nationally representative sample of over 8000 individuals from US households (ages 15 to 54) (6). While only 600 individuals from this sample were under age 18, the rates in this sample are consistent with other published data in adolescents. They found that the lifetime prevalence for major depressive disorder (MDD) in 15-to-18 year-olds was about 14%. An additional 11% were estimated to have a lifelong prevalence of minor depression, with higher rates among females than males. In support of this data, a more recent study from student health services on college campuses noted a marked increase in the requests for counseling for depression over the last decade. The authors also reported suicide as the second-leading cause of death among students (7). Adolescent depression can be chronic, recurrent, and serious. Symptoms of MDD in adolescents are similar to those in adults, and rates among females are higher (i.e., a 2-fold risk). There is also a high comorbidity with anxiety disorders, substance abuse, suicidal behaviors, antisocial behavior and educational disability (2, 3). Depression in children differs from depression in adolescents in that it occurs more frequently in males, is mood reactive with high levels of irritability and dysphoria, and has a high comorbidity with destructive behavioral disorders (4,5).

Current Treatment Strategies

Treatment for depression in adolescents can be divided into psychosocial, psychopharmacologic, somatic and combined psychosocial-psychopharmacologic, psychosocial-psychosomatic and psychopharmacologic-psychosomatic.

**Psychosocial Treatment Strategies**

The majority of psychosocial treatment studies focus on intervention trials with cognitive behavior therapy (CBT). This approach appears to be more effective than no treatment, wait list controls, or placebo controls in this age group. There is also evidence that CBT produced better results than alternate active treatments (8,9). While these results are promising, many patients continue to clinically have significant levels of depression following CBT, with the majority experiencing at least one recurrence of depression in the two years following treatment termination. As a result, 30% to 50% seek additional services following an acute trial with CBT (10). Much less is known about the efficacy of other forms of psychotherapy, such as interpersonal or family therapy.

**Psychopharmacological Treatments**

There are a limited number of blinded, randomized, controlled trials with psychopharmacological agents for depression in the child and adolescent population. To date, the only medications that have demonstrated safety and efficacy in double-blind, placebo-controlled trials for children and adolescents with MDD are the selective serotonin reuptake inhibitors (SSRIs). A single-site, 8-week, placebo-controlled trial reported by Emslie et al. (11), with fluoxetine (20 mg/day) was the first well documented SSRI reported to be effective. In addition, a multi-center study of 219 outpatient youths with MDD reported significantly greater improvement in depression as assessed by the Children’s Depression Rating Scale-Revised (CDRS-R) with fluoxetine (20 mg) compared to placebo. Further, 52% of the fluoxetine group was rated much or very much clinically improved compared to 37% of the placebo group (12). In 2001, Keller et. al. reported paroxetine was well tolerated and effective for major depression in a double blind, placebo-controlled study of 275 adolescents. New data presented on June 19, 2003, by the Food and Drug Administration (FDA) led to the recommendation that paroxetine is not be used in children and adolescents under the age of 18 due to reports of a possible increased risk of suicidal ideation and suicide attempts.

**Suicidality and SSRIs**

Suicide is the third leading cause of death in adolescents (10-14 years) in United States and the leading cause of death in this age group in countries such as China, Sweden, Ireland, Australia and New Zealand (13,14,15).
Since 2003, concerns have been raised about the safety of the antidepressants for children and adolescents. This was based on unpublished data from studies linking the use of SSRIs to suicidal ideation and self-harm behaviors. In late 2003, these reports led the British drug regulatory agency to ban the use of all SSRIs except fluoxetine in treating depression among youth under the age of 18 (16). In 2004, the FDA reviewed 33 clinical trials involving nine different antidepressants used in over 4000 children and adolescents. The results of this analysis were presented in September 2004 and suggested that these medications increased the risk of suicidal thinking and behavior in this age group (17). Specifically, 4% of all youth taking medication reported suicidal thoughts and/or potentially dangerous behavior, compared to 2% of those taking placebo. On October 15, 2004, the FDA directed pharmaceutical companies to label all antidepressants distributed in the US with a black box warning, even though their analysis investigated only nine specific drugs. The warning states that the increased risk of suicidal thinking and/or behavior occurs in a small proportion of youth and is most likely to occur during the early phases of treatment. Although the FDA did not prohibit the use of antidepressants for children and adolescents, it called upon physicians and parents to closely monitor youth taking these medications for a worsening of depression or unusual changes in behavior. While the rate of completed suicide has been decreasing in USA from the late 1980s to 2003, it began increasing in 2004 (see Figure 1).

Epidemiological studies are trying to explain the relationship between the increase in number of SSRI prescriptions and decrease in completed suicide rates. For example Gibbons and colleagues reported on the relationship between antidepressant prescription rates and the rate of early adolescent suicide. The authors concluded that more SSRI prescriptions are associated with lower suicide rates in children and that these may reflect antidepressant efficacy. Preliminary results of a large cohort study examining the link between antidepressants and suicide in actively suicidal patients were recently reported by Dr. Jari Tiihonen of the University of Kuopio (Finland). The study suggests that the discrepancy between randomized clinical trials (showing an increase in suicidal ideation and attempts) and observational studies (showing a decrease in completed suicides) is due to antidepressant use increasing nonfatal suicidal behavior but decreasing fatal suicidal behavior. The study not only explains this discrepancy but also suggests a rational terminology for suicide research.

Cognitive Behavior Therapy and Antidepressants
The Treatment of Adolescents with Depression Study (TADS) sponsored by the National Institutes of Mental Health is the largest multicenter study to evaluate the effectiveness of four different treatment strategies for adolescents with major depressive disorder. This was a randomized, controlled trial conducted at 13 US academic centers between 2000 and 2003. The results of this study indicate that combined treatment with CBT and fluoxetine were superior to CBT or fluoxetine used alone or placebo. Placebo and fluoxetine alone were administered in a double-blind design while CBT alone and CBT with fluoxetine were administered...
in an unblinded fashion. The TADS investigators reported that younger and less severely impaired adolescents were more likely to respond to acute treatment than older, more impaired or multiply comorbid adolescents. Overall, the combination of fluoxetine and CBT was effective in improving functioning, global health, and quality-of-life in depressed adolescents (19,20,21).

**Alternative Treatments**

While ECT can be effective for severe depression in adults. Despite the fact that its mechanism of action remains unclear, we have many psychiatric disorders that are well established indicators for ECT (e.g., major depression with psychotic symptoms, bipolar disorder, schizophrenia and catatonia). ECT is associated with multiple adverse effects. The mortality rate with ECT is estimated at 0.01-0.03% per patient (i.e., 1-3 per 10,000), with the majority of deaths due to cardiovascular complications. Consequently, patients with coronary artery disease, hypertension, vascular aneurysms, and cardiac arrhythmias require special observation and attention. ECT is also associated with post treatment confusion, temporary memory loss; a high cost; limited availability; and substantial stigma. This has frequently caused reluctance on the part of patients or their families to consent to this treatment (22, 23, 24, 25). While ECT can be effective for severe depression in children and adolescents when other measures fail (26), data concerning its safety and efficacy in this population are limited. For example, one trial involving 16 adolescents who received ECT for treatment-resistant bipolar disorder reported it was effective, well tolerated, and cost efficient (26). In another report, adolescents given ECT for severe bipolar disorder did not demonstrate long-term cognitive impairment (27). The American Psychiatric Association (APA) has published specific guidelines for obtaining consent for ECT in this age group. Thus, before referring children for ECT, a psychiatrist experienced in treating this population and not otherwise involved with the patient should agree with the recommendation for ECT, which is usually considered when other treatments have failed.

**Electroconvulsive therapy**

Multiple studies describe the effects of electroconvulsive therapy (ECT) in adults. Despite the fact that its mechanism of action remains unclear, we have many psychiatric disorders that are well established indicators for ECT (e.g., major depression with psychotic symptoms, bipolar disorder, schizophrenia and catatonia). ECT is associated with multiple adverse effects. The mortality rate with ECT is estimated at 0.01-0.03% per patient (i.e., 1-3 per 10,000), with the majority of deaths due to cardiovascular complications. Consequently, patients with coronary artery disease, hypertension, vascular aneurysms, and cardiac arrhythmias require special observation and attention. ECT is also associated with post treatment confusion, temporary memory loss; a high cost; limited availability; and substantial stigma. This has frequently caused reluctance on the part of patients or their families to consent to this treatment (22, 23, 24, 25). While ECT can be effective for severe depression in children and adolescents when other measures fail (26), data concerning its safety and efficacy in this population are limited. For example, one trial involving 16 adolescents who received ECT for treatment-resistant bipolar disorder reported it was effective, well tolerated, and cost efficient (26). In another report, adolescents given ECT for severe bipolar disorder did not demonstrate long-term cognitive impairment (27). The American Psychiatric Association (APA) has published specific guidelines for obtaining consent for ECT in this age group. Thus, before referring children for ECT, a psychiatrist experienced in treating this population and not otherwise involved with the patient should agree with the recommendation for ECT, which is usually considered when other treatments have failed.

**Alternative Treatments**

While CBT is effective, it is associated with a high rate of relapse. Furthermore, antidepressant medication use may be reduced by the new FDA restrictions. Thus, it is important to look for other alternative treatment approaches. While the literature on therapeutic neuromodulators in adults is encouraging, data in

the child and adolescent population are very limited. Bright light therapy (BLT), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) are potential alternative strategies. While TMS was originally introduced as a neuropsychological probe (28), it has emerged as a promising treatment for depression. TMS produces a localized, alternating magnetic pulse that induces neuronal depolarization in a small section of the cortex below stimulation coil placement. It can be delivered as multiple stimulations in a rapid fashion over a brief period of time, referred to as repetitive TMS (rTMS) (29). rTMS has demonstrated a favorable safety and tolerability profile. Numerous reviews and meta-analyses indicate that rTMS may have clinically important antidepressant properties (29, 30, 31). A large multi-center, sham-controlled trial was recently completed (O’Reandon et al in press), and another multi-center trial funded by NIMH is in progress. The first study demonstrated favorable efficacy, safety, and tolerability profiles, for real sham TMS. Decrease in depressive symptoms with rTMS has also been reported in depressed patients referred for ECT due to severity of their symptoms or unsatisfactory benefit from medication trials (31,32,33). Because TMS appears to be a safe and efficient treatment in adult depression, it is important to explore its potential in a child and adolescent population. Hirshberg and colleagues (35) reported that the number of published cases involving rTMS in the adolescent population is small. They suggested that rTMS may be considered for treatment of bipolar and unipolar disorder as well as schizophrenia in adolescents. They cautioned, however, that until controlled data are available, clinicians should limit this procedure to individuals who have had multiple medication trials with insufficient efficacy or intolerable side effects. In this context, preliminary results of an early trial indicated that five of the seven youth with MDD benefited from TMS and only one reported minimal side effects (39). The same study acknowledged that TMS was still experimental and that its safety in children and adolescents should be systematically evaluated before conducting larger studies in this population. Another review presented data from 48 reports involving a total of 1034 children. Thirty-five of the studies used single pulse TMS (980 children), 3 studies used paired TMS (20 children), and 7 studies used rTMS (34 children). Three studies used both single pulse and repetitive TMS, but the number of subjects involved in these studies was not reported. Of note, no seizures were reported in patients who underwent single pulse, paired combinations of TMS.
Conclusion

Depression in the children and adolescent population has been an area of research for over 20 years. Despite numerous studies, this topic continues to generate many unanswered questions pertaining to diagnosis, treatment approach, suicidality and medications, treatment outcome, treatment length and maintenance strategies. These questions raise the issue of novel or alternative treatments including rTMS. Thus far, TMS has demonstrated favorable side effect profile, there are no published suicide attempts associated with this treatment and it may offer an option that is not associated with stigma of ECT or medications. It is time to conduct research with unconventional treatments. Such research should provide information regarding safety, feasibility and effectiveness of alternate treatments. We believe that such research may provide hope to children, adolescents with depression and their families.

Regarding safety, rTMS appears to carry similar risks when administered as a single, paired, or repetitive pulse stimulation in adult studies. Thus, headaches, scalp pain, and a small risk of seizures are all described. To our knowledge, while no safety studies of rTMS have included children or adolescents, caution is warranted in regulating the dosing of rTMS in children because of their lower seizure thresholds.

References


(32) Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. [Clinical Trial. Comparative Study. Depression & Anxiety. 2000; 12(3):118-123


(38) Quintana H. Transcranial magnetic stimulation in persons younger than the age of 18. J. ECT. 2005; 21(2):88-95

Bosnian-Herzegovinian American Academy of Arts and Sciences
BHAAAS

“Days of BHAAAS in B&H”
Sarajevo 2009

We are only Stronger Together”

Sarajevo, Bosnia & Herzegovina

Organizing Committee
President: Eldin Karaikovic, MD, PhD
Vice President: Aleksandar Hemon
Program Co-Chair: Kenan Arnaudovic, MD
Program Co-Chair: Mirsad Hadzicad, PhD
Treasurer: Andi Arnautovic, MD
Technical secretary: Indira Arnaudovic, MD
Technical support: Adnan Karaikovic

B&H partners
University of Sarajevo: Prof Dr F. Caklovica
ANUBIH: Prof Dr B. Matic and Prof Dr S. Loga
Bosnian Medical Initiative: Prof Dr I. Gavrankapetanovic

BHAAAS Faculty
Andi Arnautovic, MD - family medicine
Access Community Health Network, Chicago
Kenan Arnaudovic, MD, MSc - neuro- and spine surgery,
Semmes-Murphey Clinic, Memphis, Tennessee
Dusica Babovic-Vuksanovic, MD, genetics
Mayo Clinic, Rochester, Minnesota
Amila Buturovic, PhD - humanities
York University, Toronto, Canada
Keith Daubt, PhD - sociology
Wittenberg University, Springfield, Ohio
Emir Festic, MD - pulmonary and critical care
Mayo Clinic, Jacksonville, Florida
Ognjen Gagic, MD - pulmonary and critical care medicine
Mayo Clinic, Rochester, Minnesota
Faris Gavrankapetanovic, MD, PhD
Clinical Center Kosevo, Sarajevo, B&H
Mirsad Hadzicad, PhD - computing & informatics,
University of North Carolina, Charlotte
Aras Konjodzic, PhD - physics, president
Federation of Balkan American Association, New York, New York
Almer Imamovic - guitarist
South Pasadena Music Center & Conservatory, Pasadena, California
Enes Kanlic, MD, PhD - trauma
Texas Tech University, El Paso, Texas

Eldin Karaikovic, MD, PhD - orthopaedics, spine surgery
University of Chicago, Chicago, Illinois
Adnan Sarcevic, MD, general and geriatric psychiatry
Albert Einstein College of Medicine, New York, New York
Philip Simmons – conductor and artistic director
American Music Festivals, Chicago, Illinois
Gordan Srkalovic, MD, PhD - oncology
Michigan State University, Lansing, Michigan

Patronage
Haris Silajdzig, PhD
Member of the Presidency of B&H

Mission
The mission of the Bosnian-Herzegovinian American Academy of Arts and Sciences (BHAAAS) is advancement and development of arts and sciences in the Bosnian-Herzegovinian Diaspora in the United States and Canada.
The Academy aims to provide connections between Bosnian-Herzegovinian scientists, artists and professionals in North America and build the bridges of cooperation with the homeland.
The Academy will promote the spirit of intellectual diversity and free exchange of ideas among the Diaspora in the belief that knowledge is shareable wealth.

Official Languages
Languages of Bosnia-Herzegovina
English

Sponsors
Sanofi-Aventis
BH Telecom
University Clinical Center Sarajevo
University of Sarajevo
Academy of Arts and Sciences of B&H
University Clinical Center, Sarajevo
U službi Vašeg zdravlja

Bosnalijek d.d.

Bogata paleta više od 200 kardiovaskularnih lijekova, antiinfektiva te lijekova za liječenje digestivnog trakta i nervnog sistema rezultat je uspješnog rada vodeće farmaceutske kompanije u Bosni i Hercegovini koja svoje proizvode izvozi na 20 svjetskih tržišta.

U 59. godini postojanja, Bosnalijek garantira kvalitet svojih proizvoda zahvaljujući velikim ulaganjima u vlastiti razvoj lijekova, primjeni najavremenije tehnologije u njihovoj proizvodnji i visokoj stručnosti kadrova.

Saznajte više o nama, posjetite našu web stranicu:
www.bosnalijek.ba