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ORIGINAL RESEARCH: REPRINT

3 Rapid and Selective Cerebral Hypothermia Achieved Using a Cooling Helmet
HUAN WANG, MD  WILLIAM ELKINS, BFA  MARY RODDE, RN, CCRC, CCRP
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GIUSEPPE LANZINO, MD  DEBRA HONINGS, RN, CNRN  DAVID WANG, DO

Although the critical duration of cerebral hypothermia required for significant neuronal rescue has not been established, in several laboratory studies this has been systematically examined and the investigators have suggested the need for prolonged cooling (48–72 hours).

SUBJECT REVIEW

13 Living with Multiple Sclerosis: Visions of a Brighter Future
CHARLES R. DAVIES MD, PHD

Acute and chronic treatments will be reviewed as well as oral medications, the first of which was recently FDA approved. With more effective treatment, there is a greater incentive to treat as early as the first clinical symptoms.

17 Epidemiology, Incidence and Prevention of Sudden Cardiac Death
ALI A. SOVARI, MD, FACP  ABRAHAM G. KOCHERIL, MD, FACC, FACP, FHRS

SCD claims more than 300,000 lives per year in the US and about 7 million lives per year worldwide. Based on the inclusion criteria used in individual studies the annual incidence of SCD has been reported from 200,000 to more than 400,000. More deaths are attributable to SCD than to lung cancer, breast cancer, or acquired immunodeficiency syndrome.

23 Tonsillectomy 2011:
Evidence-Based Indications and Intracapsular Tonsillectomy–A New Technique
WILLIAM D. YOUNGERMAN, MD

The American Academy of Otolaryngology recently published a clinical practice guideline for tonsillectomy in children. Guidelines are intended to reduce inappropriate variations in clinical care and to produce optimal health outcomes and minimize harm for patients.

27 How Nurses Can Provide Optimum Care to the Patient with Parkinson's Disease
DEBORAH DAVIS, RN, BSN

It is a balancing act to provide optimum nursing care for PD patients. No two patients will present exactly the same set of symptoms, and symptoms can change daily. Hospital admission and discharge can create enormous stress for patients; under stress, symptoms may literally change from minute to minute. The most important thing to remember is that what works for one patient may not work for another. This is one of the primary challenges inherent in caring for the patient with PD.

34 Multiple Sclerosis and Nursing Management
PATRICIA HUISINGA, RN, BSN

Multiple sclerosis patients feel a loss of control as their bodies have made altering transformations that drastically affect all avenues of their lives. They need to understand they do have choices. Fostering the nurse-patient relationship is vital to establishing trust in delivering care.
A 57-Year-Old Man Presents with Worsening Shortness of Breath and Fatigue over Ten Days

MICHAEL JAKOBY, MD, MA    SUNEETHA VYSETTI, MD    POONAM VELAGAPUDI, MD

The differential diagnosis for progressively worsening dyspnea with fatigue could be quite extensive given the underlying physiologic mechanisms responsible for it. Cardiac and respiratory disorders are the most common causes though other less common but important causes like anemia should be considered.

A Review of Rare Extra-Nodal Non-Hodgkin's Lymphoma

DIGANT BHATT, MD    VIDU MOOKALA, MD    VISHWAS VANAR, MD    FRANK J. BELLAFORE, MD    VAMSI K. VASIREDDY, DO    ANDY ARWARI, MD

Extra-nodal presentation of NHL occurs in 25–35% of cases, and the most common sites involved are stomach, skin, small intestine, breast, thyroid, lung, heart, liver, genitourinary tract, adrenals and bones. Primary renal lymphoma is a rare type of extra-nodal NHL constituting 0.7% of all extra-nodal lymphomas. It is very aggressive and associated with high mortality.

Fulminant Purpuric Rash in a Toddler

CHRISTINE H. YANG, M2    AMY K. MACDOUGALL, MD    M. NADEEM AHMED, MD, PHD

Onset of invasive meningococcal infection can be abrupt, and it can progress very rapidly from onset of fever to death in as little as 12 hours. Early symptoms are typically nonspecific “flu-like” complaints, such as fever, chills, malaise, headache, nausea, and rash. The classic petechial rash of meningococcemia can develop subtly prior to any change in mental status, and may initially appear as a nonspecific macular or maculopapular rash.
Though research at Carle remains diverse, focus areas are cancer, cardiovascular, neuroscience and digestive health. This issue of *Carle Selected Papers* includes articles in all four areas with focused interviews from two of our researchers from neuroscience and gastrointestinal research.

In the neurology area we have three articles. Dr. Charles Davies presents a better understanding of multiple sclerosis, its symptoms, signs, and current therapies and leads a discussion on future therapies.

Patricia Huisinga, RN, leads us through the classifications of multiple sclerosis and guides us to a better means of providing daily care for these patients.

Parkinson’s disease and providing optimum care for patients is the focus Deborah Davis, RN gives us in her article. Nutrition, mobility, and the patient’s daily needs drive how we provide care to these patients.

Many common questions pertaining to sudden cardiac death are addressed by Dr. Ali Sovari. Causes, management, and prevention are some of the areas presented.

Dr. William Youngerman discusses the current evidence and indications as well as the controversies around performing tonsillectomies.

Our Clinicopathological Conference article this month presents the case of 57-year-old man with worsening symptoms of shortness of breath and fatigue. The presentation and discussion are well worth the read.

We have two case reports this issue. A case of rare extra-nodal non-Hodgkin’s lymphoma is described. The other report leads a discussion on a fulminant purpuric rash in a toddler.

Profiles of physician researchers, Dr. Eugene Greenberg and Dr. John Wang, and a listing of current translational research at Carle round out the issue.

Please take a few moments to read through this issue. Feel free to drop us a line, and if you have an interesting case you would like to present through *Carle Selected Papers* don’t hesitate to contact our editorial staff.
Original Research: REPRINT

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p.3 Rapid and Selective Cerebral Hypothermia Achieved Using a Cooling Helmet

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Rapid and Selective Cerebral Hypothermia Achieved Using a Cooling Helmet

HUAN WANG, MD, WILLIAM OLIVERO, MD, GIUSEPPE LANZINO, MD, WILLIAM ELKINS, BFA, JEAN ROSE, RN, CNRN, MS, DEBRA HONINGS, RN, CNRN, MARY RODDE, RN, CCRC, CCRP, JAN BURNHAM, RN, CNRN, AND DAVID WANG, DO

OBJECT

Hypothermia is by far the most potent neuroprotectant. Nevertheless, timely and safe delivery of hypothermia remains a clinical challenge. To maximize neuroprotection yet minimize systemic complications, ultra-early delivery of selective cerebral hypothermia by Emergency Medical Service (EMS) personnel in the field would be advantageous. The authors (W.E. and H.W.) have developed a cooling helmet by using National Aeronautics and Space Administration spinoff technology. In this study its effectiveness in lowering brain temperature in patients with severe stroke or head injury is examined.

METHODS

Patients were randomly assigned to groups receiving either the cooling helmet or no cooling, and brain temperatures (0.8 cm below the cortical surface) were continuously monitored for a mean of 48 to 72 hours with a Neurotrend sensor and then compared with the patients’ core temperatures. There were eight patients in the study group and six in the control group. The mean change in temperature (brain – body temperature) calculated from 277 data hours in the study group was -1.6°C compared with a mean change in temperature of +0.22°C calculated from 309 data hours in the control group. This was statistically significant (p < 0.0001). On average, 1.84°C of brain temperature reduction (range 0.9–2.4°C) was observed within 1 hour of helmet application. It took a mean of 3.4 hours (range 2–6 hours) to achieve a brain temperature lower than 34°C and 6.67 hours (range 1–12 hours) before systemic hypothermia (< 36°C) occurred. Use of the helmet resulted in no significant complications. There was, however, one episode of asymptomatic bradycardia (heart rate < 40) that responded to a 0.5°C body temperature increase.

CONCLUSIONS

This helmet delivers initial rapid and selective brain cooling and maintains a significant temperature gradient between the core and brain temperatures throughout the hypothermic period to provide sufficient regional hypothermia yet minimize systemic complications. It results in delayed systemic hypothermia, creating a safe window for possible ultra-early delivery of regional hypothermia by EMS personnel in the field.

KEY WORDS: STROKE • HEAD INJURY • HYPOTHERMIA • BRAIN COOLING HELMET

To date, hypothermia is by far the most potent method of neuroprotection in animal studies and has the greatest therapeutic potential. Nevertheless, problems remain with timely and safe delivery of this type of therapy. Although the results of clinical trials have been mixed, two large prospective randomized clinical trials of resuscitative hypothermia for cardiac arrest have recently shown significant benefit. Preclinical and clinical investigation of hypothermia continues to receive intense attention from the scientific and medical communities. To maximize neuroprotection yet minimize

ABBREVIATIONS USED IN THIS PAPER:

EMS = Emergency Medical Service
ICP = intracranial pressure
ICU = intensive care unit
NASA = National Aeronautics and Space Administration

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systemic complications, ultra-early delivery of selective cerebral hypothermia by EMS personnel in the field would be advantageous. We (W.E. and H.W.) have developed a cooling helmet (Fig. 1) by using NASA spinoff technology. In this study we examine its effectiveness in lowering brain temperature in patients with severe stroke or head injury.

**CLINICAL MATERIAL AND METHODS**

**Study Design**

This study was designed as a randomized, controlled trial. The protocol and consent procedures were approved by the local institutional review board. Treatment assignments (cooling helmet or no cooling) were generated from a randomization table. Patients consecutively admitted to our neurological ICU with either severe stroke or head injury were eligible for the study. Patients with overwhelming systemic diseases, cervical spine injuries, and/or significant forehead and facial lacerations were excluded from the study. There were eight patients in the study group and six in the control group.

**Description of the System**

The brain hypothermia device consists of two components, the head/neck liner and the conditioning unit.

**Head/Neck Liner.** Figure 1 shows the helmet, in which the liner is constructed of a lightweight, thin, flexible, urethanelaminated nylon fabric. There are two integrated layers consisting of a conformal liquid cooling heat exchanger and a pressurizable air bladder. The liner, with its uniform flow of conditioned cold liquid, is only approximately 1/16 in thick. The outer pneumatic liner is pressurized to allow close contact with the cranium and neck. The head/neck liner has bilateral frontal openings (approximating the Kocher points) and an anterior midline neck opening for access if required. It is also adjustable and allows a close fit over a significant range of head sizes.

**Conditioning Unit.** The conditioning unit consists of an insulated ice reservoir and a control system, both contained in a portable unit weighing approximately 22 lb when fully loaded with ice and water. There is approximately 3.25 ft² of heat-exchanger area in the unit. The conditioning unit can be operated with a direct-current power supply or D-cell batteries. The control system provides the following: 1) temperature control; 2) liquid pump and pressure control; and 3) air pump (air pressure control is integrated into the liner).

The study protocol was initiated within 24 hours after admission. Standard treatment for severe stroke and head injury was administered and brain temperatures (acquired 0.8 cm below the cortical surface) were continuously monitored for a mean of 48 to 72 hours with a Neurotrend sensor (Codman & Shurtleff, Inc., Raynham, MA) and compared with the patients’ bladder (core) temperatures. In the study group, all patients’ heads were shaved before application of the cooling helmet in the ICU, and warming blankets were used to maintain a core temperature above 35°C if the patient was older than 45 years of age and 33°C if they were younger.

![Figure 1. Photograph showing the helmet worn by William Elkins, a NASA scientist, who invented this technology. The cooling helmet has an outer pneumatic liner pressurized to allow close contact with the cranium and neck. The device also is adjustable to fit a significant range of head sizes.](image-url)
RESULTS

The mean change in temperature (brain – bladder temperature) calculated from 277 data hours in the study group was -1.6°C compared with a mean change in temperature of +0.22°C calculated from 309 data hours in the control group; this was statistically significant (p < 0.0001). On average, 1.84°C of brain temperature reduction (range 0.9–2.4°C) was observed within 1 hour of helmet application. It took a mean of 3.4 hours (range 2–6 hours) to achieve a brain temperature lower than 34°C and 6.67 hours (range 1–12 hours) before systemic hypothermia (< 36°C) occurred. A mean 0.63°C/hour (range 0.15–1.45°C/hour) passive rewarming rate was observed. Use of the helmet resulted in no significant complications. There was, however, one episode of asymptomatic bradycardia (heart rate < 40) that responded to a 0.5°C body temperature increase. No rebound hyperthermia or ICP elevation was observed.

ILLUSTRATIVE CASE

This 17-year-old woman presented with severe head injury (Glasgow Coma Scale Score 7). Computerized tomography scans of her head demonstrated traumatic subarachnoid hemorrhage, a small subdural hematoma, and diffuse petechial intraparenchymal hemorrhages consistent with shear injury. Her initial ICP reading was approximately 35 mm Hg. The cooling helmet was applied after her admission to the hospital. The patient was also intubated, paralyzed, and sedated. A Neurotrend sensor, an ICP microsensor (both obtained from Codman & Shurtleff, Inc.), and a pulmonary artery catheter (Abbott Laboratories, North Chicago, IL) were placed to monitor intraparenchymal brain temperature, ICP, cardiac output, and core temperature, in addition to other vital signs that are routinely and continuously monitored in the ICU.

Brain temperature was slightly higher than core temperature at baseline. Within 15 minutes after application of the cooling helmet, the brain temperature dropped by approximately 2°C, whereas the core temperature did not drop below 37°C until 4 to 5 hours later (Fig. 2). The cooling helmet maintained brain temperature at approximately 1.5 to 2.5°C below core temperature throughout the 48-hour cooling period.

![Figure 2: Core Temperature vs Brain Temperature](image)

Graph showing that, within 15 minutes after application of the cooling helmet, the brain temperature dropped by approximately 2°C, whereas the core temperature did not drop below 37°C until 4 to 5 hours later. The cooling helmet maintained brain temperature at approximately 1.5 to 2.5°C below core temperature throughout the 48-hour cooling period. When the core temperature dropped to 32°C and brain temperature dropped to 29.4°C, active body warming was initiated to minimize the risk of cardiac arrhythmia. After the cooling helmet was removed at Hour 48, the brain temperature approached the core temperature within 1 to 2 hours, and then both rose gradually to 37°C over a 30-hour period. B-temp = brain temperature; C-temp = core temperature.
When the core temperature dropped to 32°C and the brain temperature dropped to 29.4°C, active body warming was initiated to minimize the risk of cardiac arrhythmia. The core temperature, as illustrated by the graph in Fig. 2, was maintained thereafter at 33 to 35°C with external warming blankets. After the cooling helmet was removed at Hour 48, the brain temperature approached the core temperature within 1 to 2 hours and then together both rose gradually to 37°C over a 30-hour period. No deleterious effects, such as arrhythmia, infection, clinically significant coagulopathy, and so on, were observed. At her 6-month follow-up visit, the patient had gone back to school and had resumed cheerleading activities, although she had minor right-sided tremors.

**DISCUSSION**

Resuscitative hypothermic neuroprotection has been conclusively established in animal models of both global/focal (permanent and transient) ischemic and traumatic brain injuries. The efficacy of resuscitative hypothermia likely relates to a multitude of factors, such as the delay of initiation (treatment window), the severity, type, region, and duration of injury, the rate of induction, and the depth and duration of cerebral hypothermia. These factors also intertwine and confound each other’s effects. Although the critical duration of cerebral hypothermia required for significant neuronal rescue has not been established, in several laboratory studies this has been systematically examined and the investigators have suggested the need for prolonged cooling (48–72 hours). It is relatively well accepted that interventions after longer delays are less efficacious. Prolonged cooling, however, seems to compensate for some delay in initiation of therapy. Studies of brief cooling (a few hours) demonstrated that hypothermia only delayed rather than prevented neuronal degeneration. Nevertheless, when the duration of hypothermia is prolonged (12–48 hours), permanent benefits (28 days–12 months) were documented even after an induction delay of several hours (≤ 6 hours). Whether a critical depth of hypothermia is required for effective neuronal protection remains to be determined. An extradural temperature of 34°C or less has been suggested to be necessary for substantial neuronal rescue. Also, reduction of brain temperature within the mild-to-moderate range diminished histologically confirmed injury in a dose-dependent manner. On the other hand, hypothermia beyond the mild-to-moderate range may be poorly tolerated and less effective.

The results of clinical trials in which resuscitative hypothermia was used have been mixed. In the National Acute Brain Injury Study: Hypothermia although hypothermia treatment significantly reduced elevated ICP, no functionally protective effect was demonstrated at 6 months. Two large prospective randomized clinical trials of resuscitative hypothermia for cardiac arrest, however, have recently shown significant improvement in overall survival and neurological outcome. From studies of head injuries and cardiac arrests in humans, it is generally accepted that hypothermia should be initiated as soon as possible. Therefore, ultra-early delivery of hypothermia by EMS personnel in the field would be advantageous. A target core temperature of 33°C and hypothermia duration of 12 to 48 hours are considered safe and feasible. Clinical studies of hypothermia induction for acute stroke have a relatively short history in comparison with hypothermia for head injuries and cardiac arrests, and have primarily involved only ischemic types. Two concurrent multicenter studies are in progress in which endovascular cooling is being used in patients with acute ischemic stroke. Both studies are enrolling patients within 12 hours of onset of stroke and have a target core temperature of 33°C; hypothermia is maintained for 12 to 24 hours. Preliminary results indicate that this treatment is feasible and safe.

Systemic hypothermia can cause a variety of cardiac, pulmonary, renal, electrolytic, infectious, and other complications. Prolonging hypothermia may improve neuroprotection however, it may also lead to an increase in adverse effects. Although the National Acute Brain Injury Study: Hypothermia demonstrated only a slight overall increase in complications in the hypothermia group (core temperature 33°C) in patients older than 45 years of age, there were substantially higher rates of complications, including bleeding, sepsis, and pneumonia, in the hypothermia group. Many brain-injured patients are older than 45 years of age and have multiple systemic comorbidities. Careful monitoring and prompt response to systemic hypothermia-associated complications are especially warranted.

Core temperature is often an inaccurate and unreliable guide to brain temperature; thus, the latter must be monitored directly during temperature modulation therapies such as hypothermia. The cerebral temperature gradient may be different under normothermic, hypothermic, or hyperthermic...
conditions.28,59,63 Furthermore, this gradient would most likely differ with various methods of hypothermic induction (for example, systemic compared with local).19 Therefore, it is essential to standardize the location of the intracerebral temperature sensor to make comparisons possible and meaningful among brain temperature modulation studies. Through theoretical modeling and calculation, it has been suggested that the mean brain temperature should be measured at 7.5 mm below the cortical surface in adults.71

Systemic cooling is clinically effective in achieving sustained core and brain hypothermia to a similar depth.27,58 Nevertheless, it would theoretically be ideal if the brain could be cooled more than the body to maximize hypothermia’s neuroprotection yet minimize its systemic complications. In the course of many studies to reduce hyperthermic stress in Air Force operations, the head and neck area has long been identified as the most efficient body region for heat removal.32,33,61,70 These regions have the highest skin temperature (thus the largest change in temperature) and a large, constant blood flow volume with little vasoconstriction in response to cold (in contrast with the torso, which has considerable vasoconstriction in response to cold and requires additional “cold power” to overcome the thickening insulation). Potent neuroprotection, a benign complication profile, and successful selectivity of cerebral hypothermia through surface cooling have been well documented in animal models.23,26,30,35,36,64,66 Selective brain cooling has also been attempted previously by using localized cerebral ventricular perfusion,17,50,54 fans,4 cold forced air,67 nasal lavage,49 perfusion of the brain with cold solutions or blood,7,60 and direct application of a cold substance or cooling device onto the head.28,67 Rapid and successful selective cerebral hypothermia can be accomplished with a highly invasive extracorporeal system.34,53

To date, it has not been shown in humans that it is possible to cool the brain more than the body through surface cooling, even in very superficial regions.15,67 Some researchers have suggested that, unlike small brains, humans too large to be cooled by conductive heat exchange.38 In addition, some studies on selective cerebral hypothermia were conducted in animals (for example, piglets) that have a rete caroticum.23,66 The rete is a multichannel version of the human internal carotid artery and is surrounded by the cavernous sinus; together these serve as an effective heat exchange mechanism for the brain,18 whereas humans lack such a structure for effective heat exchange. Furthermore, in animal models the cooling device may cover 100% of all available head surface area.46 This is not practical for clinical use. In our study, however, we clearly demonstrate that, using NASA spinoff technology, this specially designed cooling helmet allows initial rapid and selective brain cooling and results in delayed systemic hypothermia, creating a safe window for ultra-early delivery of regional hypothermia by EMS personnel in the field. In addition, it maintains a significant gradient between the core and brain temperatures (brain temperature < core temperature) throughout the entire hypothermic period (2–3 days) to maximize the neuroprotective effects while minimizing possible systemic complications.

By the mechanism of surface cooling,23,34,39 this helmet provides more preferential cooling of the superficial areas of the brain than the deep regions. It is therefore theoretically plausible that injuries in the cortex or nearby may be more responsive to selective cerebral hypothermia through surface cooling, whereas deep injuries may receive better neuroprotection from systemic hypothermia. Nevertheless, at least two additional confounding factors must be taken into consideration: the difference in regional temperature sensitivity25,34,69 and the rate at which neuronal death occurs.21,22,52 For example, neuronal necrosis in the caudoputamen is particularly sensitive to temperature.21 Cortical tissue may be more amenable to therapies instituted in the postinjury period because cortical cell death occurs more slowly than in the striatum.21,22,52 These two factors would be of great importance for assessing the amount of temperature dependent brain protection from injuries. Although an increase in the cerebral temperature gradient could potentially be harmful because of theoretical imbalances between blood flow and metabolism,1 this is not supported by the majority of the animal data.23,26,30,35,36,64,66

CONCLUSIONS

Using NASA spinoff technology, this specially designed cooling helmet allows initial rapid and selective brain cooling and results in delayed systemic hypothermia, creating a safe window for ultra-early delivery of regional hypothermia by EMS personnel in the field. It maintains a significant gradient between the core and brain temperatures (brain temperature < core temperature) to maximize the neuroprotective effects while minimizing possible systemic complications. Further
studies are needed in which this helmet is used in patients with head trauma and stroke; these studies are required to characterize the temperature of the skin in direct contact with the innermost lining of the helmet, to estimate heat transfer, to ascertain intracerebral temperature profiles with the head unshaved, and so on. Better technologies to control the rate of hypothermia delivery and rewarming will need to be engineered into the second generation of cooling helmets. Also, cooling helmets with modifications to suit prehospital needs better (for example, cervical spine precautions) will make it possible to study the feasibility of ultra-early initiation of selective cerebral hypothermia by EMS personnel.

DISCLAIMER
None of the authors has any affiliation with Coolsystems, Inc.

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Subject Review

p.13  Living with Multiple Sclerosis: Visions of a Brighter Future  
CHARLES R. DAVIES MD, PHD

p.17  Epidemiology, Incidence and Prevention of Sudden Cardiac Death  
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p.34  Multiple Sclerosis and Nursing Management  
PATRICIA HUISINGA RN, BSN
Pioneering work in the characterization of MS was performed by Jean Martin Charcot; based on his meticulous observations, the eponymous triad consisting of diplopia, ataxia, and dysarthria was formulated. Charcot was also the first to link a clinical description to histological findings.

Multiple Sclerosis affects 350,000 persons in the US and an estimated 2.5 million worldwide. There is a higher prevalence as distance from the equator increases. Women are affected roughly twice as frequently as men. The reasons for these unique epidemiologic features are unknown. Although disease onset usually occurs from the 3rd to 5th decade, childhood and geriatric onset have been well documented. I, personally, have treated a patient with onset in his mid-eighties. Current diagnostic criteria take advantage of a number of tools at the clinician's disposal including MRI, CSF measurements and visual evoked potentials.

Treatment options have increased substantially since the introduction of the first injectable interferon in the early 1990’s. Acute and chronic treatments will be reviewed as well as oral medications, the first of which was recently FDA approved. With more effective treatment, there is a greater incentive to treat as early as the first clinical symptoms. One experimental therapy utilizes electrical pulses along with traditional physical therapy to improve balance for MS patients.

**SYMPTOMS AND DIAGNOSTIC CRITERIA**

Multiple Sclerosis predominantly affects the white matter tracts conducting action potentials and may lead to virtually any neurologic symptom. When lesions involve the optic tract, visual field loss, eye pain and diplopia can ensue. Left-sided fronto-temporal lesions are associated with speech and language difficulties. Lesions in a variety of areas can cause sensory and motor deficits. Cerebellar lesions produce ataxia which can affect the limbs, vision and speech. Autonomic pathways controlling vegetative functions including temperature homeostasis, sleep, bowel, bladder and sexual activity can also be impacted.

An example of the typical periventricular demyelinating white matter lesions can be seen in the brain MRI in figure 1.

**Figure 1.**

Noncontrast MRI of the brain axial FLAIR image demonstrating characteristic periventricular white matter lesions.
For many years, the aphorism “two clinical attacks separated by time and space” was the guiding principle of diagnosis. This reflected both the lack of pathognomonic symptoms and a reticence for assigning an individual a progressive neurologic disease having no effective treatment and no cure. The Poser criteria expanded upon this somewhat in 1983 with “laboratory supported” and “clinically probable” definitions of disease.\(^1\) (Table 1)

By the mid 1990’s, advanced imaging techniques played a large role in the reformulation of diagnostic criteria into the McDonald criteria which have in turn been revised to the current incarnation seen in Table 2.\(^4\)

**NATURAL HISTORY**

Roughly 85% of persons diagnosed with MS fall into the category of relapsing-remitting MS. By definition, they return to normal neurologic function after each MS flare, which usually occurs once every two years. Typically, after 10–15 years, half of these patients convert to the secondary-progressive form with continuous decline thereafter. The remaining 15% of patients are primary-progressive meaning they have continuous symptoms from disease onset. About 28% of these persons eventually have occasional flares. A standard means of characterizing MS patients was codified by Kurtzke with the expanded disability status scale (EDSS).\(^3\) This metric incorporates cognition, vision, speech, swallowing, ambulation, coordination, sensation, bowel and bladder symptoms into a number from 0–10. As disability increases, the rating increases with milestones including moderate disability (3.0), assistive device for ambulation (6.0), wheelchair (7.0), confinement to bed (9.0), and death (10.0).

**CURRENT MS TREATMENTS**

Steroids remain the standard treatment for acute exacerbations. They may be contraindicated for comorbid diabetes. Until the early 1990’s physical therapy and supportive measures were the mainstays of chronic care. Given the pathophysiology of MS, research efforts focused on developing ways of suppressing the immune system. The first major breakthrough came with FDA approval of interferon beta–1a in 1993. This injectable medication provided new hope for relapsing-remitting MS patients given an approximate 30% reduction in relapse rate. Since then two other interferon-type medications have

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**Table 1.**

**Diagnosis of MS by Poser Criteria**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically definite MS</td>
<td>2 attacks in time and space</td>
</tr>
<tr>
<td>Laboratory-supported definite MS</td>
<td>1 or 2 attacks, 1 or 2 clinical lesions and CSF findings</td>
</tr>
<tr>
<td>Clinically probable MS</td>
<td>2 attacks and 1 lesion or 1 attack and 2 lesions</td>
</tr>
</tbody>
</table>

**Laboratory supported probable MS: 2 attacks and CSF findings**

**Cerebrospinal Fluid in MS**

- Oligo-clonal bands: 2 or more
- IgG index: increased
- Myelin basic protein: increased
- Total protein: increased

**Table 2.**

**McDonald Criteria**

2 or more separate attacks, with clinical findings of 2 lesions
2 attacks with 1 clinical lesion + MRI findings (space dissemination) or CSF data
1 attack with 2 or more clinical lesions + MRI or 2nd clinical attack (time dissemination)
1 attack 1 clinical lesion + MRI and/or 2nd clinical attack + CSF (dissemination in space and time)
Insidious neurological progression + 1 yr of disease progression and 2 of the following:
- Brain MRI*
- Spine MRI
- CSF

*9T2 lesions or 4 T2 lesions + Visual evoked potentials
been approved with similar response rates. The main side effects of these medications include decreased blood counts, liver dysfunction and flu-like symptoms. It has also been associated with the development of so-called neutralizing antibodies, rendering the medication ineffective. These antibodies can persist for years. Glatiramer acetate is another injectable medication that has been effective to a comparable degree in reducing relapse rates. It is comprised of four amino acids originally isolated from an animal model of MS. The mechanism of action is not fully understood. Potential side effects include fatigue, worsening of depression and skin necrosis. It is not associated with blood count depression, liver abnormalities or neutralizing antibodies.

While the above medications are most effective for the relapsing-remitting form of MS, Mitoxantrone was approved in 2000 for the treatment of secondary progressive MS. Studies indicated a decrease of 0.24 in the EDSS compared to placebo. Mitoxantrone is given as an infusion of 12 mg/m² every three months. Due to significant risk of cardiac toxicity a maximum cumulative dose of 140 mg/m² is recommended. It is also associated with depressed blood counts and liver abnormalities. Natalizumab is the first monoclonal antibody approved for the treatment of refractory MS. Due to concerns for untreatable progressive multifocal leukoencephalopathy (PML) associated with the JC virus, it was removed from the market for a time and re-introduced in 2006. The estimated risk for PML is 1–2/10,000 treated. Despite this risk, it continues to be used given a reported 68% reduction in relapses.

Supportive therapies such as gait training, hydrotherapy, alpha blockers for urinary symptoms, and amantadine for fatigue can also improve quality of life for MS patients.

**FUTURE DIRECTIONS**

With current imaging techniques and clinical criteria allowing for much quicker diagnosis, treatment may be started with initial symptoms. Kappos et al reported five year follow-up on patients given treatment vs placebo after a first event and at least two silent MRI lesions. They found that early treatment with interferon beta–1b for at least two years reduced the risk of clinically definite MS by 37% compared to placebo. Clinical benefit was limited to patients with a high lesion load (>9 T2 lesions on initial brain MRI).

Over the past year, significant attention has been focused on the first oral medications for chronic treatment of MS. Two of them, Fampridine and Fingolimod, have been approved for clinical use. A third agent, Cladribine, has shown promise in clinical trials. Fampridine is a potassium channel blocker which has improved walking speed by 35% in a recent study. Potential side effects include seizures and urinary tract infections. Fingolimod inhibits lymphocyte migration from lymph tissue and has been shown to decrease relapse rates by 50% compared to interferon. Bradycardia, infection, neoplasm and death were seen in up to 2.4%, 1.2%, 1.9% and 0.5% of subjects, respectively. Cladribine acts by inhibiting DNA synthesis in certain lymphocytes. In study subjects, Cladribine decreased relapse rates by more than 50% compared to placebo. Serious side effects including infection, neoplasm and death were seen in up to 2.9%, 1.4%, and 0.5% of subjects, respectively.

A novel approach to the problem of diminished function with MS has been the use of cranial-nerve non-invasive neuromodulation. This work was pioneered by Paul Bach-y-Rita and is currently being advanced by Y. Danilov at the University of Wisconsin. The concept involves stimulation of the 5th cranial nerve receptors on the tongue. (Figure 2) Simultaneous gait and balance therapy during tongue stimulation has led to significant improvements in EDSS for a small series of test subjects...
with MS. The results are shown in Figure 3. Additional studies utilizing a placebo control group are being considered.

CONCLUSIONS

This is an exciting time for physicians and researchers who work toward the advancement of care for patients with MS. While there is still no cure in sight, our understanding of the pathophysiology of the disease, combined with improved diagnostic tools and various treatment options, provide not only hope for MS patients but also an enhanced quality of life.

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REFERENCES


The Epidemiology, Incidence and Prevention of Sudden Cardiac Death

ALI A. SOVARI, MD, FACP
ABRAHAM G. KOCHERIL, MD, FACC, FACP, FHRS

Sudden cardiac death (SCD) is an unexpected death due to cardiac causes occurring in a short time period (generally within one hour of symptom onset) in a person with known or unknown cardiac disease in whom no previously diagnosed fatal condition is apparent. Most cases of SCD are related to cardiac arrhythmias.

Approximately half of all cardiac deaths can be classified as SCDs. Sudden cardiac death occurs as the first expression of cardiac disease in many individuals presenting as out-of-hospital patients with cardiac arrest.1 If the cardiac activity is restored by an intervention, eg, defibrillation or other advanced cardiac life support (ACLS) measures, it is called sudden cardiac arrest (SCA).

Sudden cardiac death claims more than 300,000 lives per year in the US and about 7 million lives per year worldwide.2-4 Based on the inclusion criteria used in individual studies, the annual incidence of SCD has been reported from 200,000 to more than 400,000. More deaths are attributable to SCD than to lung cancer, breast cancer or acquired immunodeficiency syndrome.

CAUSES OF SCD
The common causes of SCD include:5
• Coronary artery abnormalities
• Ventricular hypertrophy and hypertrophic cardiomyopathy (HCM)
• Dilated cardiomyopathy (DCM)
• Acute heart failure
• Inflammatory, infiltrative, neoplastic and degenerative processes
• Diseases of the cardiac valves
• Congenital heart disease
• Primary electrophysiologic abnormalities
• Sudden infant death syndrome and sudden cardiac death in children
• Commotio cordis (blunt chest trauma)
• Mechanical interference with venous return (acute cardiac tamponade, massive pulmonary embolism, acute intracardiac thrombosis, dissecting aneurysm of the aorta)
• Toxic and metabolic disturbances (electrolyte disturbances, metabolic disturbances, proarrhythmic effects of antiarrhythmic or noncardiac drugs)
• Fibromuscular dysplasia (FMD)6

Cardiac causes of SCD can also be classified as those with structural abnormality of the heart or diseases with primary electrophysiologic abnormalities. The most common structural abnormality of the heart resulting in SCD is coronary artery disease (CAD) and myocardial infarction (MI) with post-MI remodeling of the heart. Non-ischemic cardiomyopathies (eg, DCM and HCM) are the second most common cardiac structural abnormality associated with SCD. Among cardiac causes of SCD with primary electrophysiologic abnormality and no apparent structural heart disease are Brugada syndrome, long QT syndrome (LQTS) and short QT syndrome.

APPROACH TO ACUTE MANAGEMENT OF SCD
In the event of cardiac arrest, the immediate implementation of ACLS guidelines is indicated. Some of the spe-
specific considerations of acute therapy of SCA depending on the presented rhythm are:

**Ventricular Arrhythmia (VF and VT):**
Defibrillation is the mainstay of the acute therapy of SCA due to VF or VT. Epinephrine (1 mg IV every 3–5 minutes) or vasopressin (40 U single dose IV) are given. Amiodarone (300 mg IV push and 150 mg repeat IV push if needed) and lidocaine (1 mg/kg IV push every 3–5 minutes up to 3 doses) can be used as antiarrhythmic drugs if defibrillation does not control the VF/VT. In case of polymorphic VT or suspected hypomagnesaemia, a 1–2 g IV push of magnesium is recommended.

**Pulseless Electrical Activity (PEA):**
Epinephrine (1 mg every 3–5 minutes) can be used while there is no evidence supporting the use of vasopressin in PEA. Atropine (1 mg every 3–5 minutes) should be used in cases with bradycardia. Sodium bicarbonate (1 meq/kg) should be given if there is associated hyperkalemia and its use may be considered in long arrest intervals and suspected metabolic acidosis.

**Asystole:**
One study suggested that vasopressin is more effective in acute therapy of asystole than epinephrine. Atropine and sodium bicarbonate are used with similar indications in PEA.

Careful post-resuscitative care is essential to survival because studies have shown a 50% repeat in-hospital arrest rate for people admitted after an SCA event. Treatment of myocardial ischemia, heart failure, and electrolyte disturbances is essential.

**PRIMARY PREVENTION AND RISK FACTORS FOR SCD**

The conventional risk factors used in early studies of SCD are the same as the risk factors for CAD. The rationale is based on two facts. One is that coronary disease is the structural basis for 80% of SCDs in the US, and two, that the coronary risk factors are easy to identify because they tend to be present continuously over time. Coronary artery disease, smoking, obesity, hypertension, hypercholesterolemia, low functional capacity, heart failure with low ejection fraction, family history of inherited diseases associated with SCD, age and gender are associated with increased risk of SCD. However, most of the above associations have not been specific enough to be used for primary prevention and risk stratification for SCD remains a major challenge. Among the above risk factors, an ejection fraction ≤30% is the single most powerful independent predictor for SCD, but has low specificity. Nonetheless, relying on a low ejection fraction as the sole major predictor limits predictive power because a significant proportion of SCDs may occur among patients with normal or moderately reduced values. Some of the possible risk stratification tools that are under investigation are microvolt T-wave alternans, VT induced at electrophysiology study (EPS), and serum markers of fibrosis and structural remodeling of the heart.

**INDICATIONS FOR IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD)**
The ICD has remained the mainstay of prevention and therapy of SCD due to VT and VF. An ICD may be used for primary or secondary prevention.

**Class I recommendations:**
- Cardiac arrest caused by VF or VT not resulting from a transient or reversible cause
- Spontaneous sustained VT associated with structural heart disease
- Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at EP study when drug therapy is ineffective, not tolerated, or not preferred
- Nonsustained VT in patients with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at EP study not suppressible by a Class I antiarrhythmic drug
- Spontaneous sustained VT in patients without structural heart disease not amenable to other treatments

**Class II recommendations:**
- Patients with LVEF ≤0.30 at least 1 month post MI and 3 months post coronary artery revascularization surgery
- Cardiac arrest presumed to be caused by VF when EP testing was precluded by other medical conditions
- Severe symptoms (eg, syncope) attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation
- Familial or inherited conditions with a high risk for life-threatening ventricular tachyarrhythmias, such as long-QT syndrome or hypertrophic cardiomyopathy
• Nonsustained VT with CAD, prior MI, and LV dysfunction, and inducible sustained VT or VF at EP study
• Recurrent syncpe of undetermined cause in presence of ventricular dysfunction and inducible ventricular arrhythmias at EP study when other causes of syncpe have been excluded
• Syncpe of unexplained origin or family history of unexplained SCD associated with typical or atypical right bundle branch block and ST-segment elevation (Brugada syndrome)
• Syncpe in patients with advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause

CONSIDERATIONS FOR RISK STRATIFICATION AND PREVENTION OF SCD IN PATIENTS WITH PRIOR MI

Currently LV ejection fraction is the strongest predictor of SCD after acute MI. However, recovery of ventricular function occurs in a significant proportion of patients after MI. The majority of functional improvement occurs by day 14 after MI but improvement may continue until 3 months after acute MI. While up to about half of patients may show LV functional improvement, in a smaller portion of post MI patients the LVEF may reduce. Therefore, reassessment of the LV function and wall motion abnormality is recommended prior to ICD implantation. It is also important for the patient to receive optimum medical therapy before reevaluation.

The American College of Cardiology (ACC) recommends (class I) ICD therapy for primary prevention in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 30–40%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than one year and in those post-MI patients who present with hemodynamically unstable sustained VT. The ICD therapy receives a class II recommendation by the ACC for post-MI patients with the above criteria but NYHA functional class I. ICD therapy is also a reasonable therapy for post-MI patients with recurrent sustained VT episodes even if there is no significant LV dysfunction. Amiodarone is a reasonable alternative in post-MI patients at risk for SCD who cannot or refuse to have an ICD implanted.

CONSIDERATIONS FOR RISK STRATIFICATION AND PREVENTION OF SCD IN PATIENTS WITH NON-ISCHEMIC CARDIOMYOPATHY (DILATED AND HYPERTROPHIC CARDIOMYOPATHIES)

The ACC recommendations for ICD therapy in patients with DCM are similar to those patients with post-MI LV dysfunction. An ICD implantation is recommended in patients with DCM who have recurrent episodes of sustained VT (regardless of the LVEF) and in those who have an LVEF ≤ 35%, who are NYHA functional class II or III, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than one year (class I). In addition, EP study is recommended in patients with sustained palpitations, wide-QRS-complex tachycardia, presyncope, or syncope. An ICD implantation can be considered for those patients with DCM and unexplained syncope (class II).

HCM may not be associated with any systolic dysfunction of the LV. An ICD should be implanted in patients with HCM and sustained VT who are receiving optimal medical therapy and have reasonable life expectancy (class I). Utilizing ICD therapy is also recommended (class II) in patients with HCM who are receiving optimal medical therapy and have any of the following: family history of premature sudden death, unexplained syncope, LV thickness ≥ 30 mm, abnormal exercise blood pressure, nonsustained spontaneous VT. Amiodarone is an alternative therapy for patients who cannot have or refuse ICD therapy.

THE ROLE OF ANTIARRHYTHMIC DRUGS IN PRIMARY PREVENTION OF SCD

Overall, the available antiarrhythmic drugs other than beta-blockers should not be used as primary therapy in the management of ventricular arrhythmias and the prevention of SCD. The efficacy of non beta-blocker antiarrhythmic drugs is equivocal at best, and each drug has significant potential for adverse events including proarrrhythmia. Amiodarone therapy may be considered in special situations and there is a survival benefit when amiodarone is combined with beta-blockers in a subset of patients. In patients with ventricular tachyarrhythmias who do not meet criteria for ICD, beta-blockers are the first-line therapy, but if this therapy at full therapeutic dose is not effective then amiodarone or sotalol can be tried with monitoring for adverse effects during administration. Amiodarone can also be considered in patients with ICD who experience recurrent appropriate ICD discharges due to VT and VF.
SECONDARY PREVENTION

Should all survivors of SCA receive ICD therapy to prevent SCD? Contraindications to ICD therapy (ie, class III recommendations) are:

- Syncope of undetermined cause in patients without inducible ventricular tachyarrhythmias and without structural heart disease
- Incessant VT or VF resulting from arrhythmias amenable to surgical or catheter ablation (eg, atrial arrhythmias associated with WPW, RVOT VT, idiopathic LV tachycardia, or fascicular VT)
- VT or VF caused by transient or reversible disorder (eg, AMI, electrolyte imbalance, drugs or trauma) when correction of the disorder is considered feasible and likely to reduce the risk of recurrent arrhythmia substantially
- Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up
- Terminal illnesses with projected life expectancy <6 months
- Patients with CAD with LV dysfunction and prolonged QRS duration in absence of spontaneous or inducible sustained or non-sustained VT who are undergoing coronary bypass surgery
- NYHA Class IV drug–refractory congestive heart failure in patients who are not candidates for cardiac transplantation⁵

INDICATIONS FOR ICD THERAPY IN SECONDARY PREVENTION OF SCD

In general all survivors of SCA due to VF/VT should be considered for ICD therapy unless the VT or VF resulted from a transient or reversible cause. ICD therapy is also recommended when the patient presents with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at EP study when drug therapy is ineffective, not tolerated, or not preferred.⁵

ROLE OF ANTIARRHYTHMIC DRUGS IN SECONDARY PREVENTION OF SCD

In general antiarrhythmic drugs are not the preferred first line of therapy in either primary or secondary prevention of SCD. However amiodarone or sotalol can be considered in patients who cannot tolerate beta-blockers, are treated with maximum dose of beta-blockers and still have recurrent episodes of VT or VF, and those who cannot have or refuse ICD therapy.⁵ Amiodarone may also be considered in patients who receive ICD therapy but experience frequent appropriate ICD discharges due to VT or VF and are receiving maximum beta-blocker therapy when there is no contraindication to treatment with amiodarone. Adjunct therapy with catheter ablation may also be beneficial in selected patients.

POTENTIAL ADVERSE EFFECTS AND PROBLEMS ASSOCIATED WITH ICD THERAPY

Pocket or deeper infection is a potential adverse effect of ICD implantation. The ICD may be the source of infection (primary infection) or as a foreign body it may be seeded secondary to bacteremia. The rate of infection is higher with ICD implantation than the pacemaker and it has been reported up to 6.9%.¹² However, the risk is not the same for all patients and elderly patients, those with diabetes, malignancy, recent immunosuppression or anticoagulation therapy are at higher risk. Re-intervention (eg, generator change or device revision) and operator experience also play a role in the rate of infection. Superficial infection may present as wound infection and deeper infections usually present with fever, chills, low respiratory infection, endocarditis and tricuspid regurgitation. Most common pathogens are S. aureus and coagulase-negative staphylococci. Initial empirical IV antibiotic therapy is recommended with vancomycin in case of superficial pocket infection and empirical antibiotic therapy of endocarditis when deeper infection is suspected. Complete device removal is usually recommended in pocket infection, device-related endocarditis or even in recurrent and persistent bacteremia without any alternative explanation in a patient with an implanted device. Prophylactic antibiotic with staphylococcus coverage is recommended at the time of ICD implantation.

Lead failure, tricuspid regurgitation, twisting or rotating the device in its pocket resulting in lead dislodgement and device malfunction (twiddler syndrome), musculoskeletal complications in the shoulder region especially with subpectoral approach, inappropriate shocks usually due to detection of supraventricular arrhythmias, anxiety and depression are among other complications related to ICD implantation and therapy.
SCD IN SPECIFIC POPULATIONS

Although some of the primary electrophysiological abnormalities are more common in young athlete patients, most of SCD events are associated with structural heart diseases, with HCM, anomalous origin of a coronary artery and myocarditis being the three most common etiological factors in the US. The distribution of structural heart diseases associated with SCD in young athletes may vary in different regions of the world. Other structural heart diseases associated with SCD in young athletes are Marfan syndrome and aortic rupture, valvular heart diseases, DCM, premature CAD, myocardial bridge, and arrhythmogenic right ventricular cardiomyopathy. In the absence of apparent structural heart disease, Brugada syndrome, Long QT syndrome and catecholaminergic polymorphic VT are the three most common causes. Coma to cordis refers to a non-penetrating chest trauma that causes VT and VF resulting in SCD. Prior to participating in competitive sports a careful history and physical examination should be done. A baseline electrocardiogram is recommended by most experts. Further testing may become necessary depending on the findings in the initial evaluation. The decision to allow the patient to participate in a competitive sport depends on the risk stratification of the patient and the nature of the sport.

SPECIFIC ISSUES RELATED TO VT AND VF TREATMENT DURING PREGNANCY

Amiodarone may cause perinatal hypothyroidism or hyperthyroidism and possibly neurological abnormalities, intrauterine growth retardation or fetal bradycardia. Concomitant beta-blocker therapy should probably be avoided because of the fetal bradycardia. Full neonatal thyroid function tests and developmental follow-up are recommended if amiodarone should be used during pregnancy. The presence of an ICD is not a contraindication for pregnancy, and pregnancy does not increase the risk of an ICD complication or result in a high number of appropriate or inappropriate ICD shocks.

SPECIFIC ISSUES RELATED TO SCD IN ELDERLY PATIENTS

The susceptibility to both atrial and ventricular arrhythmias is particularly increased in the elderly, even though they may be clinically healthy. The incidence increases with morbidity. Current data have supported the use of implantable cardioverter-defibrillators for ventricular tachyarrhythmias, as this has improved survival in the appropriate setting. Therefore, ICD therapy is recommended in elderly population with indications similar to younger patients. However, some of the practical obstacles in ICD therapy for elderly patients are difficulty with follow up in some patients and associated physical and mental comorbidities that may limit the quality-of-life or life expectancy.

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Tonsillectomy 2011: Evidence-Based Indications and Intracapsular Tonsillectomy–A New Technique

WILLIAM D. YOUNGERMAN, MD

Tonsillectomy is one of the most common pediatric surgical procedures today with over 530,000 performed annually in the US alone on children younger than 15 years of age. Considerable uncertainty remains, however, regarding patient selection, and surgical technique. Despite a growing volume of randomized controlled trials (RCTs), study findings are often inconsistent, inconclusive, or difficult to generalize.

INTRODUCTION

Evidence-based medicine uses the best research evidence combined with clinical expertise as a starting point for patient care, offers an excellent solution for selection criteria, and provides data on current surgical techniques.

Of the children that undergo the procedure, about one half are for the indication of recurrent sore throat. There is a wealth of information supporting the positive effect of adenotonsillectomy in children with obstructive sleep apnea (OSA) and sleep disordered breathing (SDB). The evidence for tonsillectomy for chronic/recurrent acute tonsillitis is not as conclusive. In fact, there are only five prospective controlled studies, only four of which involved children, and only one demonstrated short-term efficacy.

Why is there so little proof of the effectiveness of such a common major pediatric operation? First, good studies of tonsillectomy are difficult to execute. The terms tonsillitis, pharyngitis and sore throat are not well defined. Few children meet Paradise criteria defined as severe disease of seven severe sore throats in the past year, five in each of two consecutive years, or three in each of three years. For most children with recurrent disease, spontaneous resolution is the norm, so it is difficult to know if surgery or maturation has cured the problem. Second, parents and otolaryngologists believe in the operation, so it is difficult to keep the study control population from crossing over to the surgical group. Finally, the operation is probably not very effective for some children, so large numbers of subjects are needed to show a statistical difference.

We can say with some confidence that, for children who meet Paradise criteria, tonsillectomy (with or without adenoectomy) will decrease the frequency of sore throats for two and possibly three years compared to no surgery. A procedure with a 1 in 35,000 death rate, a 5% bleeding rate and a 100% misery index should be performed where it is most likely to help.

Sleep disordered breathing represents a spectrum of disorders ranging in severity from primary snoring to OSA. The prevalence of OSA in the pediatric population is 1–4%, as many as 10% of children have primary snoring. Up to 30–40% of children with clinically diagnosed SDB exhibit behavioral problems that include enuresis, hyperactivity, aggression, anxiety, depression, and somatization. OSA is also associated with poor school performance and a decrease in quality of life (QOL). The QOL of children with OSA is similar to children with chronic conditions such as asthma and juvenile rheumatoid arthritis.

GUIDELINES

The American Academy of Otolaryngology recently published a clinical practice guideline for tonsillectomy in children. Guidelines are intended to reduce inappropriate variations in clinical care, to produce optimal health outcomes for patients, and to minimize harm. Evidence-based approach to guideline development requires that the evidence supporting a policy be identified, appraised, and summarized and that an explicit...
link between evidence and statements be defined. Evidence-based statements reflect both the quality of evidence and the balance of benefit and harm that is anticipated when the statement is followed.

Guidelines are never intended to supersede professional judgement; however, they may be viewed as a relative constraint on individual clinician discretion in a particular clinical circumstance. Less frequent variation in practice is expected for a "strong recommendation" than might be expected with a "recommendation." “Options” offer the most opportunity for practice variability.

These six guidelines for surgical indications and planning are as follows:

**STATEMENT 1. WATCHFUL WAITING FOR RECURRENT THROAT INFECTION:**

Clinicians should recommend watchful waiting for recurrent throat infection if there have been fewer than 7 episodes in the past year or fewer than 5 episodes per year in the past 2 years or fewer than 3 episodes per year in the past 3 years.

**Recommendation** based on randomized controlled trials with minor limitations and observational studies with a preponderance of benefit over harm.

**STATEMENT 2. RECURRENT THROAT INFECTION WITH DOCUMENTATION:**

Clinicians may recommend tonsillectomy for recurrent throat infection with a frequency of at least 7 episodes in the past year or at least 5 episodes per year for 2 years or at least 3 episodes per year for 3 years with documentation in the medical record for each episode of sore throat and one or more of the following: temperature >38.3°C, cervical adenopathy, tonsillar exudate, or positive test for GABHS.

**Option** based on systematic reviews and randomized controlled trials with minor limitations, with a balance between benefit and harm.

**STATEMENT 3. TONSILLECTOMY FOR RECURRENT INFECTION WITH MODIFYING FACTORS:**

Clinicians should assess the child with recurrent throat infection who does not meet criteria in Statement 2 for modifying factors that may nonetheless favor tonsillectomy, which may include but are not limited to multiple antibiotic allergy/intolerance, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis), or history of peritonsillar abscess.

**Recommendation** based on randomized controlled trials and observational studies with a preponderance of benefit over harm.

**STATEMENT 4. TONSILLECTOMY FOR SLEEP DISORDERED BREATHING:**

Clinicians should ask caregivers of children with SDB and tonsil hypertrophy about comorbid conditions that might improve after tonsillectomy, including growth retardation, poor school performance, enuresis, and behavioral problems.

**Recommendation** based on observational before-and-after studies with a preponderance of benefit over harm.

**STATEMENT 5. TONSILLECTOMY AND POLYSOMNOGRAPHY:**

Clinicians should counsel caregivers about tonsillectomy as a means to improve health in children with abnormal polysomnography who also have tonsil hypertrophy and SDB.

**Recommendation** based on observational before-and-after studies with a preponderance of benefit over harm.

**STATEMENT 6. OUTCOME ASSESSMENT FOR SLEEP DISORDERED BREATHING:**

Clinicians should counsel caregivers and explain that SDB may persist or recur after tonsillectomy and may require further management.

**Recommendation** based on observational studies, case-control and cohort design, with a preponderance of benefit over harm.

**RISK BENEFIT**

The risk-benefit assessment is clearly important when assessing any intervention. (Table)

**COBLATION/INTRACAPSULAR TONSILLECTOMY**

Because of significant morbidities and complications associated with tonsillectomy, many surgical techniques have been developed and deserve careful consideration. These include cold knife dissection, snare excision, monopolar electrocautery, bipolar electrocautery, cryo-
surgery, suction electrocautery, bipolar scissor, KTP-532 laser, CO2 laser, Harmonic Scalpel, microscopic bipolar diathermy, microdebrider, radiofrequency tonsil resection, and Coblation.

Coblation is a unique modality that can ablate tissue by generating a field of ionized sodium molecules. The device uses bipolar radiofrequency energy to ablate and coagulate soft tissue without thermal injury. During Coblation, conductive saline solution is converted in a gap between the device tip and the tissue into an ionized plasma layer. Where this plasma layer meets the tissue, there is adequate energy to break molecular bonds, resulting in molecular dissociation. Because this effect is achieved at temperature of approximately 40–70°C, thermal damage to the tissue is minimized. Coblation allows an intracapsular tonsillectomy (IT) to be accomplished.

Intracapsular tonsillectomy is a new procedure (about 9 years) with a relative paucity of literature to review. This technique removes the tonsil tissue but preserves the tonsillar capsule. By leaving a biologic dressing on the underlying pharyngeal musculature, the technique prevents injury to the muscle. The patient recovers more quickly, has less postoperative pain, and more importantly, has a significantly lower risk of delayed postoperative bleeding. When a physician or patient who is not familiar with IT examines a patient anytime after surgery he/she may observe some lymphoid tissue in the tonsil fossae or a fossae in which the underlying muscle is not so smooth. He/she may not understand that the surgery was completed properly.

Traditional tonsillectomy (TT) results in marked postoperative pain and significant limitations in activity

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Intracapsular tonsillectomy is a new procedure (about 9 years) with a relative paucity of literature to review. This technique removes the tonsil tissue but preserves the tonsillar capsule. By leaving a biologic dressing on the underlying pharyngeal musculature, the technique prevents injury to the muscle. The patient recovers more quickly, has less postoperative pain, and more importantly, has a significantly lower risk of delayed postoperative bleeding. When a physician or patient who is not familiar with IT examines a patient anytime after surgery he/she may observe some lymphoid tissue in the tonsil fossae or a fossae in which the underlying muscle is not so smooth. He/she may not understand that the surgery was completed properly.

Traditional tonsillectomy (TT) results in marked postoperative pain and significant limitations in activity
and diet. In children increased vascular congestion of the head and neck associated with crying and straining can precipitate bleeding. Impairment of swallowing increases the risk of dehydration, infection and secondary hemorrhage. The few studies looking at the IT technique have yielded positive results. Intracapsular tonsillectomy has been shown to be a reasonable alternative to TT and is effective in lowering rates of postoperative bleeding, improving postoperative recovery, has no difference in postoperative infection rates and less postoperative pain.8

CONCLUSION

Any procedure has its trade-offs. The trade-off for IT is that it is exchange for its significant benefits, the fact that tonsillar capsule is preserved means that a majority of cases may require a second procedure to remove material which may have regrown and is clinically significant. This frequency of reoperation for regrowth of tissue that is clinically significant has been less than 1%.11

While it is admirable that we should seek safer methods of surgery that are associated with less morbidity, establishing these facts can be difficult and will certainly not be achievable with small random clinical trials (RCTs). Decisions are facilitated when evidence is summarized by systematic review using explicit methods to minimize bias in selecting, appraising, and combining studies.

The new Academy Clinical Practice Guideline is helpful, but is not intended as a sole source of guidance in managing children who are candidates for tonsillectomy. Rather, it is designed to assist clinicians by providing an evidence-based framework for decision-making strategies. The guideline is not intended to replace clinical judgment or establish a protocol for all individuals.

In terms of both if we do it and how we do it, tonsillectomy seems destined to remain controversial for some time to come.

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ACKNOWLEDGMENTS

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REFERENCES

How Nurses Can Provide Optimum Care to the Patient with Parkinson’s Disease

DEBORAH DAVIS, RN, BSN

Nurses, whether in a doctor’s office, hospital or other setting, play a major role in providing patient care; therefore, knowing disease symptoms and how these symptoms affect patients’ day-to-day living helps us provide improved quality of life. For that reason providing education on chronic disease to patients and their caregivers is extremely important, and this is especially true when it comes to patients with Parkinson’s disease (PD).

INTRODUCTION

In the US alone, more than 1 million people suffer from PD and the majority are over the age of 65. While this disease typically occurs after age 40, younger patients have been diagnosed. Actor Michael J. Fox is an example of a younger person having developed symptoms as early as age 30.

Parkinson’s disease is a neurodegenerative disorder that causes a change in how the nervous system provides information to the muscles and how the muscles react to the impulses from the nervous system. The disease arises from loss of substantia nigra neurons in the brain; this leads to a loss of dopamine production, a neurotransmitter required for movement of the body. Loss of this neurotransmitter can cause debilitating symptoms, including tremors, freezing with mobility, swallowing problems, bowel and bladder dysfunction, and depression. For example, patients may have tremors that are worse at rest but improve with movement. Patients may also have rigidity and akinesia (difficulty initiating movement), bradykinesia (slow movement) and a tendency towards propulsion or retropulsion (falling forwards or backwards). When PD patients lose their balance they may look as if they are trying to run in order to regain balance. This is known as festination. Unlike the effects of a stroke, PD does not normally cause a loss of sensation in the extremities. Instead, patients may develop vague aches and pains, changes in sensation of arms or legs and diminished reflexes. Speech becomes hypophonic and dysarthric (soft and difficult to understand). Many, but not all, PD patients have some degree of dementia at the time of diagnosis. As this disease leads to loss of self-control, independence and dignity, depression is not uncommon.

It is a balancing act to provide optimum nursing care for PD patients. No two patients will present exactly the same set of symptoms, and symptoms can change daily. Hospital admission and discharge can create enormous stress for patients; under stress, symptoms may literally change from minute to minute. Therefore, in caring for a PD patient it is important to consider how that patient’s movement is affected. For example, if the patient has tremors, how does this affect his or her ability to eat, drink, wash, take medications and get in and out of bed? The same questions apply to the patient whose PD results in muscular rigidity or motor impairment. Remember that PD patients may have dysphonia and slowed responses; consequently try to provide a quiet environment and allow ample time for the patient to answer questions as the ability to answer is a vital part of the nursing evaluation process. Again, the most important thing to remember is that what works for PD patient Smith may not work for PD patient Jones. This is one of the primary challenges inherent in caring for the patient with PD.

Once you have determined the problems of your patient you must next decide the order in which to address them. For example, the PD patient with swallowing issues and pneumonia will very likely have secretion management issues. In this instance it is just as important to have suction apparatus available in the room as it is to
have an IV to administer antibiotics.

Another might have diarrhea as continence is an issue for many PD patients. Assessing how well he or she is able, if at all, to transfer to the commode would be an important issue in this patient’s care. Additionally, remembering that when PD patients become anxious or flustered their mobility can suffer (and often the necessity of moving immediately will cause a freezing episode) can help you determine if the patient can best transfer to the left or the right. This will assist in proper placement of a commode and may make all the difference between continence and incontinence. It is this type of information a nurse must work to garner from the PD patient and it is critical to relay this information in report to assist in continuity of care.

**TIME FOR MEDICATION**

Care of the PD patient is complex and needs daily assessment. (Table) Research studies in Great Britain have shown that the PD patient’s primary complaint when hospitalized is that of not receiving medication on time. This is why during admission it is most important that you ask the patient or caregiver about the medication schedule. If you are told the first dose of medication is taken at exactly 7 am, strive to administer the medication at that time. Failure to do so may cause the patient to have reduced mobility when breakfast arrives and be unable to eat.

Administering medications requires multiple efforts and even micromanagement to provide PD patients with the best possible combination of managing their symptoms and minimizing the side effects. One of the most commonly used medications is Sinemet, or levodopa/carbidopa. This drug is in the “dopamine precursor” category. Since PD results partially from a loss of dopamine production in the brain, the use of levodopa/carbidopa helps to supply this missing neuro-receptor; these drugs convert to dopamine in the brain.

Normally, our bodies produce dopamine at various rates throughout the course of the day thereby supplying dopamine on a continuous basis. This constant production is what allows us to remain mobile. The PD patient, on the other hand, receives dopamine from an external source. By staggering the dosage schedule, the physician’s orders are mimicking this production, using the known half-life to determine administration times. Something to be aware of is that added stress on the patient may alter how they metabolize medications. During hospitalization, many patients must have their doses tweaked to accommodate the effects of stress. One of the unfortunate facts with medications such as levodopa/carbidopa is that over many years, patients develop shorter and shorter periods of effectiveness. When this occurs, the physician will adjust medications, adding different medications or increasing dosages or frequencies.

In addition to dopamine replacement therapy, dopamine agonists can be used to treat PD. Instead of becoming dopamine in the brain, they mimic the effects of dopamine. This therapy becomes increasingly important as more dopamine-producing neurons die. Medications in this category include Mirapex, ReQuip, and Parlodel. While these medications have a valuable use, they are not as effective as levodopa/carbidopa to treat the symptoms of PD, and may cause drowsiness, abnormal sexual drives and gambling urges.

Research has shown that some MAO inhibitors prolong the effects of levodopa/carbidopa medications when used concurrently; however, this symptomatic benefit is not without its problems. MAO inhibitors can cause deleterious effects on the blood pressure, interact with many other medications and foods, and may cause hallucinations. COMT-inhibitors, such as Comtan, allow larger amounts of levodopa to reach the brain, which raises the level of the dopamine available to the body but there is an increased risk of dyskinesia and hallucinations. Several of the other symptoms associated with PD are treatable with anti-cholinergics. These medications can be useful in managing tremors and drooling; however, side effects include changes in memory, cognition, urination, constipation and dry mouth. Fatigue and tremor may be treated with Amantadine.

**NUTRITION**

Weight loss is a common event for PD patients. Research has shown that three out of four PD patients will experience a significant weight loss. This alteration in nutritional status can also affect how the medication works. Patients with PD may have a variety of nutritional ailments. They may experience constipation, weight loss, or diarrhea. For some patients the culprit may be their ability to swallow. In others, they simply cannot manage the fine finger motions necessary to hold a spoon or fork.
### Table. Daily Nursing Assessment for the Parkinson’s Patient

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>ACTION</th>
<th>CONSIDER</th>
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<tbody>
<tr>
<td><strong>Medication time:</strong> Meds to treat PD have a limited action span; irregular administration will affect all aspects of the patient’s ability to function.</td>
<td>THINK: ON TIME, EVERY TIME. Use patient’s home schedule as often as possible. Understand the purpose and action span of medication being given. Teach the patient and caregiver about the medications.</td>
<td>Is the effectiveness of meds decreasing? Are there new meds added?</td>
</tr>
<tr>
<td><strong>Communication:</strong> Slowed responses occur with PD and dysphonia may be present. DO NOT RUSH PATIENT.</td>
<td>Allow adequate time for the patient to formulate an answer and respond. Reduce distractions (TV, people talking, etc.). Keep the call light within reach.</td>
<td>Does the patient have a hearing aid? Is the patient confused and not understanding? Are you able to hear the patient’s answer? Would a picture communication board be helpful? Does the patient need easier access to the call light?</td>
</tr>
<tr>
<td><strong>Swallowing issues:</strong> Muscular action of esophagus may be affected or swallowing mechanism impaired.</td>
<td>Position UPRIGHT and prop to maintain body alignment. Secretion management. If swallowing guidelines are in place follow them exactly.</td>
<td>Does the patient need a speech therapy consult? Should suction be available in the room?</td>
</tr>
<tr>
<td><strong>Nutrition:</strong> May decline due to fatigue or loss of appetite.</td>
<td>Cut food into bite-size pieces, observe how the patient eats and assist as needed. Routine weights. Document intake. Evaluate fine finger control and ability to use utensils. If patient is too tired to eat 100% of a large meal, obtain an order for small meals. Involve the dietitian for supplements.</td>
<td>Does OT need to see the patient for assistive devices?</td>
</tr>
<tr>
<td><strong>Mobility:</strong> Neuromuscular function is impaired and becomes progressively worse, resulting in slow, jerky movements. Risk increases for pneumonia and DVTs when mobility is affected.</td>
<td>Plan activity around the effective time of medications. Consider which direction is easier for the patient to transfer. Do NOT rush the patient – this increases the risk of falling, freezing and anxiety. Do not use non-skid footwear. Use gait belts and assistive devices to improve stability.</td>
<td>Does the patient need a PT consult? Has the neurologist been consulted for possible medication adjustments?</td>
</tr>
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</table>
### Table. Daily Nursing Assessment for the Parkinson’s Patient (Continued)

<table>
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<tr>
<th>ASSESSMENT</th>
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<tr>
<td><strong>Elimination:</strong> Loss of neuromuscular stability contributes to loss of control and affects self-esteem and dignity.</td>
<td>Adjust the height of the commode to the individual patient. Assist to commode at first request; PD patients move slower and incontinence may occur if the transfer is rushed. Protect the dignity of the patient as much as possible. Constipation may be due to changes in mobility, hydration and nutrition. Use containment products during the day only.</td>
<td>Is there a pattern to the incontinence that allows establishment of a voiding or BM schedule? Does the primary caregiver have any suggestions? Does there need to be an OT consult for a toileting aide? Dehydration makes urine much harsher on delicate bladder tissue – is this leading to incontinence?</td>
</tr>
<tr>
<td><strong>Skin:</strong> Changes in nutrition, hydration, muscle tone and continence may affect skin integrity.</td>
<td>Cleanse gently, rinse and pat dry, use appropriate skin barriers. Promote nutrition and hydration. Reposition more often due to skin fragility.</td>
<td>Can the patient be up in a chair? Is yeast developing? Is the soap being used drying the skin excessively?</td>
</tr>
<tr>
<td><strong>Psychosocial:</strong> Loss of control and ability leads to depression, anxiety, sleep disorders, etc. Medications can exacerbate these symptoms. Dementia may develop.</td>
<td>Include the patient in all care decisions whenever possible. A flat affect may not indicate depression. Provide compassionate, respectful care. Simple steps such as adjusting the pillow and bed to mimic home will improve sleep.</td>
<td>Are meds contributing to cognitive changes? Does the patient need a psychiatric consult? Could pastoral care help?</td>
</tr>
<tr>
<td><strong>Knowledge:</strong> Patient and caregiver must understand the disease and its management in order to promote compliance with treatment.</td>
<td>Upon admission assess what the patient or caregiver needs to learn and how they learn best. Provide education frequently to avoid overloading at discharge.</td>
<td>Are you providing at least minimal information on medications, mobility, nutrition/hydration and continence?</td>
</tr>
<tr>
<td><strong>Caregivers:</strong> As the disease progresses, caregivers may become overloaded.</td>
<td>Include caregivers in decisions, planning care, education and the provision of care.</td>
<td>Is a social service consult needed? Does the caregiver need training by Therapy Services in mobility, ADL’s or swallowing? Is the caregiver sturdy enough to safely provide care? Is there help available if the caregiver needs a break?</td>
</tr>
</tbody>
</table>
Others may not be able to chew, have loosely fitting dentures from weight loss, or are suffering from cognitive loss or depression. Each of these situations can occur with any PD patient. Recognizing the situation, and then addressing it will result in better outcomes.

The PD patient may experience stress that results in decreased mobility of their hands, and therefore their ability to feed themselves. For this reason, it is important that these patients get their early morning medications on time. To help maximize the patient’s intake, there are some simple steps to take. Whenever possible, the patient should be up in the chair for meals. At the very least, the head of the bed should be upright and the body in good alignment. This will help to keep the esophagus from being twisted, which helps food progress to the stomach once the patient swallows. If the patient drifts to one side or the other when sitting upright, use pillows to provide support. Ask for physical therapy and occupational therapy consults to evaluate mobility and balance issues. Fine finger control may be poor so cutting foods into bite-sized pieces may help. If the PD patient is having difficulty with the mechanics of eating, staff should feed them.

Occupational therapists are available to help the patient learn to use adaptive equipment that may make it easier for them to feed themselves. Built-up utensil grips, plate guards, dishes with skid-resistant features, and lightweight cups with handles are just a few devices available. Have someone stay with the PD patient during the first hospital meal to monitor for swallowing concerns and choking. Be alert for signs of aspiration. Oral motor exercises can be very beneficial in helping the patient overcome dysphagia. Many PD patients can only eat about 50% of a meal. The nurse needs to ask questions to determine why this is occurring: Are they full, or are they too tired to eat more? Some PD patients are afraid of being considered a bother and will not report that they are simply too tired to eat more. Scheduling smaller, more frequent meals may help increase intake. The hospital dietitian is an excellent resource for supplements.

**MOBILITY**

As nurses, we all know that patients with decreased mobility are at increased risk for skin breakdown, pneumonia and blood clots. The PD patient is at higher risk when mobility concerns arise. Many PD patients have difficulty walking and may spend a great deal of time sitting or lying in bed. To maximize the PD patients’ mobility, nurses have to understand the various mobility malfunctions that can occur. One of the most frustrating concerns these patients experience is a sudden freeze while they are walking. Generally, there is no warning: they can be walking along easily and suddenly stop. Freezing often occurs when the patient walks through a narrow area such as a doorway, or between two objects and furniture. If this happens, encourage them to shift their weight from one foot to the other in a rocking manner. Another possibility is to have them count either silently or aloud. The concentration required to count in a logical manner sometimes will allow the patient to begin to walk again. Imagining a line drawn in front of their foot and telling themselves to step over it can help. It is important never to rush a PD patient – this can frighten them, make them move unsafely and increase the risk of falls. Unfortunately, many of the gait disturbances experienced cannot be helped by mind over matter techniques. There are products available, designed to help with mobility, such as walkers and canes that use laser pointers as a guide or cues to keep the patient moving forward. A heavier walker with wheels or a seat may also be useful. Physical therapists are experts at assistive device selection and should be consulted when needed.

The PD patient is the exception to the rule for non-skid footwear in the home or the hospital. Patients should wear sturdy shoes with a normal sole. Non-skid footwear may glue the PD patient to the floor, contributing to falls. Sandals and slippers are just as dangerous. The PD patient must wear a comfortable shoe that is not likely to slip off their foot.

**Exercise, within the limitations of PD is important.** Not only does this keep stiff joints mobile, it helps keep the person active. Being able to do simple tasks can promote emotional well-being. Ask for a physical therapy consult for the patient as soon as they are medically stable. In-bed exercises, such as aerobics, can make the difference in how these patients transfer. Nurses should involve therapists with coordination of therapy sessions with medication ‘effective’ times. It does no good to have therapy five minutes after the first dose of medication is given – the patient will not be able to participate for at least 30–60 minutes. The mobility disturbances ex-
experienced with PD can make it difficult to do complex exercise programs. Walking is one of the best exercises for PD patients. Therapists have used yoga to help patients become calmer and more aware of their body. This increased awareness has been shown to improve patients’ understanding of their body and the stretching improves overall mobility.¹

Music to accompany exercise can also benefit the patient. The beat can help with timing of movements and reduce the chance of freezing.¹ Modern advances are helping, too. Many patients have benefited from Wii sports games. The focus needed to hold the remote, press the button and swing the arm to “throw” a bowling ball down a virtual lane is the same as that needed to throw a ball down a real lane — without the strength required to pick up the ball.⁹

ELIMINATION

What is more personal to any person than toileting? When you go to the bathroom you are exposed and vulnerable. This is no less embarrassing to the PD patient than it is to anyone else. Respecting the patient’s feelings by closing the door and pulling curtains are simple things to help reduce this exposure. When providing a bedside commode, adjust the leg height (higher or lower) to make it easier to use. This is very important with PD patients as they do not bend easily and need this help. Another simple thing to do is get a drop-arm commode. This gets a barrier out of the way when you help the patient stand and pivot to the commode and may reduce accidents. Personal hygiene can be difficult due to reduced ROM or reach. Occupational therapy has “toilet tongs” — similar to a food-service tong — that the patient can use to hold toilet paper. This device extends their reach and may allow them to perform hygiene after using the toilet.

Constipation is a common problem, and is rooted in decreased nutrition, hydration, and decreased mobility. Find out how often the patient normally has a bowel movement and what they use to promote elimination. If the patient’s routine includes a cup of hot water and a bowl of bran every day then try to be sure this is provided. If dependent on a suppository every other day, talk to the doctor.

Incontinence is also common. If the patient is incontinent, nurses must protect the skin from prolonged wetness. Urine is very harsh, especially if concentrated from dehydration. Fragile skin breaks down rapidly and yeast can develop. Thorough peri-care with a mild cleanser, followed by gently drying, then applying a protective barrier is necessary. During the day, use adult diapers or pull-ups to contain wetness and check often to see if the patient needs to be changed. Keeping track of when the patient is incontinent may allow nurses to establish a timed voiding plan. For example if the patient is always incontinent two hours after a meal, plan on getting them to the commode at that time. This will not only help promote patient self-esteem but can reduce costs associated with incontinence supplies. Urine containment products such as Attends are not recommended for night-time use as they hold wetness against skin and can increase risk of breakdown.

PSYCHOSOCIAL

Chronic illnesses can lead to emotional distress, for patients as well as caregivers. Parkinson’s disease can result in poor concentration, memory lapses, depression, anxiety, sleep disorders, hallucinations, and more. Changes in environment and caregivers may make it worse. While PD patients often develop a mask-like facial expression and may appear to have a flat affect this is not always reflective of how the patient feels. Fighting depression when your body betrays you is hard. Offering patients a simple touch if they are crying, and approaching them with a non-judgmental manner during outbursts will show the PD patient the nurse is caring and concerned. If antidepressants are ordered, the neurologist managing the medication regimen should be contacted as many PD medications interact adversely with antidepressants.⁴

Reality orientation and reminders will benefit the confused patient. Use simple signs reminding the patient to not get up alone; pad the nurse call button to make it easier to find; get a pancake call button so less pressure is needed to depress the signal. Speech therapy may be helpful with cognitive losses, so investigate that as an option if needed. Remember that PD patients can be overwhelmed by noisy environments, and may have difficulty responding if more than one person is speaking at a time. Reducing the number of visitors at a single time, turning the television down or off, and dimming harsh lights may improve how the patient is able to handle conversations. The decrease in noise will also help the nurse hear what the patient is saying.

Sleep disorders can occur from medication, pain, depression, etc. Helping the patient get ready for bed in a manner similar to their home routine can be help-
ful. Help them adjust the pillows, head of bed, leg positioning and covers. These simple things are comforting. Be wary of hypnotics as they may exacerbate confusion and hallucinations. Simple analgesics are better than narcotics for pain in most PD patients. Narcotics tend to increase confusion and can make patients jumpy.¹

THE IMPORTANCE OF KNOWLEDGE

When a patient is admitted to a healthcare facility one of the most common assessment questions is asking the patient if there is anything he or she feels the need to learn about during their stay and inquiring how they feel they are best able to learn. Investigate this need every day. At a minimum, the PD patient and his/her support person needs to know about the medication dosing, timing and side effects. A simple way to teach is to tell a patient what each medication is for, and explain the major side effects. When the next dose is due, have the patient tell you about it before you administer. Patients and their caregivers also need to know how to support nutrition, deal with bowel and bladder issues and where they can go to get additional information.

An internet search on Parkinson's disease will return many sites. Below are two that are simple to navigate and contain extremely useful information.

The National Parkinson Foundation:
http://www.parkinson.org

Michael J. Fox Foundation:
http://www.michaeljfox.org

CONCLUSION

Parkinson's disease is a progressive neurodegenerative disease. Loss of the neurotransmitter dopamine leads to loss of mobility. This loss affects all aspects of life for the PD patient. Nurses, as caregivers, must understand the disease in order to provide effective, compassionate care. The tools nurses use – caring, assessment, critical thinking, and implementation of a plan of care – can make a difference in the life of any hospitalized patient but especially those with neurological disorders.

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REFERENCES

Multiple sclerosis (MS) is a chronic, progressive and often debilitating autoimmune disease that involves damage to the myelin sheath (the fatty composition that covers the axons of many of the nerves in the body) including the brain, optic tract and underlying nerve fibers within the spinal cord.

**INTRODUCTION**

The damage creates plaque formation which hardens and causes manifestation of symptoms. More prevalent in Caucasians, MS affects more women than men at a ratio of 2:1 and is commonly diagnosed between the ages of 20 and 50. There is no clear understanding of these phenomena but investigations are currently underway. There are approximately 400,000 thousand cases in the US and 2.5 million worldwide.

**CLASSIFICATIONS**

There are four types of MS: relapsing-remitting MS (RRMS), secondary-progressive, progressive-relapsing and primary-progressive MS. The RRMS involves recurrent attacks of neurological dysfunction that evolve over days and weeks. It may be followed by complete, partial or no recovery. There is no progression of symptoms between attacks. Relapsing-remitting MS is most often seen early on in the disease and is the most common, accounting for 80% of patients. Secondary-progressive involves gradual neurological deterioration with or without acute relapses, minor remissions, and plateaus in a patient who had previous MS. With the progressive-relapsing form, from onset there is gradual progression of disability; unlike RRMS, the disease continues to progress without stabilization. In primary-progressive MS, there is a pattern of gradual neurological deterioration from onset of symptoms but with superimposed relapses.

**DIAGNOSIS**

There is no definitive diagnosis for MS. Diagnosis is based on history, symptoms and clinical findings. The neurologist will perform a neurological assessment. An MRI of the brain and spinal cord will be ordered to look for plaques or lesions in two distinct areas of the central nervous system (CNS), plaques in the white matter of the CNS that have no other explanation besides MS, and evidence that the plaques occurred at discreet points of time. The EEG studies will show the demyelinated neurons transmitting nerve signals slower than normal. However, diagnosis can take months or even years. McDonald Criteria includes a combination of attacks and clinical findings. The criteria equates to neurological progression plus one year of disease progression and two of the following: a positive MRI, positive brain MRI or positive CSF results showing increases in IgG index, total protein, myelin basic protein and 2 or more oligoclonal bands.

**SYMPTOMS**

Primary symptoms are fatigue, visual disturbances, spasticity, muscle weakness, ataxia symptoms and sensory changes involving pain, temperature or touch. Discern if pain is acute or chronic in nature arising from neurological origins, spastic or muscle cramps, and/or musculoskeletal pain. Monitor bowel and bladder dysfunction, euphoria, and cognitive impairment. Secondary symptoms are indirect manifestations of MS and include UTIs, muscle atrophy, osteoporosis and fatigue related to sleep disorders or deconditioning. Tertiary symptoms occur from the chronic nature of MS and can be psychological, vocational or social-related.
M.O.S.P.

This acronym stands for the areas of rehabilitative therapy that can often benefit the MS patient:

- Mobility
- Occupational
- Speech
- Psychosocial

Mobility is greatly affected with the MS patient. The causes of mobility deficits are varied and include muscle spasticity, weakness, tremors, ataxia, sensory dysfunction, depression, motivation, cognitive defects and pain. The physical therapist evaluates, defines and initiates treatment based on the individual’s level of need and will recommend equipment to help with mobility, including wheelchairs, walkers, canes, commodes, orthotics and lift devices such as the Hoyer. The therapists will meet with the patient and family to discuss goals and perform home evaluations to determine if modifications to their environment are needed. Recommendations may include placement of a ramp or arrangement of furniture to allow ease of access. Pain management with use of analgesics as prescribed to offset discomfort is important. Always interact with the patient and family to include them in decisions regarding plan of care.

Occupational dysfunction, including drinking, bathing, grooming, dressing, toileting, balance and transfers is common for the patient with MS. The occupational therapist will develop individual therapy strategies to improve strength and recommend techniques to facilitate personal care. This is also a good time to discuss skin issues with the patient and family as pressure sores and incontinence issues are common place. Inspect the skin often. Position changes need to be done at least every two hours. Teach the patient to observe for signs of skin breakdown. Have them use a mirror to inspect their skin. Perform and promote perineal hygiene. Climate temperatures can pose a problem as they are heat sensitive. Keeping cool is important. Measures to use include air conditioning, cold beverages, thin clothing and ice.

Speech disorders involving memory, cognition, visual disturbances and dysphasia can often occur. A memory book is a tool that is implemented for time, date, recall of events, scheduling and so forth. Since disease onset occurs at a younger age, speech and intelligence are usually intact. Therefore that part of speech therapy may not be needed. Swallow evaluations are done in those patients who manifest dysphagia or difficulty in managing their secretions, fluids or food. Swallowing guidelines are then implemented to prevent aspiration or pocketing of material. Supervision at mealtimes and with drinking fluids may be indicated. Feeding tubes may be necessary to maintain nutrition and fluid requirements. Visual changes may require a new prescription as well as adaptive devices such as large print materials with plain black lettering. Other strategies include organization of living space and developing consistent daily routines. Give simple and concise directions. Include the family, significant others and friends in the plan of care. They are a valuable resource to understand the function level and routines of the MS patient and can help develop a routine that is workable to their lifestyle.

Psychosocial conditions involve cognition, memory, attention, concentration, judgment, depression, anxiety and mood changes. A neuropsychology consult is appropriate to establish the psychological impairment to allow the team members (physicians, nursing, therapy services, clergy, family and the patient) to form the best treatment plan.

Keep in mind that the MS patient is often young. While speech and intellect are usually intact, memory and cognition skills may be impaired. This condition exacerbates with the aging process. Remind the patient of care given or treatment scheduled. A memory book is a tool that is implemented for time, date, recall of events, scheduling and so forth. The memory book is a useful tool to promote compliance. The nurse should interact but not react to the patient’s misconceptions. Allowing the patient to take part in care decisions helps increase his or her self-worth.

MEDICATIONS

Medications used to treat MS are Betaseron, Rebif and Copaxone which are given S/Q. Avonex, Novantrone and Tysabri are given by IM injection. Side effects include cardiac arrhythmias, cardiotoxicity, cardiovascular disorders, chest pain and palpitations. Other symptoms to watch for are throat constriction, dyspnea, and flu-like symptoms that include muscle aches, headaches, fever, chills and fatigue. Assess for UTI, abnormal menstruation, and psychological disorders such as depression or anxiety. Review lab results for abnormalities of either hematologic or hepatic function. Finally, evaluate injection reactions...
that could be local or systemic, including flushing or urticaria. Ice can be applied to the injection site both before and after administration of medication to prevent pain and redness.

Timely administration of medications is imperative. Pain control, bowel and bladder maintenance, depression or anxiety relief are continual concerns. Pain is derived from muscle spasticity, positioning or is nerve-based. It is important to be able to control pain to promote adherence to therapy routines and daily living activities. Late administration or skipping medication altogether can make the difference in controlling muscle spasticity, mood control and alleviating pain. Many patients will express the difference it makes in getting their medications on time vs five minutes off schedule. Additionally, keep in mind the side effects of any medications in use. Are you in a vicious cycle of medicating for pain but having constipation as a result, requiring another intervention? Are you treating a depressive disorder but now the patient has become more somnolent? Are respirations impaired, requiring resuscitation? Be knowledgeable of the uses, indications and adverse reactions of the patient’s medications.

BLADDER AND BOWEL DYSFUNCTION

Bladder dysfunction is a common problem in MS and includes frequency, urgency, incontinence, inability to start or stop a stream, retention, nocturia and spasticity. What do we, as nurses, do to help patients with this problem that can be quite embarrassing? We can assess bladder status every 4–6 hours and place them on timed toileting schedules; usually every two hours during the day and every four hours at night. If the patient has not voided or voided only small amounts then check the bladder by measuring the post-void residual. If the bladder shows greater than 350ml the patient needs straight catheterization. Educate the patient on the proper technique of straight catheterization and signs of UTIs. Encourage drinking adequate fluids. Indwelling catheters, such as supra-pubic, may be an option. While the chances of UTIs are greater with catheter use, they can reduce dribbling or urgency which are problems that can make a patient reluctant to participate in social situations. Anticholinergic medications may be ordered as they facilitate urine flow by relaxing the sphincter; side effects are dry mouth and constipation. To reduce UTIs, try cranberry juice or caplets and limiting caffeine. Encourage the use of protective undergarments such as pull-ups or Depends to absorb urine and keep it away from the body. It is important to teach skin care and hygiene management to reduce chance of skin breakdown.

What are the usual reasons for bowel dysfunction? Decreased mobility, medications, poor fluid intake and lack of fiber in the diet can lead to either constipation or diarrhea. What can we do? Abdominal assessments should include palpation to determine if the abdomen is soft, hard or tender. Measure the abdominal girth. Is the patient flatulent? Are they having diarrhea because they are impacted? Why are they constipated? What is their normal routine? Initiate a bowel program that includes scheduled toileting. Are medications to control diarrhea, or to initiate or soften stools ordered? The patient may need to be taught digital manipulation. A bowel program that is initiated at the same time every day can lead to a desired pattern for elimination. The dietician can assist with nutritional management to include the bulk and fiber that is needed. Encourage adequate fluid intake. The ability to become more mobile will also facilitate bowel elimination.

CONCLUSION

What does it mean to you to be a care provider? Are you on autopilot as you begin performing your work, or do you begin by introductions and explaining what is to be done and the patient’s role? Keep in mind, the psychological aspect of the disease can cause emotional disorders and cognitive deficits that impair memory and create the need for repetition. The MS patients may have substance abuse histories that add to the dilemma. The use of memory books or being in an environment that is quiet as well as limiting distractions is helpful. Give simple instructions or augmentative material that is easily understood. When we begin educating patients about the disease process, medications, treatment plan and so forth, teach the importance of adherence.

As nurses working with patients with MS, or any disease for that matter, we act as care providers, facilitators, advocates, educators, counselors and innovators. These six categories merge together in our jobs. Multiple sclerosis patients feel a loss of control as their bodies have made altering transformations.
that drastically affect all avenues of their lives. They need to understand they do have choices. Fostering the nurse-patient relationship is vital to establishing trust in delivering care.

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REFERENCES


A 57-Year-Old Man Presents with Worsening Shortness of Breath and Fatigue over Ten Days

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A 57-Year-Old Man Presents with Worsening Shortness of Breath and Fatigue over Ten Days

We present an interesting case of anemia as part of the monthly clinicopathological conference (CPC) of the University of Illinois College of Medicine. In this conference, a clinical faculty member is presented with a case of which he or she has no prior knowledge and then proceeds to describe the clinical reasoning involved in reaching a final diagnosis. This case was discussed in April 2010.

DISCUSSANTS

Chief Discussant: Ronnie Luyun MD
Pathologist: Ike Uzoaru, MD

CASE PRESENTATION

A 57-year-old male presented to the emergency department and later was admitted to the hospital for evaluation of progressively worsening fatigue and shortness of breath. The patient was in his usual state of health until 10 days prior to admission when he experienced a mild sore throat and headache which resolved spontaneously. However, since that time he noticed constant fatigue which was progressively worsening. The patient also complained of shortness of breath even on mild exertion and occasional light headedness. He reported subjective low grade night time fevers and sweats. In the three days before hospital presentation, the patient's skin had become noticeably yellow and urine was colored brown.

On review of systems, the patient denied experiencing similar symptoms in the past. He denied chest discomfort, cough, abdominal discomfort, nausea or vomiting, change to bowel habits, and skin changes such as rashes or easy bruising. The patient was unaware of any recent sick contacts and denied travel outside the US since immigrating or any changes to medications. The remainder of a detailed review of systems was non-contributory.

Medical history was significant for gout. The patient's only medication was allopurinol. He had immigrated to the US approximately a year before presentation. The patient was unemployed and living with his wife, who is employed as a nurse. He denied use of tobacco or alcohol.

DISCUSSION

The key features in the presentation include worsening shortness of breath, fatigue, jaundice, dark colored urine, and low grade fevers. The differential diagnosis for progressively worsening dyspnea with fatigue could be quite extensive given the underlying physiologic mechanisms responsible for it. Cardiac and respiratory disorders are the most common causes though other less common but important causes like anemia should be considered. The initial step in the evaluation of red to brown urine is centrifugation of the urine to see if color is in the urine sediment or the supernatant. In hematuria, the supernatant is clear. A red to brown supernatant that is positive for heme by dipstick is due to myoglobinuria or hemoglobinuria. Jaundice can be classified into unconjugated hyperbilirubinemia and conjugated bilirubinemia. In the event of hemoglobinuria the likely cause of jaundice would be a disorder causing unconjugated hyperbilirubinemia.

CASE PRESENTATION

The patient was afebrile on presentation. He was tachycardic (pulse 102) and tachypneic (respiratory rate 20). Blood pressure was 100/70 mmHg. Oxygen saturation was 98% breathing room air. Physical exam was significant for icterus and generalized pallor. No lymphadenopathy was appreciated. Breath sounds were clear, and no murmurs, rubs, or gallops were noted on cardiac auscultation. Abdominal examination revealed an enlarged spleen palpable 4 cm below the left costal margin. No hepatomegaly was appreciated. The remainder of examination was unremarkable.
**DISCUSSION**

Pallor makes it likely that tachycardia and tachypnea are due to anemia. Icterus and splenomegaly certainly point to increased extravascular destruction of red blood cells.

**CASE PRESENTATION**

Hematological studies on admission revealed a severe normocytic anemia with hemoglobin 3.3 g/L (13–17) and hematocrit 13.5% (41–50) (mean corpuscular volume [MCV] 98.2 fL). White blood cell count was 15,500/mm3 (52% neutrophils, 7% bands, 29.7% lymphocytes, 31% monocytes). Absolute reticulocyte count was high at 5.52% (0.5–2.0) and reticulocyte index was 2.2 (1.0–2.0). Serum chemistries revealed hyponatremia (123 mM, 135–145) and hypochloremia (90 mM, 95–109). Other electrolytes and serum creatinine were unremarkable. Alkaline phosphatase, transaminases, total protein, and albumin were within their respective laboratory reference ranges. Total and direct bilirubin were elevated at 3.3 mg/dL (0.3–1.0) and 2.6 mg/dL (0.0–0.3), respectively. Coagulation studies revealed a modestly elevated international normalized ratio (INR) of 1.6 (0.9–1.3) and activated partial thromboplastin time (aPTT) of 29.6 seconds (25–35).

**DISCUSSION**

With such severe anemia the first step in evaluation is to obtain a peripheral blood smear. Hemagglutination at room temperature which resolves on warming the slides is an important diagnostic clue to the presence of cold agglutinins. It is also important to exclude schistocytes. Increased MCV could be a spurious finding in acute hemolysis. With an elevated total bilirubin, other laboratory findings to support a hemolytic process include decreased serum haptoglobin, increased lactate dehydrogenase (LDH) and urinalysis (UA) to look for hemoglobinuria. A test for fecal occult blood should be obtained in order not to miss concurrent gastrointestinal bleeding. The direct antiglobulin test (Coombs’ test) is important at this stage to confirm an immune hemolytic anemia. If Coombs’ test is positive, the next step would be to identify the type of antibody responsible for hemolysis.

**CASE PRESENTATION**

Temperature dependent red blood cell agglutination is shown in Figure 1. There were no schistocytes. Serum haptoglobin was less than 6 mg/dL (36–195), and LDH was elevated at 1145 IU/L (132–268). Coombs’ test was positive for anti-C3d antibodies. Fecal occult blood was undetectable. Urinalysis was notable for large blood, but few red blood cells were seen on microscopy.

**DISCUSSION**

Agglutination of red blood cells at room temperature which resolves upon warming the slides is a strong diagnostic clue for the presence of cold agglutinins. Coombs’ test, also known as the direct antiglobulin test (DAT), is performed with the patient’s red cells washed free of adherent proteins and reacted with anti-human globulin (Coombs’ reagent). If agglutination takes places then it indicates that they are autoantibodies (usually IgG class) and/or complement present (C3d). The sample is then tested separately with reagents specific for anti IgG and anti-C3d. The patient’s findings are confirmative of a cold agglutinin autoimmune hemolytic anemia. The next step would be to check cold agglutinin titers.

There are two major types of cold agglutinin disease, cold agglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH). The disorders are idiopathic or secondary to another underlying disorder. Common secondary
causes include lymphoproliferative disorders, infections, and autoimmune diseases. To evaluate for potential etiologies of cold agglutinin disease several laboratory tests and imaging studies should be performed. Testing for evidence of *Mycoplasma pneumoniae*, Epstein-Barr virus (EBV), cytomegalovirus, herpes simplex virus, varicella-zoster virus, rubella virus, parvovirus, human immunodeficiency virus (HIV), and hepatitis C should be performed depending on clinical circumstances. Screening for anti-nuclear antibodies and lupus anticoagulant should be done to evaluate for autoimmune etiologies. Imaging should include plain films of the chest and/or computed tomography (CT) of the neck, chest, and abdomen to search for evidence of infection or lymphadenopathy.

Many lymphomas involve the spleen and present with splenomegaly. Diffuse large B-cell lymphoma is the most common lymphoma in adults in the US, but it does not commonly present with splenomegaly in the absence of prominent nodal and extra-nodal disease and typically produces mass lesions within the spleen rather than diffuse enlargement. Follicular and mantle cell lymphoma often present with splenomegaly, but both usually also have prominent generalized lymphadenopathy. Chronic lymphocytic leukemia or small lymphocytic lymphoma is a common indolent B-cell neoplasm in patients older than 50 years that frequently involves the spleen as well as peripheral blood and lymph nodes. Lymphoplasmacytic lymphoma typically infiltrates the bone marrow, lymph nodes, spleen and other organs and often produces an immunoglobulin M (IgM) paraprotein, a syndrome known as Waldenström's macroglobulinemia. Splenic marginal-zone lymphoma is a rare indolent B-cell lymphoma that most commonly involves the spleen and bone marrow. Patients typically present with splenomegaly, minimal lymphadenopathy and autoimmune hemolytic anemia.

**CASE PRESENTATION**

Cold agglutinin titers were significantly elevated at 1:512 dilution (< 1:32). No lymphadenopathy of the neck or chest was apparent on initial CT imaging, though splenomegaly without lymphadenopathy was eventually confirmed on a CT scan of the abdomen. Work up for infectious etiologies was negative except for increased titers of immunoglobulin G (IgG) EBV cap AB antigen (1:10,240 dilution). However, IgM antibodies were undetectable, and the elevated IgG titer was felt only to reflect prior EBV exposure. PCH was ruled out with a negative Donath Landsteiner Antibody test. Flow cytometry immunophenotyping (FCIP) of the peripheral blood revealed a predominant population of monoclonal B-cells, lambda light chain and lymphocyte markers including CD19 and CD20. The findings on peripheral blood FCIP were confirmed by flow cytometry on a bone marrow aspirate obtained on hospital day three. (Figure 2)

The patient was admitted to the intensive care unit. He received 4 units of packed red blood cells (PRBC) hospital day one that increased his hemoglobin to 6 g/L. High dose intravenous methylprednisolone was initiated on hospital day two followed by high dose oral prednisone. On day two the patient's hemoglobin dropped to 4 g/L, and he required daily transfusions during the first five days of hospitalization due to ongoing hemolysis. Plasmapheresis was initiated on day two and continued for a total of five days. Rituximab, Danazol, and cyclophosphamide were added to the patient's treatment regimen on hospital days three, four and five, respectively. Despite plasmapheresis, immunosuppressive therapy, and daily transfusions, anemia (hemoglobin 5–6 g/L) persisted and markers of hemolysis (LDH, haptoglobin) remained abnormal consistent with a continuing hemolytic process. The patient was transferred to a tertiary care center on hospital day five.

**Figure 2.** A: Bone marrow aspirate under high power showing erythroid hyperplasia (pink areas) and immature lymphoid cells (blue areas). B: Bone marrow aspirate under high power demonstrating lymphocytes stained brown with immunostain CD-20.
At the tertiary care center, the patient continued to require daily PRBC transfusions. Repeat bone marrow biopsy showed pathology consistent with non-Hodgkin’s large B-cell lymphoma. Staging CT again revealed splenomegaly without lymphadenopathy. Whole body positron emission tomography (PET) imaging showed increased uptake of fluorodeoxyglucose (FDG) in the spleen and mild, diffuse increased FDG uptake in the axial skeleton. Two cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) were administered, and anemia stabilized. Unfortunately, hemolytic anemia recurred shortly after hospital discharge. Splenectomy was performed during the second hospital admission, and post-operative pathology confirmed large B-cell lymphoma. After a brief remission, hemolytic anemia recurred. No etiology was identified, and the patient became transfusion dependent. He expired just four months from initial presentation and diagnosis.

**FINAL DIAGNOSIS**

Cold agglutinin autoimmune hemolytic anemia due to large B-cell lymphoma involving the bone marrow and spleen.

**DISCUSSION**

Immune hemolytic anemia (IHA) occurs when IgG and/or IgM antibodies bind to red blood cell (RBC) surface antigens and initiate RBC destruction through the complement and reticuloendothelial systems. Autoimmune hemolytic anemia (AIHA) is characterized by the production of auto-antibodies against RBC antigens. AIHA is a fairly uncommon disorder with an incidence of 1–3 cases per 100,000 per year. Classification of AIHA is presented in the Table. Depending on the patient population studied, a secondary cause of AIHA is determined in 20–80% of patients. Lymphoproliferative disorders are the most common secondary cause of AIHA. Other etiologies include autoimmune disorders, infections, immunodeficiency disorders, and solid tumors.

Cold hemagglutination was first reported by Landsteiner in 1903 and found to occur in humans in 1918. The association of cold hemagglutination with hemolysis was first described in 1937 by Rosenthal and Corten, and cold agglutinin hemolysis caused by monoclonal antibodies was reported in 1957. The term “cold” is primarily derived from immune biology as cold agglutinins bind to erythrocyte surface antigens at a temperature optimum of 0–4°C.

Cold agglutinin disease (CAD) is an extravascular immune hemolytic anemia caused by IgM class monoclonal antibodies that accounts for 16–32% of AIHA cases. CAD has traditionally been classified into a primary or idiopathic type and a secondary type most often associated with malignant diseases such as lymphomas. The prevalence of “idiopathic” primary cold AIHA is 1.6/100,000 and the incidence is 0.1/100,000/year.

Patients with idiopathic CAD are typically middle aged or elderly. Clinical manifestations of CAD vary significantly from patient to patient depending on the thermal range of the cold antibody. Idiopathic cases are often indolent. Signs and symptoms include fatigue, dyspnea on exertion, weakness, dark urine, acrocyanosis, pallor, jaundice, hepatosplenomegaly and lymphadenopathy.

<table>
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<tr>
<th>Table. Classification of autoimmune hemolytic anemia</th>
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<tr>
<td>Warm antibody AIHA</td>
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<tr>
<td>Idiopathic</td>
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<tr>
<td>Secondary (eg, chronic lymphocytic leukemia, lymphomas, lupus)</td>
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<tr>
<td>Cold antibody AIHA</td>
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<tr>
<td>Cold agglutinin syndrome</td>
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<tr>
<td>Idiopathic</td>
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<tr>
<td>Secondary (eg, Mycoplasma pneumoniae, Epstein-Barr virus, other viral infections)</td>
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<tr>
<td>Malignant disorders (eg, lymphoproliferative disorders)</td>
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<tr>
<td>Paroxysmal cold hemoglobinuria</td>
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<tr>
<td>Idiopathic</td>
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<tr>
<td>Secondary (viral syndromes, syphilis)</td>
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<tr>
<td>Combined cold and warm AIHA (“mixed AIHA”)</td>
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<td>Drug induced immune hemolytic anemia</td>
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Autoagglutination of anticoagulated blood samples as blood cools to room temperature is characteristic and frequently the first observation made to suggest the diagnosis. Spherocytosis and anisocytosis are seen on peripheral blood smears. Bone marrow aspirates show a variable degree of erythroid hyperplasia and a slight increase of lymphoid cells. The direct antiglobulin test (DAT) is positive with anti-C3 sera but negative with anti-IgG sera. A cold agglutinin titer >1:256 dilution also helps confirm the diagnosis.5

Most patients with idiopathic CAD experience a fairly stable mild to moderate anemia and suffer little or no disability. Though classified as a chronic hemolytic anemia without precipitating cause, recent studies have demonstrated that most idiopathic CAD patients have evidence of subclinical non-Hodgkin’s lymphoma (NHL) or monoclonal gamopathy of uncertain significance (MGUS).4 Indolent NHL progresses to diffuse large cell lymphoma in a median time of five years.

CONCLUSION

Although the occurrence of AIHA in patients with NHL is well known, little is published regarding the impact of AIHA on the clinical course of NHL patients. In a small retrospective study that included 16 patients, Sallah and colleagues found that the co-occurrence of AIHA and NHL shortened NHL survival time.6 Based on these findings they recommended immunomodulators such as cyclosporine for treatment of patients with NHL who develop AIHA to control hemolysis as rapidly as possible. This group also recommended that AIHA be included in the risk stratification of NHL patients as an adverse prognostic factor.

Management for CAD is dependent on etiology and severity. Idiopathic CAD patients typically have mild anemia, and avoidance of cold exposure is the primary therapy.1 However, the basis for this common recommendation is primarily anecdotal.3 Folic acid supplementation is also recommended for these patients.1

Treatment of secondary CAD is directed at the underlying cause.3 The hemolysis of CAD is caused by activation of the complement system and complement-mediated phagocytosis in the liver, explaining in part why splenectomy is not effective treatment.5 Glucocorticoids are also rarely helpful. Recognition of CAD as a clonal lymphoproliferative CD20 B-cell disorder has led to attempts at treatment with the monoclonal anti CD-20 antibody rituximab. Several centers have reported that rituximab improves the therapeutic response to the disorder.3 In particular, addition of rituximab to the CHOP regimen for treatment of large B-cell lymphoma complicated by CAD as in the case of this patient has been demonstrated to increase complete response rate to treatment and prolong event free survival.1,7 Cyclophosphamide, chlorambucil, Danazol, intravenous immunoglobulin, and plasmapheresis are also used to manage cases of severe hemolysis as in this CPC case.1,7,8

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REFERENCES

Case Reports

p.45  A Review of Rare Extra-Nodal Non-Hodgkin’s Lymphoma
DIGANT BHATT, MD
VIDU MOOKALA, MD
VISHWAS VANAR, MD
FRANK J. BELLAFOIRE, MD
VAMSI K. VASIREDDY, DO
ANDY ARWARI, MD

p.48  Fulminant Purpuric Rash in a Toddler
CHRISTINE H. YANG
AMY K. MACDOUGALL, MD
M. NADEEM AHMED, MD, PHD
A Review of Rare Extra-Nodal Non-Hodgkin’s Lymphoma

DIGANT BHATT, MD; VIDU MOKKALA, MD; VISHWAS VANAR, MD; FRANK J. BELLAFIORE, MD; VAMSI K. VASIREDDY, DO; ANDY ARWARI, MD

Non-Hodgkin’s Lymphoma (NHL) constitutes 5% of all cancers worldwide. Of these, 10–35% are extra-nodal in origin. Renal involvement in lymphoma occurs in 30–60% of cases as per a 2008 report. Primary renal lymphoma is a rare entity defined as NHL arising from renal parenchyma, not resulting from invasion of an adjacent lymphomatous mass. Common presenting symptoms include flank pain, renal insufficiency, hematuria, fever, and weight loss. In the absence of chemotherapy, it can disseminate rapidly from the primary site and 75% of patients die within a year.

CASE DESCRIPTION

A 35-year-old man with a significant history of diabetes mellitus 2 and hypertension presented with a 30 pound weight loss in the last 6 months, bilateral facial weakness with dysphagia, dysarthria, and gradually increasing intermittent bilateral flank pain for one month. He had an episode of hematuria four months prior to this hospitalization.

On examination, right lumbar tenderness was present. Neurologically, he had cerebellar nystagmus, opsoclonus, facial diplegia, bilateral facial numbness, palatal weakness and truncal ataxia. Abdominal CT showed a 14x10 cm right renal mass. (Figure 1) MRI brain showed T2 flair hyperintensities involving genu, inter-body and splenium of corpus callosum, periventricular deep white matter surrounding lateral ventricles, optic tract, hypothalamus, superior cerebellar peduncle, right cerebral peduncle, bilateral middle and inferior cerebellar peduncles, and upper medulla. (Figures 2,3) The CT of the chest did not show evidence of any primary or metastatic tumor. Infectious disease workup for HIV, hepatitis B, Lyme titer, HSV 1 and HSV 2, VDRL and mycoplasma antibody were negative. Cerebrospinal fluid analysis showed lymphocytic pleocytosis, high protein with normal glucose, negative cryptococcal and lyme antigens and negative anti-Ro, Hu, YO and Ma2 antibodies. Based on the MRI findings and clinical presentation, a diagnosis of paraneoplastic brainstem encephalitis was made.

Figure 1. Figure 2. Figure 3.
Pathology of the resected right kidney showed features of a large lymphocytic infiltration. (Figure 4) Subsequent immunohistochemistry was positive for CD 20, CD 10, and BCL-6 consistent with diffuse large B-Cell lymphoma. (Figures 5, 6, 7) Patient was started on Rituxan, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy. Despite chemotherapy, a repeat MRI brain showed progressive bilateral medial temporal lobe involvement interpreted as limbic encephalitis. Due to worsening mental status, the patient was transferred to the intensive care unit where he passed away due to respiratory failure.

**DISCUSSION**

Extra-nodal presentation of NHL occurs in 25–35% of cases, and the most common sites involved are stomach, skin, small intestine, breast, thyroid, lung, heart, liver, genitourinary tract, adrenals and bones. Primary renal lymphoma is a rare type of extra-nodal NHL constituting 0.7% of all extra-nodal lymphomas. It is very aggressive and associated with high mortality. There are three criteria for diagnosing primary renal lymphoma: (1) lymphomatous renal infiltration, (2) non-obstructive uni- or bilateral kidney enlargement, and (3) absence of extra-nodal localization at time of diagnosis. Using the above criteria, of all the 60 cases originally reported, only 28 cases met the diagnostic criteria. Histopathologically, renal lymphoma usually of small cells (Burkitt’s) or large B-cell type and will be positive for CD 20 and CD 10 upon immune-histochemical examination.

Cases of primary renal lymphoma with paraneoplastic brainstem and limbic encephalitis have been reported. Brainstem encephalitis is characterized by nystagmus, opsoclonus, cranial nerve paresis, dysarthria, dysphagia and central autonomic dysfunction. Limbic encephalitis is characterized by a subacute onset of short-term memory loss, seizures, confusion, and symptoms of hypothalamic dysfunction. MRI of the brain will show unilateral or bilateral medial temporal abnormalities in limbic encephalitis. Our patient was a unique example of both, as he initially presented with nystagmus, opsoclonus, and facial diplegia, and during his hospital course progressed to altered mental status and confusion.
CSF analysis in paraneoplastic syndrome will show an inflammatory picture in 80% of cases with mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), increased protein levels and variable presence of oligoclonal bands (due to intrathecal synthesis of IgG). These types of paraneoplastic neurologic syndromes are associated with presence of Anti Hu, Ma2, Yo, Ro antibodies. The presence of anti-neuronal antibodies in serum or CSF may help in making diagnosis but they are positive in only 60% of cases. Therefore it is important to exclude other differential diagnoses that can mimic the same neurological picture. In our case, CT of the whole body was performed and found to be negative for any other primary or metastatic disease. Infectious workup for HIV, hepatitis, fungal serology, Lyme serology was negative and CSF examination for infectious etiology was also negative. The ACE level was checked to rule out sarcoidosis (low sensitivity, high specificity) and was negative. The diagnosis of paraneoplastic encephalitis was made due to lack of evidence for other causes including other malignancies (especially small cell lung cancer, breast cancer, etc.). The cause of paraneoplastic syndrome with primary renal lymphoma has not been well established yet. Encephalitis associated with such paraneoplastic syndrome responds poorly to treatment, and the role of plasmapheresis, IVIG and immunosuppressive therapy has not been established.

**CONCLUSION**

There is no solid evidence that can establish the predisposition for development of primary renal lymphoma. Reported cases have been increasing since 2000. Paraneoplastic syndromes have been reported to be associated with primary renal lymphoma. **Despite chemotherapy, this tumor is very aggressive and there is a need for further research into treatment options.**

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**REFERENCES**

Fulminant Purpuric Rash in a Toddler
CHRISTINE H. YANG; AMY K. MACDOUGALL, MD; M. NADEEM AHMED, MD, PHD

A previously healthy 15-month-old male born at 36-week gestation presented to an outside emergency department with a 1-day history of low-grade fever, nasal congestion, cough, and worsening maculopapular erythematous rash. He was reported to have normal developmental milestones and up to date immunization except his first MMR vaccine. Patient did not attend day care and there was no recent history of travel or sick contacts in the family. His temperature was 104°F, heart rate was 200 beats/minute, and blood pressure was not measurable.

CASE REPORT
Within the next few hours, the rash became generalized and progressed to purpuric lesions. An intraosseous line was accessed and crystalloid fluid was administered, along with intravenous ceftriaxone, vancomycin, and dexamethasone. He was then airlifted to our facility’s intensive care unit. Initial physical assessment was significant for a toxic-appearing child with a temperature of 103.1°F, heart rate of 220 beats/minute, and respirations of 60 breaths/minute; neither blood pressure nor pulse oximetry could be detected. There were generalized purpuric lesions in his entire body, with predominance over the face, torso, and lower extremities. (Figure 1) He was cyanotic with poor peripheral perfusion and impalpable distal pulses. He was emergently intubated and placed on mechanical ventilation, along with central venous and arterial catheters. Central venous pressure was measured to be 3 cm H2O. Complete blood count was significant for leukocytosis 22250 cells/mm3 with 20% bands, decreased hemoglobin 10.2 gm/dL, decreased hematocrit 29.7%, and thrombocytopenia 34,000 platelets/mm3. Complete metabolic panel was significant for hyponatremia 128 mmol sodium/L, azotemia with BUN 27 mg/dL, and elevated AST 99 IU/L. Coagulation profile revealed the presence of disseminated intravascular coagulation, with significantly elevated INR 3.7, and prolonged PTT 89.8 seconds, depleted fibrinogen 64 mg/dL, in addition to his thrombocytopenia. Arterial blood gas analysis revealed compensated metabolic acidosis, with pH 7.35, pCO2 20 mmHg, HCO3 11 mmol/L, and base deficit 12 mmol/L. He was stabilized initially with copious volume expansions, and dopamine, nitroprusside and milrinone infusions to achieve adequate blood pressure. His condition was too labile to attempt lumbar puncture, but latex agglutination studies from the referring hospital detected Neisseria meningitidis antigens of serogroups C and/or W-135 in serum and urine. He was given a ten day course of intravenous ceftriaxone, and high-risk contacts received oral rifampin prophylaxis.

The patient’s hospital course was complicated by several factors. His anemia and thrombocytopenia initially worsened, with hemoglobin decreasing to 7.5 g/dL on hospital day two, and platelets decreasing to 8000 platelets/μL on day four. This was treated with multiple infusions of packed red blood cells, fresh frozen plasma, and platelets. His liver enzymes also initially continued to increase, peaking on day three with AST 2780 IU/L and ALT 2087 IU/L, before trending towards normal, which suggested ischemic liver injury. Additionally the patient’s ears and lower legs became increasingly cold, hard, and discolored, and creatine kinase was found to be massively elevated at 145,900 IU/L. Later his areas of purpuric skin began forming small blisters that eventually progressed to large, tense bullae. (Figure 2) Despite precautions, the bullae began to slough off, leaving significant areas of denuded skin. He was transferred to the regional intensive care burn unit where he eventually required bilateral amputations below the knee and reconstructive surgery for
the external ears. At last follow-up he was reported to be active and playing catch with burn unit staff. Long-term neurological outcome remains unknown.

**DISCUSSION**

Along with inflammation of the meninges, invasive meningococcal infection can result in fulminant septic shock, and less commonly, pneumonia, pericarditis, or septic arthritis. The incidence of invasive meningococcal infection in the US is approximately 0.5–1.1 cases per 100,000 people, with the highest incidence among children under age five. Among children, the highest incidence occurs in children <1 year old at 9.2 cases per 100,000.1 *Neisseria meningitidis*, the causative agent of invasive meningococcal disease, is an encapsulated Gram-negative diplococcal bacteria carried by asymptomatic colonizers in the upper respiratory tract. It is transmitted via respiratory secretions. The incubation period is on average four days ranging from two to ten days. While epidemics can occur, over 95% of cases are sporadic.²

There are at least 13 strains, or serogroups, of *N. meningitidis*, with classification based on chemically-distinct capsular polysaccharides. Serogroups A, B, C, Y, and W-135 are most commonly implicated in invasive disease, though the proportion of cases caused by each specific serogroup varies by location and host age group. In the US, serogroups B, C, and Y each account for approximately 30% of cases, while A and W-135 are more frequently associated with cases in the Middle East and Africa.³,⁴ Among infants, more than 50% of cases are caused by serogroup B, for which there is currently no available vaccine.⁵ Besides close living conditions, children with immunodeficiencies, such as late component complement deficiency or anatomic or functional asplenia, are at increased risk for invasive disease due to limitations in host immunity.⁶,⁷

**CLINICAL PRESENTATION AND MANAGEMENT**

Onset of invasive meningococcal infection can be abrupt, and it can progress very rapidly from onset of fever to death in as little as 12 hours. Early symptoms are typically nonspecific “flu-like” complaints, such as fever, chills, malaise, headache, nausea, and rash. The classic petechial rash of meningococcemia can develop subtly prior to any change in mental status, and may initially appear as a nonspecific macular or maculopapular rash. However, signs of meningeal irritation are not necessarily always present. A patient with fever and non-blanching petechial rash should strongly be considered to have invasive meningococcal disease until proven otherwise and appropriate testing and treatment must be initiated without delay.²

When meningococcal infection is suspected, blood and CSF cultures should be collected, though lumbar puncture could be deferred in circumstances in

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**Figure 1.**

**Figure 2.**
Regardless of obtaining samples or test results, treatment—with intravenous penicillin G, cefotaxime, ceftriaxone or ampicillin, or chloramphenicol in patients with penicillin allergy—should be started immediately upon suspicion of meningococcal infection. Droplet precautions should be maintained for at least 24 hours after initiation of antibiotics. Supportive measures and rapid transfer of the patient to a tertiary care center, preferably a facility with pediatric ICU capabilities, is recommended. Patients transferred to tertiary centers with antibiotics initiated at the referral source have better outcomes than those sent without their first dose of antibiotic. Volume resuscitation requirements are often extensive, and early intubation and ventilation should be considered to optimize oxygenation in the poorly perfused patient. Despite rapid treatment, some patients may still deteriorate rapidly and require supportive care for shock, Waterhouse-Friderichsen syndrome, multi-system organ dysfunction, ischemic extremities, disseminated intravascular coagulation, and coma. Early diagnosis, appropriate antibiotic therapy, and supportive measures have contributed to a significant reduction in overall case-fatality rates, which have decreased from 50–10%. However, about 10–20% of survivors have significant permanent neurological sequelae or limb loss.

POST-EXPOSURE PROPHYLAXIS

Antibiotic prophylaxis is indicated for high-risk contacts of individuals with meningococcal disease, as the attack rate for household contacts is 500–800 times higher than the rate in the general population. High-risk contacts include those having close contact with the infected individual over the 7 days prior to the onset of disease, and up to 24 hours after initiation of antibiotics. Ideally, all high-risk contacts should receive antibiotic prophylaxis either with rifampin (5–10 mg/kg/dose x 4 doses), or alternatively, single dose of ceftriaxone or ciprofloxacin within 24 hours of diagnosis of the index case. Prophylaxis is considered unnecessary if contact occurred more than 14 days earlier, as the incubation period for invasive disease is usually 4 days and no greater than 10 days. Antibiotic is not recommended for low-risk contacts, and mass chemoprophylaxis is not encouraged to control outbreaks, due to the cost, drug side effects, and emergence of resistant organisms.

VACCINATION GUIDELINES

There are currently two vaccines available against N. meningitidis in the US, both of which provide protection against serogroups A, C, Y and W-135 but not serogroup B: meningococcal polysaccharide vaccine (MPSV4 or Menomune®, Sanofi Pasteur Inc, Swiftwater, PA), and meningococcal conjugate vaccine (MCV4 or Menactra®, Sanofi Pasteur Inc, Swiftwater, PA). The Advisory Committee on Immunization Practices recommends routine vaccination of 11–18 year olds with MCV4 at the earliest opportunity, preferably during the routine preadolescent visit at age 11. MCV4 vaccine should be offered to all unvaccinated college freshmen living in dormitories, and to military recruits. MCV4 is also recommended for children age two to ten years old with risk factors for invasive meningococcal disease.

VACCINATION FOR CHILDREN YOUNGER THAN TWO YEARS

Currently, there are no vaccines licensed in the US for children younger than two years of age, as both MPSV4 and MCV4 are poorly immunogenic in this population. However, there is an investigational quadrivalent vaccine, MenACWY-CRM197 (Mencevo®, Novartis Vaccines and Diagnostics, Cambridge, MA), now under phase III clinical trial which has shown high levels of immunogenicity in infants two months of age and older, with comparable safety and efficacy to MCV4.9,10

CONCLUSION

Because of initial vague symptoms, rapid progression, high mortality rates, and devastating sequelae, it is critical that healthcare providers recognize this dis-
ease in its early stage, initiate antibiotic therapy and supportive care, and seriously consider referral to tertiary health-care facilities in no time if necessary.

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Research at Carle
PHYSICIAN PROFILES

p.53  Gastroenterology: Eugene Greenberg, MD
p.58  Neurology: Huan (John) Wang, MD
1. **PLEASE DESCRIBE THE TYPE OF RESEARCH YOU’VE BEEN INVOLVED WITH.**

We’ve been involved in three areas of research: translational, clinical and inflammatory bowel disease support. Translational research is basically bench to bedside. It is conducted in conjunction with the University of Illinois (U of I) and I am working with Dr. Rex Gaskins. This came about as a concept Carle CEO Dr. James Leonard had about closer cooperation between Carle and the U of I, particularly with the opening of the Institute of Genomics. Dr. Gaskins has had a long-standing interest in bowel bacteria which is applicable to my field of interest. As a result the two of us have been working for the past three years investigating hydrogen sulfide-producing bacteria and the role of mucus cells in the gut. There are different types of mucus cells which support sulfide-producing bacteria, and Dr. Gaskins had previously demonstrated in research that hydrogen sulfide is toxic to some of the cells. He has published on the fact that hydrogen sulfide can alter the genetic makeup of some of the cells, so it actually can damage the cells.

At the university Dr. Gaskins mostly works on mice and other animals while we mainly work with humans, so this merges basic science with the ability to investigate human diseases and to test some humans—which sometimes turns out differently than tests performed on mice. Our first project was a feasibility and reproducibility study. At the time of colonoscopy we obtained mucosal stool samples and mucosal samples so that we could analyze the microbiota of the colon in normal, healthy human beings undergoing screening and also analyze the type of mucus cells that were present in various portions of the colon. That study has been completed. Dr. Gaskins and I presented a poster that won a distinction

Ten years ago, we never would have thought we’d find a cure for IBD—we could only treat it. And now we’re talking about not only treating it, but trying to find a cure for it.
at the last Digestive Disease Week. The final papers are in production.

From there we moved on to our second study which looks at the role of bacteria and the role of mucus cells in inflammatory bowel disease (IBD). This is an ongoing study where we want to accumulate 150 subjects with IBD (ulcerative colitis, or Crohn's disease) or other abdominal complaints, not necessarily normal people who are having a colonoscopy as a screening procedure. We hope to get 150 patients; I think we're up to about 80 now. We've had some interesting observations in looking at inflamed vs non-inflamed tissue. We're looking at the role of bacteria and mucus cells and the role they may play in the development of cancer. That's translational research and it's strictly a basic science.

The second area of research we're involved in is clinical research, and that takes two different tracks. One track is clinical studies with pharmaceutical companies that we are compensated for participating in. These are based on pharmaceutical contracts to investigate phase III studies on new medications used in the treatment of IBD. So over the course of the couple of years we've been doing this we took part in the OSIRIS study which was a study of autologous stem cells for the treatment of Crohn's disease. I took part in several other studies including antibiotic studies for the treatment of Crohn's, tacrolimus for the treatment of Crohn's Fistulizing Disease, and a study looking at antibiotics pre-use and *C diff* colitis.

We also currently have been approved to take part in a stem cell study for ulcerative colitis run by Pfizer. We are involved now in a study of a monoclonal antibody Vedolizumab, which is a phase III study; it's an alpha4beta7 integrin blocker. Integrins basically interact with the gut to recruit inflammatory cells and lymphocytes, and this med blocks that. It works differently than the current monoclonal antibodies such as Humira, Infliximab and certolizumab. Those are all approved by the FDA but Vedolizumab is still in phase III studies, so it's not approved. From time to time we get approached about participating in other studies. A lot of them we turn down if we don't think they're appropriate or if we don't have the personnel to handle it.

Other pharmacological studies involve medications not currently available in this country. One is a domperidone study. Domperidone is a medication used for nausea and vomiting; it is not available in this country and may never be available here. There is some history behind this status. Domperidone was developed by GlaxoSmithKline and they developed two drugs: Propulsid and domperidone. They both were prokinetic agents. Propulsid received FDA approval and it was a very popular drug until it was recalled for some cardiac irregularities. Meanwhile, domperidone was used all over the world because they didn't have restrictions. So, when Propulsid was recalled, we didn't have any treatment options. We applied to the FDA for an IND number which meant that we were allowed to use domperidone and prescribe it legally, but in the form of a research study so that all subjects are monitored closely for safety and efficacy. I think we are the only ones around here who offer a research study involving domperidone. We do require certain restrictions to make it safe. We have a lot of patients with gastroparesis, and patients who have persistent nausea and vomiting that we can't control with other medicines. So we can use that drug through this strictly controlled research study.

A final piece of research is that Carle is 1 of 53 institutions around the country that is tied in with the Crohn's Colitis Foundation of America (CCFA). Basically, the CCFA is an organization that offers support and education to patients, and also conducts their own research and provides grant support for additional research. Some years ago the CCFA decided that the major medical centers might have gotten a skewed view of the disease because only the most complicated cases that couldn't be managed locally were being sent to them. And so when the CCFA did research, they found that the major institutions may be biased in their approach. The CCFA also found that these institutions weren't offering ongoing care for the disease because they were providing opinions, telling the patient what to do, then sending them back to the local hospital. They weren't offering long-term care and follow up like those of us in a community hospital such as Carle.

Several years ago, we decided to start the Clinical Research Alliance which would involve working with community hospitals and allowing them to take part in studies by pooling their data with major institutions. This provided a broader experience and spectrum of disease rather than just the most severe cases. So Carle became a member of the Clinical Research Alliance of the CCFA. And there are 53 institutions—we're the only such approved institution in Illinois outside of Chicago. The biggest study we're in now is conducting a registry of people with IBD who are pregnant. It's run out of California by Uma Mahade-
van at the University of California, San Francisco. As part of this study we try to recruit patients who are pregnant who have IBD. It basically is a study that involves interviewing patients three times during their pregnancy, and interviewing them maybe three to four times in the first year after pregnancy.

What we’re trying to determine is the role of IBD on the pregnancy and the developing fetus. Follow-up over the year after delivery is looking to see if having the disease and taking medications for the disease or having vaccinations affected the health of the baby. For years, our thought has been that a healthy mother has a healthy baby. So our approach has been that the first thing we have to do is make sure that the patient with Crohn’s disease or ulcerative colitis is healthy and then to not stop their medication or their disease may flare up. For years women would say, “I’m on an immunosuppressor—now that I’m pregnant, I’ve got to stop medicine. It’s not good for the baby.” Then they would flare. When they flared, they got sick. When they got sick they had a miscarriage or the child suffered from being born at low birth weight or pre-term. We use a lot of immunosuppressors, namely Imuran. It’s a class D pregnancy drug; however, that’s based on animal studies and based on transplant patients who have been pregnant. We know that it’s absolutely safe, so for years we have told people, “Do not stop your Imuran. Do not stop your biologic, your Remicade. We can continue it.” We have studies so far that have shown it’s absolutely safe. Again, this is going back to the fact that if you’re a healthy mom, you have a healthy child. If you’re sick, you have trouble conceiving; you have trouble with miscarriage. If you’re healthy going into the pregnancy, you’re likely to stay healthy if you continue on your medications, and therefore you’re more likely to have a healthy baby. So this is something that female patients worry about when they have IBD and get pregnant in that they don’t want to take their medications during their pregnancy. The evidence today is that you stick with your medicine. So CCFA started a study because they wanted to accumulate a large volume of patients, 2000 or so, that would be powerful enough to sufficiently and definitively state that it is safe for pregnant women to take their IBD medications. We can assure them and give direction to their physicians that it is safe to take their medications. I think this is an important study.

We also were involved with the Clinical Research Alliance of the CCFA in a study regarding the enlarging of a tissue databank. We’re trying to get involved in a study with them using methotrexate to treat ulcerative colitis. In addition, we hope to get involved in education. Unfortunately, we don’t have a local chapter of CCFA here. So we work through the chapter in Chicago—the Carol Fisher chapter. We put on the biggest conference in the country—that’s at the Rosemont Center once a year in February. It is a conference for physicians, health personnel, patients—different venues all at the same time at the Rosemont. It usually draws close to a thousand participants of patients and healthcare workers. And so we’ve set up a fund to assist patients with IBD to pay for kids who want to go to their camp. We try to encourage patients to go up to this conference and learn about their disease and we’re willing to pay their registration fees. We try to encourage health personnel, nurses to go to this and try to provide buses or transportation for them. Recently we purchased 100 patient books to hand out to patients with IBD for education. My hope is that, eventually, the new Digestive Health Center will get to the point where we have education, cancer prevention, education on healthy lifestyles and diets for all our patients. I hope to be able to recruit a full-time nurse educator who could set up meetings with patients to have a big support group. We do already have an enterostomal therapist available if someone has an ostomy.

From my standpoint the biggest challenge is changing the mindsets of physicians to understand that research is not just publicizing or publications; it makes available to them experimental medications which are not ordinarily available. I think if you want to provide better medical care, then a secondary goal needs to be established in the minds of practicing physicians, that when they see a patient who has an unusual problem, they should think — do we have a research study that can address this problem? Is there another way to try to help a patient not responding to approved drugs by utilizing experimental drugs not yet available to the general public? And I think in that way, we can establish ourselves as a center for IBD. And in fact, for other GI disease in general.

When I first came here, I would see patients from Indianapolis to St. Louis to south Chicago. But over time, as more doctors have moved into the area, now there are gastroenterologists in Bloomington, Decatur, Springfield and Danville. So how can we maintain a strong practice and presence? Well, the only way we can is if we can offer what others can’t. I think research gives us the ability to offer what they can’t and keeps us on the cutting edge of technology. So
the only way to continue growth is to offer services that are either not available in the surrounding community, or to increase our expertise. And so referring physicians would be willing to send us their complicated cases rather than have patients travel to Chicago or St. Louis. To that end, we’re working to increase the number of people that we can get here, and the procedures we can offer and the expertise, and along with that, the research. But, in many ways, we have to distinguish ourselves that we’re not just a community hospital. We’ve got to think about the things that we can offer that aren’t available elsewhere, which will assist you in finding options for complicated cases.

2. SO, TO EXPAND ON WHAT YOU WERE JUST DISCUSSING, WHAT ARE THE GOALS YOU WISH TO ACCOMPLISH THROUGH RESEARCH—NOT JUST FOR WHAT IT WILL DO FOR HERE BUT IN A BROADER SENSE—WHAT YOU PERSONALLY WISH TO ACCOMPLISH?

My goal since coming here has been to establish Carle as a center of excellence in IBD. Our database is quite large. We see a large number of those patients. We have considerable experience with IBD. And my first goal was to establish this as a center, and a center means you have to be involved in education and research. Additionally, as a member of the Digestive Health Center, I think we want other specialty areas to develop the same approach. For instance, we are the only place in central Illinois that has not only all board certified gastroenterologists, but two board certified hepatologists. We have lipid clinic, and my associate Dr. Batey, treats more chronic hepatitis than most anybody around central Illinois. We now have a second one, Dr. Habib, who is also a hepatology certified gastroenterologist. So I think we need to offer more procedures that are not available. As an aside, we’re now looking at recruiting an individual who has an excellent resume of teaching and research—good publications, nationally recognized, who can step in and perhaps be in our department and have protected time to work with the university, to teach in the medical school, and to have his or her own lab for future development, and someone who is significant enough to bring grants with them. Someone who is known on a national level, and we’re working to that end to establish that.

3. ARE THERE ANY BREAKTHROUGHS YOU’VE SEEN THAT HAVE CHANGED HOW YOU PRACTICE, OR HAVE BEEN ESPECIALLY EFFECTIVE IN YOUR DAY TO DAY TREATMENT OF PATIENTS?

Crohn’s disease was first described in 1932. It was described at Mt. Sinai hospital in New York, just shortly before I was born. I trained at both Mayo and Mt. Sinai in New York. Both locations have had long-standing interests in IBD. When I first started practice, I had nothing to treat IBD except emotional support, Azulfidine and diet. And it was that way for 10 or 15 years. After that we developed some medications rather slowly in terms of steroids and immunosuppressors that over the next 15 years could treat and alter the disease. But it wasn’t until the last ten years, we developed biologics. And now the development has progressed almost geometric so that every year we have more and different biologics developed to treat these conditions. We’ve seen treatments develop particularly over the last ten years and the future is becoming even brighter with more agents that attack the immune system. So by being engaged in research and education we have these newer drugs offered to us before they are available to the general community. I think that’s the one big benefit about being recognized and involved in treatment of IBD. I think I personally have seen a progression in treatments. Initially we treated symptomatically. Then we had drugs that treated the inflammation. Then we had drugs that decreased the immune response. We’ve gone back to drugs which actually attack the beginning of the immune response and the acquired immune system. Now we recognize that bacteria plays a role, and so we have antibiotics that can affect the interaction of the microbiota in the intestine, with the inflammatory cells in the immune reaction that takes place. And I think the future is going to be stem cells where we actually attack the genetic makeup because we know now that the cause of all these diseases is an altered immune response in a genetically predisposed individual to toxic agents in the gut of which the most likely is either bacteria or bacterial products. There are billions of bacteria in your gut and they’re separate from the rest of your human cells by a single cell layer. There are some bacteria that are good and they live well with us. But there are some that produce some type of toxic agent in someone who’s genetically predisposed gets through and sets up a reaction that causes this disease. And so we’re getting to the point where we’re now looking at disease and this new area. And if we can conquer that, then we can somehow find a cure.

Ten years ago, we never would have thought we’d find a cure for IBD—we could only treat it. And now we’re talking about not only treating it, but trying to find a cure for it. And our goals have changed. The goal used to be, symptomatic treatment—surgery when necessary. The goal then became quality of life. The goal after that became deep remission, and now
we're looking at mucosal healing back to normal. But in spite of everything we've had up until the present time, since the last ten years we've used biologics. The drugs we had we didn't alter that natural history so that Crohn's still was a disease with remissions and exacerbations that were constantly progressive, resulting in surgery in about 80 or 90% of the patients over a 30 year period. Nothing ever was able to alter that natural history.

We're now defining studies—when to use the drugs, how to use them, new drugs to use—so that our goal now is to alter the natural history. We're entering a new field, so it's exciting.

4. IS THERE ANYTHING YOU WANT TO SAY REGARDING YOUR ASSISTANCE FROM CARLE OR THE UNIVERSITY OF ILLINOIS IN YOUR RESEARCH?

Several years ago, Dr. Leonard had the vision to understand that Carle was missing an opportunity of interacting with such a great institution as the U of I, and they have phenomenal research people. But it was parallel—we didn't know the studies they were doing and they didn't know the ones we were doing. So, it was his vision to start cooperative studies in several areas—oncology, OB/Gyn and gastroenterology. There was a grant that was started by The Foundation to enable the initial studies to get started between the U of I and Carle. Initially the grants were small, so we were limited in what we could do. Nevertheless, we applied for several grants and received them through the U of I or Carle Foundation. I think we need to be more productive to get larger grants. The current study we're working on with Dr. Gaskins is a feasibility study. We had thought it would be a really big, significant study because we're also looking at genetics. We had hoped to get 250 people so it would power it sufficiently to make some conclusions. We wanted 125 IBD and 125 controls with other diseases, but because we're limited in funds, we've had to shrink that down to 150 total people. So it really becomes a study, that if successful, could be used to apply for a large NIH grant where the studies can be enlarged.

5. WHAT KEEPS YOU MOTIVATED?

Well, it's called the practice of medicine. Therefore, I'm still practicing. Most of us in medicine recognize that you learn a great deal when you get out of medical school—you're pretty smart and pretty up to date, and certainly your mind retains a lot better than when you get older. But nevertheless, I think anybody recognizes that as someone practices, he gains experience, and as he gains experience, one would hope that he gets better, and profits from the experience in treating patients. We are not computers. A lot of it is based on the individuality of the patient and our experience in dealing with certain problems. And as you practice more and more you get more and more experience. So, I continue to practice for three reasons. First, I enjoy it, and if I like golf better than this, I'll quit and play golf, but I enjoy this. Second, I think that I'm smarter now than I was 10 years ago—my knowledge base is better, my experience is better, and I think I can better deal with the diseases. And third, as long as I don't have a decrease in hand motor skills or cognitive decline, I'm doing something I enjoy. And it's very gratifying because the treatment of this disease is moving so fast that I'd hate to be in a position where I suddenly quit now and next year they have a cure for it. Or next year they've got a better drug that makes people well and I missed the opportunity of being able to use that drug. So, that's what keeps me going.
Neurology: Huan (John) Wang, MD

It is clear that the brain is very sensitive to temperature change; it can be injured with elevation and protected by lower temperature. And it is clear we know very little about it. That’s why we need a field that’s designated for this parameter as the central piece of the study.

1. PLEASE DESCRIBE THE TYPE OF RESEARCH YOU PERFORM.

It’s a new field of research, called thermal neuroscience. We have a thermal neuroscience laboratory at the Beckman Institute and clinical projects being conducted at Carle. The emphasis of the research is to investigate – at a fundamental level – what cerebral temperature means and what potential therapeutic interventions can be derived from such understanding. That’s the essence of this whole new field.

We have very little knowledge of what brain temperature means or what it is, simply because most of the time we have no access to it. We make the assumption that brain temperature is the same as rectal temp or body temp, but that’s not so. We at least know that much because of those occasions that we – as neurosurgeons – have had the privilege to put monitoring devices into the brain for severe head trauma or severe stroke. As doctors you know about blood pressure, you know about heart rate – but what do you do about the brain when the brain is the organ of injury? You need to monitor numbers yet those numbers don’t exist.

We know the brain has pressure just like the body has pressure. However, because the skull is an enclosed compartment it doesn’t expand, so the pressure phenomenon is much more dangerous for the brain than for the rest of the body. Once the pressure builds up from swelling – from bleeding, from a mass growth of a tumor, for whatever reason – the skull doesn’t yield. However, while we have an understanding of brain pressure, we have very little knowledge of brain temperature or oxygenation.
The key of brain temperature is that the thermostat, the thermal control center, is in the center of the brain so your body temperature is actually controlled by the brain. While brain temperature is a very critical parameter for the brain’s well-being, embarrassingly we know hardly anything about it. We do know the brain works to maintain its temperature within a very narrow range. It has a very strict mechanism to protect its own temperature stasis and by doing so it also controls body temperature. That’s why we are warmblooded. We are always maintaining a physiological temperature.

It has been established that brain temperature dramatically affects cerebral function. If the temperature is high, even by just one degree, people can get confused. If it goes up several degrees it can be fatal. On the other hand, low temperature has been noted to protect the brain from injury. For example, if you have a child drowning in a lake in the wintertime, you can resuscitate the child after 40 minutes of drowning and the child has a great future. However, in the summertime, after only 15 or 20 minutes the child would not survive. The brain would not take that kind of period without oxygen. The brain is the most sensitive organ to lack of oxygen and the most sensitive to temperature change. It is clear that the brain is very sensitive to temperature change; it can be injured with elevation and protected by lower temperature. And it is clear we know very little about it. That’s why we need a field that’s designated for this parameter as the central piece of the study.

When you have a heart attack you can pop an aspirin, you can call 911. If your heart stops, we have defibrillators available to shock it back in to action. We have cardiac resuscitation. But what if you are having a stroke? What if you need brain resuscitation? There is absolutely nothing; nothing at all. But we do know the brain likes to be cold when it’s injured. And as a neurosurgeon, my work is to be interventional. I would like to do something to change the outcome when it comes to brain injury. What if there was a cooling helmet you put in the refrigerator, and if you witness your family having a stroke you take it out and put it on their head? While that’s like a scientific fantasy at this point, maybe it doesn’t have to be.

So that’s where we stand now. We have a project funded by the Department of Defense. They are interested in this concept and we are testing to see if it’s feasible to put the helmet in the field. We know that cooling needs to start as soon after injury as possible. If it’s documented to be feasible and safe, then the next phase is does it work? Does it help the patient’s outcome? That’s much more of an elaborate test. You need to randomize the patient. You need to have a large number. You need to follow them out and that’s a more definitive, elaborate phase. We’re not there yet. We’re in the feasibility and safety phase.

That’s the clinical aspect of the research. Then there is the laboratory aspect of it. So in the laboratory we’re trying to develop an MRI protocol to measure brain temperature. I know I can’t directly measure brain temperature because the only way you directly measure temperature right now is to have a probe somewhere. MRI is a start to finding this. We have to know what the brain does under physiological conditions. Then we ask, how does the temperature of your brain change with different disease states? If you’re in coma? If you’re having a migraine headache or you’re having a seizure—how does that affect your brain temperature? What we’re trying to do is develop a tool to investigate the brain temperature and then understand the physiological conditions—how the brain temperature changes its spatial and temporal distribution.

2. TELL HOW YOU BECAME INTERESTED IN THIS FIELD.

When I was in training as a neurosurgery resident I would round before surgery, at about 5:30 or 6:00 in the morning and I would round in the evening after surgery. And the patients were always doing better in the morning. And that seemed so weird. You would think you’d wake them up and they would not be doing so hot but that wasn’t true. I started noticed their temperature was higher when they were not doing well; they were not quite right. So I observed this very clear correlation between your temperature and your performance neurologically. I’m talking about higher temperature—a slight fever. I thought, gee, that’s such an easy correlation, you’d think it’s easy to take care of. Then I started thinking, “Oh well, just design a helmet to cool the head that’s all I need to do.” And it turns out people have made this observation for decades. Once you realize something, you start to research into it and you realize often times you’re not the only one making the observation. A lot of people have done so too. You’re not
so unique under the sun. And then, as I looked more into it, it becomes clear that we need this field. Then I say, “Well, might as well start one.”

3. WHERE DID YOU ATTAIN YOUR RESEARCH TRAINING?
I attained my research training at the University of Illinois Peoria campus. I did my neurosurgery training there and that’s how I started. Then I did two fellowships in Boston, in the Harvard system. But the research training is more of a process.

4. DO YOU WORK SOLITARILY OR AS PART OF A TEAM?
I think nowadays it’s critical to collaborate. Because you have limitations on what’s your expertise. And sometimes the same idea can expand into a more mature idea after you discuss it with people of similar interests. In other words, if the world hates me I’ll work alone, but if not, I’ll work with other people.

5. WHAT IS THE MOST COMPELLING ASPECT OF YOUR WORK?
What the compelling aspect to the work is, is that you see the practicality of it. You see the importance of it when you interact with patients. I don’t envy the PhDs in the laboratory because they don’t get that degree of reward. They don’t interact with the patient. They may have a different reward from a different perspective, but I don’t see it from their perspective. For me it’s critical that I interact with patients. I see the practical importance of my interest in the research.

6. WHAT’S THE MOST DISAPPOINTING FEATURE?
The disappointing feature is that I constantly have to struggle to balance between clinical involvement and research involvement. Ideally I would have a perfect balance but, unfortunately, as a neurosurgeon you can’t clock out. Ideally you want to say, “Between eight and twelve I’m going to be a neurosurgeon, but between one and five, I’m going to be a scientist.” However, it doesn’t work like that. If you take out a brain tumor, you can’t clock out after surgery is done.

7. HOW HAVE YOUR FINDINGS IMPACTED YOUR PRACTICE?
First of all, at this point the field is in its very infancy. So, there are no major findings that are breakthrough. I can’t really comment on how it impacts my practice because it doesn’t—I have not applied any findings to patient care.

8. WHAT KNOWLEDGE HAS BEEN MOST USEFUL TO YOU AS YOU INTEGRATE RESEARCH INTO CLINICAL PRACTICE?
It’s actually not so much of a knowledge base as it is a perspective. Reasoning. Deduction. Logic.

9. WHAT INFLUENCE HAVE YOUR FINDINGS HAD ON HEALTHCARE IN GENERAL?
None at this point.

10. WHAT ARE THE GOALS YOU WISH TO ACCOMPLISH?
The goals I wish to accomplish would be to bring something that will be of proven benefit for patient outcomes.

11. WHAT KEEPS YOU MOTIVATED?
The interaction with the patient, with both good and poor outcomes keeps me motivated. The good ones are reinforcing my enthusiasm. And the poor ones are encouraging me to explore further for what more we can do. When it comes to head trauma and stroke, sometimes we see them three months out and you see where we certainly can do a lot better in the future.

12. WHAT IS THE SINGLE MOST IMPORTANT DISCOVERY YOU PERSONALLY HAVE MADE?
I have not had any breakthrough discoveries so far. What I have discovered I have noticed that other people have noticed too. It’s just whether or not you’re doing it—you’re following through with your observation and I’m still early in that track. In other words, I haven’t discovered anything that I find myself to be the brightest star under the sun. Somebody else has already made comments on that too.

13. HISTORICALLY, WHAT IS THE SINGLE MOST IMPORTANT DISCOVERY EVER MADE IN YOUR FIELD? HOW? WHERE? AND BY WHOM?
Well the field, the thermal neuroscience—I’m the starter of this field. Whether or not this field will flourish or die—we wait. Let’s see how history writes this book.
14. **HOW IS CARLE AND/OR THE UNIVERSITY OF ILLINOIS ASSISTING YOU IN YOUR RESEARCH?**

Carle is providing me with a fantastic array of support ranging from staffing to applying for research grants and facility-wise—in other words I’m doing both clinical arm and laboratory arm. I get a lot of support from the University of Illinois for the laboratory aspect—I have a laboratory. But Carle is providing me with all the support I need for the clinical aspect. So it’s two parallel arms going forward. That’s why I think I’m fortunate in that aspect.
Research at Carle
Current gastrointestinal and neuroscience translational and clinical research studies

p.63 Gastrointestinal
p.65 Neuroscience
## Research at Carle

<table>
<thead>
<tr>
<th>PROTOCOL</th>
<th>STATUS</th>
<th>TITLE</th>
<th>PRIMARY OBJECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>03101</td>
<td>Open, Closed to Accrual</td>
<td>The Crohn's Therapy, Resource, Evaluation and Assessment Tool Registry</td>
<td>To assess long-term safety outcomes specifically associated with the use of Remicade.</td>
</tr>
<tr>
<td>06070</td>
<td>Open</td>
<td>Genetic Variation in Mucosal Defense and Inflammatory Bowel Disease</td>
<td>To determine if defined clinical features of Crohn's Disease and/or individual colonic microbiotic status are associated with surface molecules that recognize microbial components and alert the host to the presence of bacteria or with goblet-cell specific genes that secrete the mucous coat that intestinal microbes colonize.</td>
</tr>
<tr>
<td>08153</td>
<td>Open</td>
<td>08-153 Oral Domperidone for relief of gastrointestinal disorders in patients who failed standard therapy</td>
<td>The purpose of this study is to make the use of oral domperidone available to subjects with gastrointestinal disorders who have failed standard therapy who might benefit from it.</td>
</tr>
<tr>
<td>08446</td>
<td>Open</td>
<td>Traditional Hospital Bed versus Recliner Chair in post surgical phase 2 recovery time for Laparoscopic Cholecystectomy</td>
<td>To determine if those individuals who recover in recliner chair following laparoscopic cholecystectomy have a shorter recovery time in comparison with those who recover in traditional hospital bed during Phase 2 of recovery.</td>
</tr>
<tr>
<td>09008</td>
<td>Open</td>
<td>The role of Inflammatory Bowel Disease (IBD) Serology in Predicting the Course of the Disease and Management Decisions</td>
<td>To retrospectively follow the disease course of patients with CD who underwent IBD serology testing and correlate the serology values to the aggressiveness of the disease. Secondly, to determine the role of IBD serology in categorization of patients with IC into CD or UC and thereby improve in their management.</td>
</tr>
<tr>
<td>09105</td>
<td>Open</td>
<td>Utilization of Video Capsule Endoscopy in a Community Hospital</td>
<td>To review the utility of performing VCE in a community hospital setting and identify factors which can improve its diagnostic yield. To identify the complications of VCE and factors that can predict their occurrence.</td>
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<tr>
<td>Protoclo</td>
<td>Status</td>
<td>Title</td>
<td>Primary Objective</td>
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<tr>
<td>09107</td>
<td>Open</td>
<td>To evaluate the efficacy of radiofrequency ablation using HALO technique in treatment of Barrett’s Esophagus with dysplasia</td>
<td>To study the efficacy of radiofrequency ablation in regressing dysplastic changes in patients with Low, Intermediate or High grade dysplasia, to identify the incidence of dysplasia with Barrett's esophagus in a community hospital setting, to identify potential complications of the technique in patients undergoing multiple ablations.</td>
</tr>
<tr>
<td>09117</td>
<td>Open</td>
<td>Bariatric Outcomes Longitudinal Database (BOLD)</td>
<td>The establishment of the Bariatric Outcomes Longitudinal Database (BOLD) is to study the mid- and long-term outcomes of patients who have undergone bariatric surgery in compliance with the fundamental requirements of the BSCOE. The second aim is to provide the most comprehensive database on bariatric surgery, patient outcomes and risk stratification.</td>
</tr>
<tr>
<td>09121</td>
<td>Open</td>
<td>A Multicenter National Prospective Study of Pregnancy and Neonatal Outcomes in Women with Inflammatory Bowel Disease</td>
<td>To investigate the effects of certain medications used to treat IBD on pregnancy outcome and newborn outcome to one year of age.</td>
</tr>
<tr>
<td>P06-134</td>
<td>Open, Closed to Accrual</td>
<td>A 5-Year Non-interventional Registry Study of HUMIRA® (Adalimumab) in Subjects With Moderately to Severely Active Crohn’s Disease</td>
<td>The primary objective of this Registry study is to evaluate the long-term safety of adalimumab in CD adult subjects (18 yrs and older) who are treated as recommended in the product label.</td>
</tr>
<tr>
<td>09128</td>
<td>Submitted to Carle IRB</td>
<td>Gastroenterology and Hepatology Consultations for Abnormal Liver Function Tests</td>
<td>The aim of the proposed project is to assess the health outcomes following Gastroenterology and Hepatology consultations for abnormal LFTs. The health outcomes measured will be diagnosis of liver disease, mortality from liver disease and mortality from other causes.</td>
</tr>
<tr>
<td>10009</td>
<td>Open</td>
<td>Traumatic Abdominal Wall Hernias</td>
<td>We present 10 cases of high energy traumatic abdominal wall hernias that were seen at a rural level I trauma center from 2008 to 2010. These cases will also be compared with literature. Thorough assessment and proper identification of all injuries is important in the treatment and successful management of these uncommon cases.</td>
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<tr>
<td>10014</td>
<td>Open</td>
<td>Electrophysiological Signals to Predict Age-Related Cognitive Decline</td>
<td>We will use brain electrophysiology and sophisticated measures of memory to differentiate healthy memory functioning from that in patients with mild cognitive impairment and early stages of Alzheimer’s disease, and thereby to improve the ability to identify and predict the onset of cognitive decline in humans.</td>
</tr>
<tr>
<td>10029</td>
<td>Open</td>
<td>Transient Modulations of Inhibitory Control in Children with ADHD: The Effect of a Single Bout of Physical Activity</td>
<td>The aim of this proposal is to examine the effect of a single bout of moderately intense aerobic exercise on preadolescent children with attention-deficit/hyperactivity disorder (ADHD). The investigation of the effects of a single bout of aerobic exercise on aspects of cognitive control in children with ADHD may be valuable for increasing the cognitive health and effective functioning of this population.</td>
</tr>
<tr>
<td>09010</td>
<td>Open</td>
<td>Pitch and Tonal Patterns Among Hearing Impaired Children</td>
<td>The student researcher will observe seven hearing impaired children, aged approximately six years old, enrolled in the kindergarten and first grade classes of the Carle Auditory School. The researcher will attempt to isolate pitch and tonal patterns and document their usage via audio recording and writing of field notes.</td>
</tr>
<tr>
<td>03012</td>
<td>Open, data analysis only</td>
<td>Temporal Features of Sound and Level Discrimination in Hearing-Impaired Listeners</td>
<td>The general purpose of this study is to better understand the relationship between temporal processing ability and speech recognition in hearing impaired listeners.</td>
</tr>
<tr>
<td>07031</td>
<td>Open</td>
<td>Development of Auditory Skills in Young Deaf Children with Bilateral Cochlear Implants</td>
<td>To track patient outcomes for bilateral cochlear implant recipients in a cohort of 60 children, ages 12-36 months at time of surgery, who receive two implants in the same operation or in two different surgeries with the initial fitting of the devices separated by no more than 6 months.</td>
</tr>
<tr>
<td>08002</td>
<td>Open</td>
<td>Coherent Optical Detection of Middle Ear Disease</td>
<td>To develop an otoscope that is coupled with Optical Coherence Tomography to non-invasively detect and quantify the presence of middle-ear biofilms.</td>
</tr>
<tr>
<td>08367</td>
<td>Open</td>
<td>Emergence of auditory, memory and cognitive skills in children with hearing loss</td>
<td>The purpose of this study is to study how children who use a cochlear implant in one ear and either a second cochlear implant or a hearing aid in the other ear are able to understand speech in noisy rooms.</td>
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<tr>
<td>UIUC 09021</td>
<td>Open</td>
<td>Using Non-Invasive Brain Imaging to Investigate Functional Change in Auditory &amp; Language Processing in Adult Cochlear Implant Patients</td>
<td>The purpose of this study is to obtain an increased understanding of normal auditory and language processes and changes in these processes associated with cochlear implant.</td>
</tr>
<tr>
<td>UIUC 09560</td>
<td>Open</td>
<td>MRI of the Velopharyngeal Mechanism</td>
<td>We would like to understand how particular muscles in your throat perform different speech tasks.</td>
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<tr>
<td>07040</td>
<td>Open</td>
<td>Head impacts, Accelerations and Outcomes in Interscholastic Football</td>
<td>Head Impact Telemetry Systems and standard concussion assessments will be used to detect and assess concussions during high school football practices and games.</td>
</tr>
<tr>
<td>08003</td>
<td>Open</td>
<td>Vermont Oxford Network Registry for Neonatal Encephalopathy</td>
<td>To improve quality and safety of care for infants with encephalopathy, monitor diffusion of hypothermic therapy, assess neurodevelopment outcomes of infants treated with hypothermia, and conduct research and define questions for a prospective study.</td>
</tr>
<tr>
<td>05021</td>
<td>Open</td>
<td>Attention Deficit Hyperactivity Disorder and Restless Legs Syndrome: A Familial Risk Analysis</td>
<td>To evaluate the inheritance patterns of attention-deficit/hyperactivity disorder (ADHD) and restless legs syndrome (RLS) in first-degree relatives of children who have been diagnosed with both these disorders.</td>
</tr>
<tr>
<td>00009</td>
<td>Open, data analysis only</td>
<td>A Randomized Double-Blind Parallel Placebo-Controlled Study of Dopaminergic Therapy in Attention Deficit Hyperactivity Disorder (ADHD) and Restless Legs/Periodic Limb Movements in Sleep (RLS/PLMS)</td>
<td>The first aim of the study is to determine if dopaminergic therapy is superior to placebo in treating ADHD symptoms. The second aim is to determine if ADHD improves more in the patients with PLMS/RLS than in those without PLMS/RLS.</td>
</tr>
<tr>
<td>10010</td>
<td>Open</td>
<td>Depth and distribution of the symptoms of restless leg syndrome</td>
<td>Administer a questionnaire about the depth and distribution of RLS symptoms to patients with primary RLS, secondary RLS, and mimics of RLS who meet the diagnostic criteria for RLS. It is our hope that differences in the depth and distribution of RLS symptoms will help us to more adequately discriminate patients with idiopathic/familial RLS, secondary RLS, and the mimics of RLS.</td>
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<tr>
<td>10019</td>
<td>Open</td>
<td>Is Iron Deficiency Associated with Specific Neuropsychiatric Disorders? A Population-based Study</td>
<td>The primary objective is to determine if lower iron status is associated with ADHD, MDD, GAD, panic disorder, conduct disorder, and/or tobacco dependency. A secondary objective is to determine if an optimal ferritin level is suggested from the data.</td>
</tr>
<tr>
<td>10011</td>
<td>Open</td>
<td>Variability of leg movements in restless legs syndrome</td>
<td>The goal of this study is to determine whether leg movements during sleep, including periodic leg movements in sleep (PLMS) and isolated leg movements in sleep (ILMS), are more variable for control subjects as compared to those with Restless Legs Syndrome.</td>
</tr>
<tr>
<td>10028</td>
<td>Open</td>
<td>Evaluation of a Risk Assessment Program for Post Partum Depression</td>
<td>To determine the impact of education on risk assessment of Post Partum Depression.</td>
</tr>
<tr>
<td>10051</td>
<td>Open</td>
<td>Auditory Oral Education Data Repository (Option Schools)</td>
<td>OPTION Schools will use the LSL-DR to collect, aggregate and summarize data from LSL programs to describe the population and to assess overall outcomes. Individual schools will use this program for quality monitoring of their schools.</td>
</tr>
<tr>
<td>10036</td>
<td>Open</td>
<td>fMRI in Patients with lumbar radiculopathy from a work related injury: A longitudinal Study</td>
<td>This study investigates the progression of acute pain to chronic pain in patients with low back pain and lumbar radiculopathy using fMRI.</td>
</tr>
</tbody>
</table>