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Catriona McDonald Harrop, MD, FACP, SFHM

Issue Editor
Clinical Assistant Professor

Dear Colleague,

It is my pleasure to welcome you to the latest issue of the JHN Journal.

The Department of Neurosurgery here at Thomas Jefferson University has been at the leading edge of the advancement of the medical care of the neurosurgical patient for the past decade. By creating a vibrant hospital medicine program for neurosurgery, Dr. Robert Rosenwasser has paved the way for a successful collaboration between medicine and neurosurgery. This issue of the JHN journal highlights that special relationship.

Here at Thomas Jefferson University our surgeons and hospitalists work as one team co-managing the patients and their diverse needs. As a tertiary referral center, our teams see a significant number of patients with both medical and neurosurgical disease. This issue highlights the patients that we encounter and their special considerations.

I am very proud of the work that we do, and the collaboration of our teams. I hope you find these articles to be interesting and useful.

Sincerely,

Catriona McDonald Harrop, MD, FACP, SFHM

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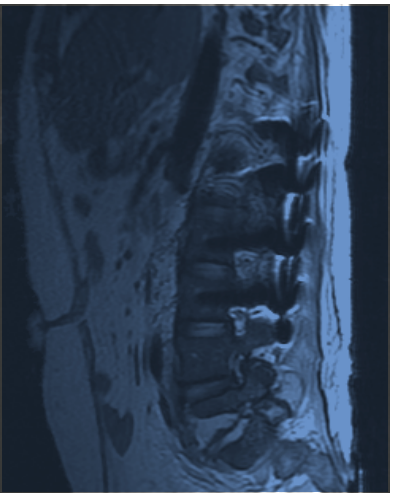
Table of Contents



Farber Hospitalist Service – Last 5 Years Of A Service Dedicated To The Medical Management Of Neurosurgical Patients
Rene Daniel; Catriona McDonald Harrop 2

Cardiac Risk Stratification of Neurosurgical Patients
Aditya A Munshi 5

Epidural Abscess of the Central Nervous System.
Katherine Belden; Jack Jallo; Linda Mwamuka 9

Spinal Metastasis – Diagnosis, Management, and the Role of the Hospitalist
Bharath Ganesh; Catriona McDonald Harrop; Jesse Edwards 15

Texbook Spotlight
Medical Management of Neurosurgical Patients 20

Management of Hyperglycemia in the Neurosurgery Patient
Rene Daniel; Satya Villuri; Kevin Furlong 21

Opportunities and Challenges – The Next 5 Years of A Service Dedicated to the Medical Management Of Neurosurgical Patients
Rene Daniel; Catriona McDonald Harrop 29

Farber Hospitalist Service – Last 5 Years of a Service Dedicated to the Medical Management of Neurosurgical Patients

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Keywords: *medical management, preoperative risk stratification, prevention, perioperative management, postoperative management*

ABSTRACT

Neurosurgery hospitalists are closely involved in management of patients that undergo neurosurgery. In this article, we outline and discuss the major aspects of the work of these physicians. We emphasize the crucial role of these physicians in both preoperative and postoperative care as well as their roles in education and research. We also highlight the work of the Farber Hospitalist Service (FHS) for the last 5 year period, and point out the differences between FHS and other neurosurgery hospitalist services nationwide. It is hoped that this article will shed light on the work of neurosurgery hospitalists and help to clarify their roles in patient care.

INTRODUCTION

In 1996 Drs. Lee Goldman and Robert Wachter coined the term Hospitalist in their seminal article for the NEJM "The Emerging Role of "Hospitalists" in the American Health Care System"[1]. Hospitalists are physicians that specialize in the care of hospitalized patients, and can come from many specialties including Internal Medicine, Family Medicine, Pediatrics and Obstetrics and Gynecology. According to recent data, there were more than 50,000 physicians working as hospitalists in the United States in 2015. Of course, there are many more hospitalists worldwide, although the exact data are not available.

For the adult medical population, Hospitalists typically care for general medicine patients and their associated medical diagnoses such as hypertension, diabetes, etc. However, in recent years, different sub-specializations emerged. For example, there are hospitalists which, together with oncologists, co-manage cancer patients. Similarly, there are hospitalists that focus on taking care of hospitalized gastroenterology patients. This type of collaboration appears to result in effective care, since Hospitalists are better attuned than specialists to the multiple medical problems that most patients have.

A new breed of Hospitalist has recently emerged; Hospitalists who co-manage neurosurgery patients. The role for Hospitalist in this setting has emerged by demand as Hospitalists provide preoperative risk stratification, manage preoperative and postoperative complications and make decisions when to involve specialists other than neurosurgeons. There are over 3500 board certified neurosurgeons in the U.S.A,[2] and many more worldwide. Of those 3500 neurosurgeons, the exact number who have a Hospitalist care for or co-manage their patients is not known. Yet it is safe to assume that a significant number have their patients cared for or co-managed by a Hospitalist. Therefore, Hospitalists play an important role in management of these patients, and their role will be discussed below. As a final note, it is important to note that these physicians are sometimes called "neurohospitalists". This is a misnomer and should be noted as such. A "neurohospitalist" is a term typically referring to a neurologist which takes care of hospitalized patients[3]. Thus, throughout this article, we will use the term "neurosurgery hospitalist" or NH when referring to an internal medicine or family medicine trained physician that specializes in the care of neurosurgical patients.

THE CLINICAL WORK OF THE NEUROSURGERY HOSPITALIST

Neurosurgery hospitalists are physicians that are trained in internal or family medicine, and have specialized in the care of the neurosurgery patient. That said, there are some important features of the neurosurgery hospitalist's work which are different from the general hospitalist. These include a focus on management of CNS infections, management of bleeding in the context of CNS surgery, management of coagulation issues, management of central fevers, management of patients on steroids and steroid-induced hyperglycemia, and many others, as outlined below. Despite the multitude of differences between the work of neurosurgery and general hospitalists, there is no specialized training for the former. At present, NH rely on their own reading and internal hospital guidelines. The Faber Hospitalist Service (FHS) of the Department of Neurological Surgery at Thomas Jefferson University is one of the few hospitalist services around the country. That said, there are unique features of this service, which so far have not been replicated by other similar services. These features, in addition to the all other services provided by FHS, will be discussed below.

Preoperative optimization

Minimizing risks is crucial for the success of a surgical procedure. To do so, it is necessary first to establish the potential risks for a given patient. This process is called preoperative risk stratification. There are inherent risks for every individual procedure. A brain surgery will have different risk than a hernia repair, due to a different organ which is treated, a

different surgical approach etc. That said, every time patient undergoes a surgical procedure, he or she will experience risks which are due to the overall health status and chronic illnesses he or she may have. While a crucial part of the preoperative examination is the evaluation of the cardiovascular health, other illnesses can also increase surgical risk. These include kidney disease, diabetes mellitus, chronic pulmonary disease and autoimmune disease.

At Thomas Jefferson University Hospital, all Neurosurgery patients are evaluated preoperatively by a Physician. These patients are evaluated in the outpatient setting for elective surgeries, and in the inpatient setting by NHs for patient transferred from other hospitals and patients admitted from the Emergency Department. NHs will refer patients to specialists if needed for additional risk stratification and optimization.

FHS has 14 full time physicians, two of which are involved at a full time basis in preoperative risk stratification of patients undergoing elective surgery. In addition, FHS is involved in preoperative risk stratification of patients admitted to the Thomas Jefferson University Hospital dedicated spine unit and the Jefferson Hospital for Neuroscience. On average (this is a conservative estimate), FHS performs this service for around 10 – 20 patients daily in outpatient setting and a similar number in the inpatient setting. This does include weekends, when these patients are evaluated in the hospital setting. Thus, FHS evaluates approximately 120 cases per week, which comes to 6.240 patients per year and 31,200 cases per last two years. This larger number, however, does not tell the full story. Risk stratification is only one part of the preoperative management by NHs in general and FHS in particular.

The second aspect of preoperative care is the optimization of the patient for the procedure. Once the risk is established, it is important to address the issues which can be improved prior to the operation. These include medication management. NHs will make recommendation which medications should be stopped prior the procedure, and the timing of the stoppage. They will also recommendations for stress dose steroids in steroid dependent patients. At the same time, they will manage medical issues which have not been properly addressed prior to procedure. These typically include diabetes mellitus management, since poor blood glucose control may negatively affect wound healing. Similarly, they will make recommendations with the respect to blood pressure management and electrolyte imbalances which are found during preoperative testing. Importantly, if a patient takes anticoagulants, they will recommend discontinuation at an appropriate time before surgery or refer the patient to a specialist. Finally, they will determine if a patient is at risk of infection (for example due to MRSA colonization of nares) and recommend appropriate treatment, and, if acute infection, recommend delaying surgery until infection resolves. In complicated cases, they recommend patient be followed by NH's once admitted to hospital.

Taken together, NHS and FHS play a crucial role in preparation of a patient for a neurosurgical procedure.

Postoperative care

Post-operatively, care for neurosurgical patients is typically managed by a team comprised of neurosurgery nurse practitioners (NPs) and residents who function under the supervision of the neurosurgery attending physician. Common areas for primary team to address are the prevention of deep vein thrombosis, pain management and wound healing. Physical and occupational therapy are also valued members of the team and help to determine the placement of the patient post discharge. In our current model the NH functions as an integral team member as co-managers. Currently we round daily at the bedside with the nurses, NPs, OT, PT and case management. Our FHS hospitalists participate in the management of blood pressure, blood glucose levels and other medical issues including postoperative infection. The FHS is involved as co-managers of the patient alongside neurosurgery, addresses in these issues at a daily basis, and again participates in care of multiple neurosurgical patients.

FHS as a primary care service for neurosurgical patients

Hospitalists traditionally participate in the care of surgical patients as consultants or co-managers in the United States health care system. FHS here, to our knowledge, constitutes an exception. Over last several years, FHS became a primary service for a number of neurosurgical patients. This model developed out of the need to care for highly medically complex patients who were being transferred to Thomas Jefferson University Hospital from outlying community hospitals, particularly those patients that have certain spine related diagnoses. Specific criteria were created by the FHS in conjunction with Neurosurgery and Orthopedic Spine where certain medically complicated patients being transferred to TJUH could be admitted directly onto the FHS. In these cases the spine surgeon acts as the consultant and the FHS as the attending. The vast majority of patients we care for are patients with infection i.e. epidural abscesses, osteomyelitis, and discitis. This model then allows the neurosurgical team to concentrate on the procedure itself, whereas NH assumes the overall management role. This approach also allows more time for the neurosurgical team to devote to the surgical procedures. In this role, since 2015, FHS took care of 1,100 primary patients, of which 300 had spinal infections including osteomyelitis and epidural abscesses. Of note, the mortality of these patients was much lower than Jefferson average of these patients at other services and the difference was statistically highly significant (unpublished data).

EDUCATION

As noted above, there are some important features of the neurosurgery hospitalist job, which are different from the general hospitalist work, and there is no specialized training for neurosurgery hospitalists. At present, NHs rely on their own reading and internal hospital guidelines, which may well differ from a hospital to a hospital.

This situation may, and likely does, result in different outcomes for neurosurgery patients. Thus, there is an urgent need for a standardized source of information for neurosurgery hospitalists, which would provide a common ground and improve their knowledge and training, in other words, a textbook. FHS realizing the need and demand, thus, together with other

services, produced the first book in the NH field. The "Medical Management of Neurosurgical Patients",[4] edited by Drs. Rene Daniel and Catriona Harrop, was published in October 2019 by the Oxford University Press. Thus, FHS started to create medical guidelines for NHs, which will help nationwide standardization of care for these patients and thus improve outcomes.

Outside of the textbook, NH's are involved in one on one training of neurosurgery NPs and residents. This is a daily process and a necessary component of the NH's work. In addition, FHS provides lectures for Nurse Practitioners and Nurse Practitioner students on a regular basis.

RESEARCH

Many, if not most neurosurgery departments are located in an academic setting, where research is an important component of their work. As all academic services, FHS is developing its own research program. This include a preoperative care studying role of new tests in preoperative risk.[5] The other areas include retrospective studies evaluating the impact of FHS on patient care, morbidity, mortality and length of stay. Finally, FHS is working of development of a research project with the Division of Infectious Diseases, which address identification of bacteria in spine biopsies using state of the art high throughput sequencing. Altogether, FHS published 16 articles this academic year, so far, with six more planned. Research emerged as an important way to contribute to the improvement of outcomes and care for neurosurgical patients.

SUMMARY

Taken together, NHs in general and FHS in particular play a very significant role in management of neurosurgical patients, as well in academic research and education. The next three articles in this issue describe management of illnesses and issues of neurosurgical patients, which are typically managed by FHS.

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Cardiac Risk Stratification of Neurosurgical Patients

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ABSTRACT

The role of an internal medicine physician in the perioperative setting includes the assessment of peri-operative risk, optimization of modifiable risk factors to decrease this risk and management of post-operative medical complications that may occur. Every patient undergoing surgery is at risk for procedural and anesthesia complications, in addition the patient is at risk of developing adverse medical events. Unlike surgical risk which is related to the procedure being performed and the risk of anesthesia, the factors affecting the medical risk are often modifiable. These modifiable risk factors form the principal basis of risk stratifying patients prior to surgery.

Neurosurgical patients pose certain unique challenges in the peri-operative setting and the pre-operative assessment forms a starting point in the prevention of not just post-operative cardiac complications but also thrombotic events and in reducing the overall morbidity and length of hospital stay.

In this chapter, we summarize our approach to the cardiac risk stratification of patients undergoing neurosurgery. We review recommendations from accepted guidelines and provide a step wise approach to the cardiac risk assessment of a patient undergoing elective surgery.

INTRODUCTION

The medical pre-operative evaluation has primarily comprised of assessing a patient's risk of developing major adverse cardiac events in the post-operative period. However, any patient undergoing surgery is exposed to a risk of several complications affecting different systems. These include pulmonary, cardiac, thrombotic, bleeding events, complications from the surgical procedure and anesthesia. The risks associated with anesthesia and the procedure itself are not modifiable and not discussed in this chapter. We cover the pre-operative assessment of a patient undergoing neurosurgery with a focus on cardiac risk assessment. Medical risks are modifiable in many cases and are affected by a patient's overall health, nutritional status, comorbid conditions and baseline activity level. The aim of this article shall be to review the most up-to-date guidelines and summarize our approach to a risk stratifying a patient undergoing neurosurgery from a cardiac standpoint.

CARDIAC RISK STRATIFICATION OF NEUROSURGERY PATIENTS

Around 235 million surgeries are performed globally every year.[1] Cardiac events are the leading cause of post-operative complications,[2] the risk of a patient developing cardiac complications depends on the patient's baseline risk. This is the principle of pre-op risk assessment and the aim of the pre-op cardiac assessment is to estimate this baseline risk and determine if the patient needs additional cardiac testing. The ACC/AHA guidelines form the cornerstone of pre-op assessment today. Per these guidelines, the risk stratification approach should consider the type of surgery, the urgency of the procedure being performed and clinical status of the patient.[3] The guidelines define low risk procedures as those with a <1% risk of major adverse cardiac events (MACE) based on combined patient and surgical characteristics. Whereas, the elevated risk group comprises of those with a ≥ 1% risk of MACE3. The latest ACC/AHA guidelines, published in 2014, stratify procedures into these two categories. The approach to the patient depends on the category they fall into.

The timing of many neurosurgical procedures is urgent or emergent and this makes them high risk from the cardiac standpoint even if the patient has a low baseline risk. In addition, a large subset of the neurosurgical patient population is chronically ill and with multiple comorbid conditions that increases the risk of surgical complications.[4,5]

CHOOSING PATIENTS WHO SHOULD UNDERGO A PRE-OPERATIVE ASSESSMENT:

In choosing patients who should undergo a cardiac pre-operative assessment, certain factors need to be considered. Urgent and emergent surgery should not be delayed for a pre-operative evaluation. In these situations, the risk of delaying the procedure far outweighs the potential benefit of identifying underlying medical or cardiac problems. As an example, this situation often arises in neurosurgical patients who present with intracranial or spine pathology requiring immediate surgical intervention. Delaying surgery to assess cardiac risk in these patients would lead to devastating consequences.

The guidelines on pre-operative assessment are directed at patients undergoing elective surgery and do not recommend delaying surgery for assessment.[3,6] These patients have a higher risk of cardiovascular adverse events even if their baseline risk level is low, risk indices are based on data from elective surgeries and are not accurate in patients undergoing urgent or emergent procedures and should not be used for these patients. Whenever possible, a thorough history and physical exam should be obtained for all patients. This should be to look for a history of

bleeding events, serious drug allergies, and a history of medical comorbidities that could complicate the post-operative course.

For all other patients a step wise approach to cardiac risk stratification is outlined below.

Step 1: Is the patient at very high risk for MACE?

This group of patients includes patients with hemodynamically significant valvular heart disease, decompensated heart failure, high grade conduction blocks, supraventricular tachycardias with uncontrolled ventricular rate, malignant arrhythmias, symptomatic bradycardia, recent MI and unstable angina.[7] They need to be referred to a specialist for workup and treatment of these conditions and should not undergo elective surgery without a consultation.

Step 2: Is the patient at low (<1%) risk of MACE?

The next step of the assessment is to use a risk estimation index to determine if the patient is at low risk of MACE (<1%). There are several risk indices and Lee's Revised Cardiac Risk Index (RCRI) is one of he most widely used. Two additional risk indices based on the National Surgical Quality Improvement Program NSQIP may also be used. These are the Gupta scale and the NSQIP Myocardial Infarction and Cardiac Arrest (NSQIP MICA). Factors used in calculating the RCRI score are outlined in **Table 1**.

These scales are used to estimate the risk of MACE. A ≥1% risk of MACE puts the patient in the elevated risk category. Patients who are <1% risk of MACE are considered low risk and no further cardiac testing is recommended.[3]

After the publication of the original RCRI, many estimates of cardiac events based on the RCRI points scored have been published. Pooled risk estimates showed that the event rates were higher than the original estimate.[6,8] These differences are discussed in the Canadian Cardiovascular Guidelines published in 2017 and are attributed to the use of troponin measurement and inclusion of emergency surgery patients in the more recent data.[6] We follow the recommendations of the Canadian guidelines in

Table 1. Lee's Revised Cardiac Risk Index

Factor	Points Assigned
Ischemic heart disease[#]	1
History of heart failure*	1
History of stroke or transient ischemic attack	1
On insulin for diabetes	1
Serum creatinine (>2.0 mg/dl) pre-operatively	1
High-risk surgery[†]	1

[#] Defined as patient with a history of myocardial infraction (MI), positive exercise stress testing, ongoing chest pain, presumed to be due to ishemia or use of nitrates or electrocardiogram with Q waves.

* History of congestive heart failure, pulmonary edema, radiographic evidence of pulmonary vascular congestion, paroxysmal dyspnea or physicial exam finding of S3 gallop/bilateral rates.

[†] High risk surgery was defined as intraperitoneal, intrathoracic, suprainguinal vascular procedures.

Modified version of index published by Lee TH et al. *Derivation prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 199 Sept 7; 10(10):1043-9*

Table 2. Risk Estimates from The Revised Cardiac Risk Index

RCRI score (Points)	Risk estimate (%) and 95% CI based on original data*	Risk estimate and 95% CI based on pooled data3[#]
0	0.4% [0.05%–1.5%]	3.9% [2.8%–5.4%]
1	0.9% [0.3%–2.1%]	6.0% [4.9%–7.4%]
2	6.6% [3.9%–10.3%]	10.1% [8.1%–12.6%]
≥3	11.0% [5.8%–18.4%]	15.0% [11.1%–20.0%]

* Estimates from the original published data by Lee TH et al. *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999 Sep 7; 100(10):1043-9*

[#] Risk estimates from Duceppe et al. *Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Mamagement for Patients Who Undergo Noncardiac Surgery.* These estimates were based on external validations published after the original study by Lee TH et al (1999).

Table 3. Metabolic Equivalents (METS) of some common activities

Activity	METS
Resting state[#]	1 MET
Cooking	2-3 METS
Car Driving	2 METS
Walking (3 miles/hr or 5 km/hr)	3 METS
Climb Stairs	4-5 METS
Snow Shoveling	5 METS
Running (8 miles/hr or 13 km/hr)	13 METS

For a 70 kg individual. Values are approximate values based on data published by Jette et al. in Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiology 1990 Aug;13(8):555-65*

using a RCRI score of ≥1 point and do not recommend using the estimated percent risk to classify patients under the elevated risk category **(Table 2)**.

Step 3: Assess Functional Capacity

Under the AHA guidelines, the next step in assessing patients under the elevated risk category is to estimate functional capacity. Self-reported functional capacity is the most widely used method of estimation. The patient is asked what level of exertion they can tolerate without experiencing symptoms. Metabolic equivalents (METS) of many common activities are outlined in **Table 3**.

The Duke activity status index (DASI) is a standardized tool for estimating functional capacity.[9] A study comparing the DASI, self-reported functional capacity and cardiopulmonary exercise testing showed that only scores on DASI correlated with cardiac events in the post-op period.[10] Therefore, if functional capacity is included in the pre-op assessment, it is recommended that a standardized estimation tool like the DASI be used.

Per the approach outline in the ACC/AHA guidelines, patients at elevated risk, tolerating >4 METS without symptoms do not need additional cardiac testing. Whereas, patients at elevated risk with an unknown functional capacity or not able to reach 4 METS require additional cardiac testing. Various modalities for cardiac testing in these patients is outlined below.

CARDIAC TESTING MODALITIES

Stress Testing

The ACC/AHA guidelines recommend stress testing (exercise or pharmacologic with dobutamine stress echocardiography (DSE) or myocardial perfusion imaging (MPI) in patients at elevated risk for noncardiac surgery and have an unknown or poor (< 4 METS) functional capacity if it will change management.[3]

Routine stress testing just because a patient is undergoing noncardiac surgery is not recommended.[11] A stress test showing a large area of ischemic myocardium or multiple reversible defects on MPI is associated with a higher incidence of post-op death from cardiac causes or non-fatal myocardial infarction.[12,13]

Additionally, findings from several single center studies have shown that a negative stress test has a high negative predictive value. This is useful for patients who are moderate risk but limits the utility of stress testing in the highest risk patients.[14,15]

Resting Echocardiography:

Echocardiography to assess left ventricular function is recommended if the patient has dyspnea of unknown etiology, if they patient has heart failure and there is a change in their clinical condition or if a patient with stable heart failure has not had an echocardiograph in one year.[3,16]

Echocardiography to assess valvular function should be performed if a patient has known valvular disease and presents with a change clinically or if the patient presents with clinical signs of moderate or severe valvular heart disease.[3,16]

The Canadian guidelines published in 2017 favor biomarker testing and recommend a move away from resting echocardiography for pre-op testing, this is based on evidence showing that biomarker testing is superior to echocardiography in predicting adverse perioperative outcomes.[17] It is suggested that a resting echocardiogram should not be performed as a substitute to stress testing or biomarker measurement for high risk patients. However, resting echocardiography should be performed in patients suspected of having systolic heart failure to evaluate their left ventricular ejection fraction. It should also be done in patients with suspected moderate or severe valvular heart disease if they have not had an echocardiogram in the last one year or there has been a significant change in their clinical status since the last evaluation.

Role of pre-operative electrocardiography (ECG):

The ACC/AHA guidelines recommend obtaining an electrocardiogram in patients undergoing intermediate or high risk noncardiac surgery if they have a history of structural heart disease, arrhythmias, or vascular disease (includes CAD, stroke, TIA, or peripheral arterial disease). ECGs are not recommended for low risk surgery. Routine ECGs based on age cut-offs are also not recommended.[3,18]

The electrocardiogram is often performed in patients undergoing surgery based on arbitrary age cut-offs. A resting echocardiogram is useful in the detection of arrhythmias and to compare to baseline for patients with known CAD, peripheral vascular disease, cerebrovascular disease or ischemic heart disease.[19,20] However, its utility is significantly limited when a patient's baseline ECG is unknown or if nonspecific abnormalities are found on the ECG. These limitations make it less useful in diagnosing asymptomatic CAD in patients undergoing noncardiac surgery.

THE CANADIAN CARDIOVASCULAR SOCIETY GUIDELINES

The Canadian guidelines published in 2017 changed long standing recommendations on cardiac pre-operative evaluation and advocated a move towards biomarker measurement and post-operative troponin level testing.[6] We summarize the main recommendations from the paper below.

- Measurement of biomarkers (proBNP or NT-proBNP) prior to surgery in patients who are >65 years of age or have RCRI ≥ 1 or are 45-64 years old with cardiac comorbidities.
- Advise against performing resting echocardiography, coronary computed tomography angiography, stress testing or cardiopulmonary exercise testing or nuclear imaging as a part of perioperative risk assessment.
- Recommend daily troponin measurement for patients with elevated biomarker (pro-BNP or NT-proBNP) or if biomarkers are not measured but they score 1 or more points on the RCRI scale.

Additionally, The Canadian Cardiovascular Society guidelines recommend the following for continuing or initiating medications in the perioperative period.

- Acetylsalicylic Acid (ASA) should not be continued or initiated for cardiovascular protection or prevention. Exceptions include patients who had a recent coronary stent placement or will undergo carotid endarterectomy

- B-blockers or α2-agonist initiation is not recommended in the 24 hours prior to surgery.
- Recommends holding angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers 24 hours prior to surgery.
- If a patient develops myocardial infarct or injury in the post-operative period, a statin and ASA should be started.

CONCLUSION

Our article summarizes existing guidelines into a stepwise approach that provides a picture of our current practice as a hospitalist group providing perioperative care to neurosurgical patients. We attempt to highlight appropriate indications and use criteria for cardiac testing methods. Neurosurgical patients, both spine and intracranial can have high morbidity and need careful perioperative care. Keeping this in mind, it is even more imperative that appropriate testing be performed when indicated and unnecessary testing be avoided.

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Epidural Abscess of the Central Nervous System

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An epidural abscess is a localized collection of purulent fluid between the dura mater and the overlying vertebral column (spinal epidural abscess) or skull (intracranial epidural abscess).[1,2] Early diagnosis of epidural abscess is essential as without timely intervention neurologic injury with permanent sequelae can develop.[3]

SPINAL EPIDURAL ABSCESS

Epidemiology

Spinal epidural abscess (SEA) is more common than intracranial epidural abscess and is increasing in incidence. In 1975 the reported incidence of SEA was 0.2-2 per 10,000 hospitalized patients. Over the past four decades this has risen to 10-12 per 10,000 hospitalized patients in some referral centers.[4–6]

This increase is likely due to a rising number of patients with risk factors for SEA including intravenous drug use (IVDU), diabetes mellitus, advanced age, renal failure, and compromised immunity as well as degenerative spinal column disease and the growing use of therapeutic spinal interventions including instrumentation, injections, catheter placement and anesthetic procedures.[7,8] The ongoing opioid epidemic in the United States has had a particular impact on the increased incidence of SEA given the risks of endovascular infection and metastatic seeding associated with intravenous drug use.[9] The clinical utility of associated risk factors in the diagnosis of SEA in unclear, however, given their apparent absence in 20-50% of patients.[10] Detection of SEA with the wide-spread availability of sensitive imaging modalities such as magnetic resonance imaging (MRI) has also improved diagnostic accuracy in recent decades.[8]

Pathophysiology

One-half of SEA infections are caused by hematogenous spread from a remote site of infection. Common sources include the skin, urinary tract, oral cavity, infection of an indwelling vascular access and endocarditis.[3,5,11,12] Several regions of the spine may be involved in hematogenous infection. Hematogenous spread via the pelvic cavity's venous drainage system which connects with those of the spine forming Batson's plexus may facilitate infection from a urinary source.[13]

Contiguous extension of infection from osteomyelitis in an adjacent vertebral body or from a psoas or retropharyngeal muscle abscess or decubitus ulcer is estimated to account for up to one-third of infections.[3,11] Vertebral body infection usually results from hematogenous seeding of the adjacent avascular disc space.[12,14]

Direct inoculation of the epidural space from spinal surgery, injection or catheter placement is another route of infection. Infection can be acquired during the procedure itself or from ascending microorganisms from the skin when a device is retained.[5,15,16] Additionally, a hematoma secondary to osseous or ligamentous injury can become seeded by bacteria leading to SEA formation.5 In up to 30% of patients no source is identified.[5,17,18]

Neurologic impairment resulting from SEA is usually the result of spinal cord compression by the infected mass with possible contribution of vascular occlusion.[19]

Table 1. Symptoms of Epidural Abscess at Different Stages [adopted from (20).

Symptom	Stage I	Stage II	Stage III	Stage IV
Back or Neck Pain	+	+	+	+
Ridiculopathy	–	+	+	+
Weakness and/or Bladder Symptoms	–	–	+	+
Paralysis	–	–	–	+

* Estimates from the original published data by Lee TH et al. *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999 Sep 7; 100(10):1043-9*

Risk estimates from Duceppe et al. *Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Mamagement for Patients Who Undergo Noncardiac Surgery.* These estimates were based on external validations published after the original study by Lee TH et al (1999).

Clinical presentation

Four stages of disease severity have been recognized in patients presenting with SEA.[20] (**Table 1**) Presentation in stages I or II is more common, while greater residual deficit is found in those presenting in stages III or IV. Fever is present in 50-60% of patients while the classic triad of fever, back pain and neurologic deficits is seen in only a minority.[21–23] Back pain, present in 95% of patients, with associated nerve root pain, radiculopathy and paresthesia may be the worst of a patient's life, distinct from chronic back pain. Depending on

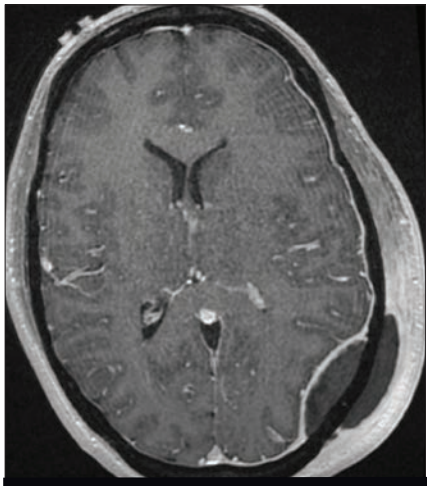

Figure 1a.

T1-weighted axial MRI image showing a left occipital region epidural and extracranial fluid collection/abscess.
Reprinted with permission from Priolo SM et al. Acupuncture induced cranial epidural abscess. *World Neurosurg 2019* May;125:519-526.

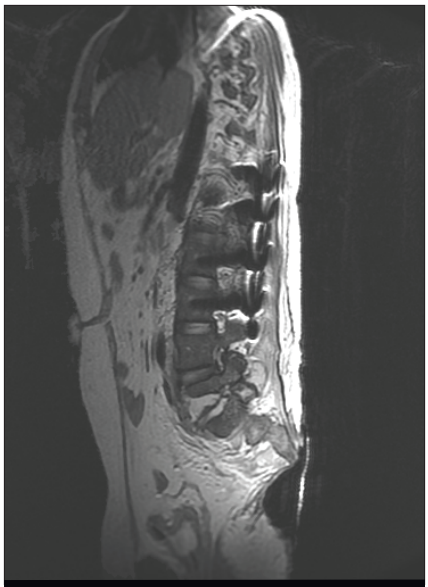

Figure 1b.

Saggital T2 weighted MR image of the thoracic spine showing a mid-thoracic dorsal epidural abscess.

the spine level, pain can radiate to the abdomen, chest or neck, mimicking other conditions.[5,18] Focal weakness in either the upper or lower extremities is present in 40% of patients and neurologic deterioration may develop within hours to days or over weeks to months.[10,11,18,24]

Physical examination findings include spinal tenderness in up to 75% of patients which can be focal or diffuse. Neurologic deficits including spinal cord dysfunction with motor weakness, sensory loss, sphincter dysfunction and paralysis may be found in advanced stage presentation. Once paralysis develops (stage IV), it quickly becomes irreversible, emphasizing the critical need for timely diagnosis.[5,18,24]

Diagnosis

The diagnosis of SEA may be delayed with up to 75% of cases misdiagnosed on first presentation. Back pain, with a wide differential diagnosis, may be attributed to arthritis or muscular pain.[7,10] Patients presenting with sepsis and/or altered mental status may be unable to provide a history.[25] One series looking at 63 patients found that a correct diagnosis of SEA was made after 2 emergency room visits in 51% of cases , while a further 11% were identified on a third visit. This is significant as residual motor weakness was identified in up to 45% of the cohort who experienced delays vs 13% of those who did not.[22] The increased incidence of SEA has not impacted this diagnostic delay.[6,21] Recognition of SEA prior to the onset of neurologic symptoms is critical in patients who present with back pain. Diagnosis should be suspected based on clinical presentation and supported with testing. Definitive diagnosis of SEA requires drainage and culture.[2]

Laboratory Testing

Inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate(ESR) are sensitive tests for the diagnosis of SEA and are usually elevated with an ESR >20 mm/h reportedly found in 95% of cases. Leukocytosis is also common, reported in 60-80% of cases. These tests are not specific for SEA.[5,10,26] Blood cultures should be obtained and may be positive in up to 60% of cases.[22,27]

Imaging Studies

MRI with gadolinium is the imaging study of choice with a high sensitivity and specificity for detection of SEA (**Figure 1b**). Imaging the entire spine to exclude noncontiguous SEA is recommended.[28] MRI is also the study of choice for detection of vertebral osteomyelitis and/or discitis in patients presenting with back pain.[18,29] Comparison of T1 and T2 weighted contrast enhanced images is used in anatomic localization of SEA and to define the extent of infection including assessment for multi-level involvement.[30]

Computed tomography (CT) with intravenous contrast is an alternative diagnostic imaging study with lower sensitivity and specificity than MRI.[18] Myelography followed by CT scan is a highly sensitive study although an invasive procedure requiring exposure to ionizing radiation with a lower specificity than MRI. Myelography is usually reserved for patients who cannot undergo MRI. Spinal puncture for myelography should be performed distant from the area of suspected infection.[5,17,18] Echocardiography is indicated in all cases of epidural abscess to exclude endocarditis.

Microbiology

Pathogen identification is very important

Table 2. Pathogens in Spinal Epidural Abscess

Pathogen	Percent %
Staphylococcus aureus	60–90
Gram-negative bacilli	10–15
Streptococcus species	10
Coagulase-negative staphylococci	3–6
Enterococci	1–2
Fungi	1–2
Anaerobes	1–2
Mycobacteria	<1
Polymicrobi	5–10

Based on references 1, 3–7, 15, 17, 18, 22, 23,25

Table 3. Antimicrobial Therapy for Epidural Abscess of the Central Nervous System

Microorganism	First Choice	Alternatives for Anaphylactic Allergy or Resistance.
Staphylococci, oxacllln susceptible	nafcillin or oxacillin 2 g IV q4-6 h; consider adding rifampin 600 mg PO q24 h if retained hardware	cefazolin 2g IV q8 h, vancomycin 15-20 mg/kg IV q12 h or daptomycin 6-8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h; consider adding rifampin 600 mg PO q24 h if retained hardware
Staphylococci, oxacillin resistant	vancomycin 15-20 mg/kg IV q12 h, consider adding rifampin 600 mg PO q24 h if retained hardware	daptomycin 6-8 mg/kg IV q24 h or linezolid 600 mg PO/ IV q12 h or trimethoprim-sulfamethoxazole 5mg/kg IV/ PO q8-12 h, consider adding rifampin 600 mg PO q24 h if retained hardware
Streptococci, confirm susceptlblllty testing for vlrldans streptococci	penicillin G 18-24 million units IV q24 h continuously or in 6 divided doses, or ceftriaxone 2g q 12-24 h	vancomycin 15-20 mg/kg IV q12 h
Enterococci, penicillin susceptible	penicillin G 20-24 million units IV q24 h continuously or in 6 divided doses, or ampicillin sodium 12g IV q24 h continuouslv or in 6 divided doses	vancomycin 15-20 mg/kg IV q12 h or daptomycin 6-8 mg/kg IV q24 h or linezolid 600mg PO/IV q12 h
Enterococcl, penicillin resistant	vancomycin 15-20 mg/kg IV q12 h	daptomycin 8-10 mg/kg IV q24 h or linezolid 600 mg PO/ IV q12 h
Enterococci, vancomycin resistant	daptomycin 10-12 mg/kg IV q24 h	Linezolid 600 mg PO/IV q12 h
Cutibacterium acnes	penicillin G 20 million units IV q24 h continuously or in 6 divided doses, or ceftriaxone 2g q12-24 h	vancomycin 15-20 mg/kg IV q 12 h or daptomycin 6-8 mg/ kg IV q24 h or clindamycin 600-900 mg IV q8 h
Enterobacteriaceae, confirm susceptibility testing	ceftriaxone 2g q 12-24 h or cefepime 2g IV q8 h or ertapenem 1 g IV q24 h	meropenem 1-2g q8 h or ciprofloxacin 400 mg IV q12 h(or 500 mg PO q12 h) or trimethoprim-sulfamethoxazole 5mg/ kg IV/PO q8-12 h
Enterobacteriaceae, confirm susceptibility testing	ceftriaxone 2g q 12-24 h or cefepime 2g IV q8 h or ertapenem 1 g IV q24 h	meropenem 1-2g q8 h or ciprofloxacin 400 mg IV q12 h(or 500 mg PO q12 h) or trimethoprim-sulfamethoxazole 5mg/ kg IV/PO q8-12 h
Pseudomonas species, confirm susceptibility testina	cefepime 2 g q8 h, ceftazidime 2 g q8 h or meropenem 1-2 g q8 h	azactam 2 g q8 h or ciprofloxacin 400 mg IV q8 h (or 750 mg PO q12 h)
Acinetobacter species, confirm susceptibility testina	meropenem 1-2 g IV q8 h	ciprofloxacin 400 mg IV q12 h (or 500 mg PO q12 h) or ampicillin- sulbactam 3g/1.5g IV q6 h or polymyxin B 1.5-2.5 mg/kg IV q24 h in 2 divided doses
Candida species, confirm susceptibility testina	liposomal amohotericinB 5 mg/kg IV q24 h	fluconazole 400-800 mg IV/PO q24 h, consider adding flucytosine 25 mg/kg q6 h

*doi:10.1056/NEJMra1301635

in the management of SEA. SEA is most commonly due to Staphylococcus aureus (60-90% of cases) with methicillin-resistant S. aureus (MRSA) accounting for a significant number of infections, up to 40% in some series.[2,5,17,18] Aerobic gram-negative bacilli including Escherichia Coli, Klebsiella spp. and Pseudomonas aeruginosa cause SEA in patients with a history of urinary tract infection and account for 10-15% of cases. Other pathogens causing SEA include aerobic and anaerobic Streptococcus spp., Enterococcus spp. and coagulase-negative staphylococci with the latter associated with spinal procedures such as the placement of catheters for analgesia, steroid injections, and surgery. Candida spp. are also associated with spinal instrumentation. 5-10% of infections may be polymicrobic. Atypical pathogens including Brucella species, mycobacteria (tuberculous and non-tuberculous) and fungi can be seen in endemic regions or immunocompromised hosts.[5,17,18] Environmental organisms, for example, the fungus Exerohilum rostratum that was responsible for a multi-state outbreak of spinal infections associated with steroid injections, have been reported with spine innoculation.[31] **Table 2** summarizes the microbiology of SEA.

An intraoperative or image guided sample of the infected fluid should be obtained and sent for culture. Cultures for mycobacteria and fungi and serology for Brucella should be sent if epidemiologic or host risk factors are suggestive of atypical infection.[2,32] As noted, blood cultures should be obtained and may be positive in up to 60% of cases.[10,17,27]

Management

Prompt surgical decompression and abscess drainage is indicated in most cases of SEA to minimize neurologic injury and for control of sepsis. If there are focal neurologic changes, surgical debridement should be performed urgently.[5,7,10,33] Over the past decade,

conservative management with antibiotics alone has become more common in patients without neurologic deficits who have an established causative pathogen confirmed either with an image guided aspiration culture or a blood culture growing a virulent pathogen such as *S. aureus*. The rate of failure with this conservative approach, however, is estimated to be 30-40% therefore necessitating close monitoring.[7,34,35] Of note, while paraspinal and psoas abscesses and intradiscal spaces are routinely aspirated for microbiologic diagnosis, aspiration and/or drainage of SEA under CT guidance is a technical challenge and only dorsally located SEA without advanced bone destruction on MRI qualify for percutaneous drainage attempt.[36]

As noted in the 2015 Infectious Diseases Society of America guidelines for Native Vertebral Osteomyelitis, empiric antimicrobial therapy should be withheld until after cultures from blood and other possible sources of infection have been obtained except in cases of sepsis or neurologic deficit.[29] Empiric antimicrobial therapy should include coverage of staphylococci (including MRSA), streptococci and gram-negative pathogens. While the majority of cases of SEA are caused by gram-positive bacteria and therefore empiric coverage for gram-negative organisms may not be necessary in all cases, it is recommended and often implemented.[5,18,29] Vancomycin plus an third or fourth generation cephalosporin or carbapenem (Ceftazidime, Cefepime or Meropenem) is considered first line therapy with alternative coverage for gram-positive organisms including Daptomycin or Linezolid, and alternative coverage for gram-negative organisms including Azactam or Ciprofloxacin.[11,29,32]

Once a pathogen is identified, a course of targeted parental or highly bioavailable oral antibiotic therapy is recommended. (**Table 3**) While parenteral antibiotic therapy is typically preferred, especially in treating staphylococcal infection, a recently published randomized, non-inferiority trial found no difference in the treatment of a variety of bone infections including 39 cases of spinal infection some of whom had SEA, between standard parenteral therapy and an early switch (within 7 days) to oral antibiotic therapy.[42] Any patient in whom there is a concern for meningitis should be treated with parenteral therapy dosed for CNS penetration for at least 2 weeks.[43]

Recommendations for the duration of therapy for SEA range from 4 weeks to 3-6 months depending on many factors including the concurrent presence of endocarditis, vertebral osteomyelitis and/or retained spinal hardware.[5,29,32,37] Vertebral osteomyelitis commonly occurs with SEA and is usually treated with at least 6 weeks of antibiotic therapy.[37–39] Few randomized controlled trials(RCT) specifically focusing on the duration of antimicrobial therapy for SEA and/or vertebral osteomyelitis are available. An open-label, non-inferiority, RCT of 359 patients compared 6 weeks of antibiotic therapy to 12 weeks in patients with pyogenic vertebral osteomyelitis finding no difference in cure rate at 1 year.[40] Information on outcomes with different antimicrobial regimens and durations is often derived from observational studies.[14,37,41]

Some patients may be at higher risk for relapsed SEA and/or vertebral osteomyelitis including those with undrained paravertebral or psoas abscess, concomitant endocarditis, MRSA infection, IVDU, end-stage renal disease, or those with local spinal wound infection.[41,44] In cases of infection in patients at risk for relapse or related to retained spinal implants extension of antimicrobial therapy (>8 weeks) can be considered. The optimal duration of sequential oral antibiotic suppression in spinal implant infection has not been established but has been shown to decrease the risk of relapse especially in early-onset infections (<1 month from fusion surgery). In delayed onset SEA infections associated with vertebral osteomyelitis, removal of hardware is associated with improved outcomes.[12,39,45]

Patients with SEA should be followed to ensure response to therapy. A 25% improvement in ESR and CRP at 4 weeks of therapy in combination with improved clinical assessment should be anticipated. A failure of CRP levels to decline can be a poor prognostic marker.[16] End of treatment imaging is not routinely recommended although a poor clinical response to therapy merits repeat MRI imaging and surgical evaluation.[5,18,46]

Outcome

The most important predicting factor for neurologic outcome in SEA is the patient's neurologic condition prior to surgical decompression. Patients presenting with stage III or IV infection show the worst recovery rate.[4,5,18,47] An outcome of stable or improved neurologic function in comparison to the preoperative status is anticipated. Patients presenting with paralysis for up to 24-36 hours are expected to regain some neurologic function after surgery and this has been correlated with the rapidity of surgical intervention (within 24 hours).[34,47] Patients may continue to regain neurologic function and will benefit from rehabilitation through the first year after treatment.[34,44]

Mortality associated with SEA has declined significantly with the availability of advanced cross-sectional imaging, expanded surgical techniques and effective antibiotic therapy.[7] Death usually results from severe sepsis. Approximately 5-7% of patients with SEA do not survive in the hospital and 90-day mortality is estimated at [13%.4,7,48] The best outcomes in the management of SEA are achieved with multidisciplinary care.

INTRACRANIAL EPIDURAL ABSCESS

Epidemiology

The incidence of intracranial epidural abscess (ICEA) and its related mortality have decreased since the introduction of antimicrobial therapy. As ICEA can cross the dura via the emissary veins an accompanying subdural empyema is often present.[2,49]

Pathophysiology

Intracranial epidural abscess (ICEA) can occur following trauma or after neurosurgery including craniotomy, transnasal or transmastoid procedures. Subdural empyema can also result from direct infection of the subdural space during these procedures.[2,3] ICEA may also develop as a complication of sinusitis, otitis media or mastoiditis and this route of infection is more common in children and young adults. Valveless, bidirectional blood flow

between the frontal sinus mucosa and dural venous drainage is more common in children given their highly vascular diploic bone. Drainage empties into the superior sagittal sinus, increasing the risk of subdural extension.[49,50] While longitudinal spread is common in SEA, ICEA without subdural empyema is usually a localized, slowly expanding lesion that rarely extends into the spinal column given the tight adherence of the dura around the foramen magnum.[50]

Clinical Presentation

Presentation includes fever and headache with variation in time to presentation. Concern for sinusitis and otitis media at presentation may distract from the appropriate diagnosis of ICEA. Periorbital cellulitis and frontal edema are commonly seen.[2,3,51] ICEA without subdural empyema may present with insidious onset as the space between the dura and cranium is contained, limiting abscess expansion and delaying the development of focal neurologic changes.[2] If a cranial subdural empyema is also present, however, deeper extension of the infection may lead to more rapid neurologic findings. Epidural abscess after neurosurgery can present with rapid progression given the risk of subdural involvement.[3,16] With or without a subdural empyema, ICEA will eventually lead to neurologic changes with possible seizures as well as signs of increased intracranial pressure including papilledema.[2,3,51] Gradenigo syndrome, unilateral facial pain and weakness with involvement of cranial nerves V and VI, can develop in patients with otitis media and/or mastoiditis as ICEA extends along the temporal bone.[2,52] Both cranial epidural abscess and subdural empyema can be complicated by meningitis, cortical venous thrombosis and brain abscess.[53,54]

Diagnosis

Laboratory testing

Laboratory testing in evaluation for ICEA is non-specific. Leukocytosis may be present.

Imaging Studies

MRI with gadolinium enhancement is the imaging study of choice in evaluation for ICEA. An area of diminished intensity is seen on (**Figure 1a**) T1 weighted images with hyperintense patterns and pachymeningeal enhancement on T2 weighted images.[55] Gadolinium enhancement helps to differentiate infected fluid from hematoma or sterile collections that can be seen after trauma or neurosurgery. The presence of subdural empyema, brain abscess or other pathology can also be assessed with MRI. Of note, ICEA can cross the midline of the brain which subdural empyema typically does not.[2,3,50,55] CT scan is less sensitive although can be used to assess bone and may detect a low attenuation extra-axial mass.[3]

Microbiology

Common causative pathogens in ICEA arising after neurosurgery include *Staphylococcus aureus*, coagulase-negative staphylococci and gram-negative bacilli. Infection arising from the paranasal sinuses or ear is typically caused by aerobic and anaerobic *Streptococcus spp.*, anaerobic gram-negative bacilli including *Bacteroides spp.*, and *S. aureus*. While no one organism predominates in this setting, Streptococcus anginosus is common. Infection may be polymicrobic. *Pseudomonas aeruginosa* infection can arise from otitis media and fungal infection can arise from chronic sinusitis.[3,50]

Management

Given the risk of progression and neurologic deterioration in ICEA, surgical intervention should be undertaken at the earliest sign of worsened neurologic status. Combined neurosurgical and otolaryngologic approaches may be needed. Open or minimally invasive craniotomy for drainage of ICEA are options depending on the location and degree of bone involvement. Single burr hole drainage may be associated with recurrence. Cranialization of the frontal sinus may be indicated in patients with ICEA secondary to frontal sinusitis.[3,56]

Patients presenting with a small ICEA can be treated with antimicrobial therapy with close observation and serial imaging to monitor response. Empiric antimicrobial therapy should target the anticipated pathogens causing ICEA including aerobic and anaerobic cocci and bacilli with adequate central nervous system penetration.[3,50,51] Antimicrobial therapy should be tailored based on available microbiologic testing of abscess fluid with confirmation of antibiotic susceptibilities (**Table 3**). Treatment duration for ICEA has not been established. Extended duration is typically preferred and can be extrapolated from the treatment of brain abscess with courses of 4-6 weeks often used including at least 2 weeks of parenteral therapy.[43,50,57]

Outcome

The availability of antimicrobial therapy and advances in neuroimaging have decreased morbidity and mortality from ICEA. Poor prognosis is associated with diagnostic delay in patients presenting with vague symptoms as well as brain herniation.[2,3] The absence of severe neurologic deficits on presentation, minimal co-morbid conditions and young age are associated with improved outcomes.

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Spinal Metastasis – Diagnosis, Management, and the Role of the Hospitalist

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ABSTRACT

Management of spinal metastases is a complex process which includes services ranging from neurological surgery to medical oncology to radiation oncology. Neurosurgery hospitalists increasingly play a crucial role by coordinating diagnostic and therapeutic strategies, tailoring them to each patient's individual needs. In this article, we review each step of the management of the spine mass from diagnosis to treatment. An emphasis is placed on the diagnosis and management of metastatic spinal cord compression. Finally, we review in detail the role of the neurosurgery hospitalist in this process.

INTRODUCTION

Metastatic disease in patients with solid and hematological malignancies is an important adverse prognostic factor, as it is associated with significantly higher rates of morbidity and mortality. Autopsy studies of patients with cancer reveal that up to 70% had also developed metastases to bone.[1,2,3] Greater than 80% of these bone metastases are attributable to three primary malignancies: breast, prostate, and lung (though many others, including thyroid, renal, and colon cancer also frequently metastasize to bone).[2,3] The spine is the most common site of osseous metastasis, and its increasingly high prevalence on autopsy is in large part due to the improved overall survival of patients living with cancer.[2,3]

Physiologic factors contributing to the origin and severity of spinal metastases include (a) Batson venous plexus, which is responsible for drainage of the abdominal and pelvic organs, and (b) growth factors released from bone marrow stroma by tumor-mediated structural degradation, which then induce growth and proliferation of the invading tumor cells (in addition to osteoblastic and osteoclastic activity).[2,4,5] Bone metastases are either sclerotic, lytic, or mixed, depending on the degree to which they stimulate osteoblasts, osteoclasts, or both.[5,6]

The most dreaded complication of spinal cord metastasis is metastatic spinal cord compression (MSCC), first described by William G. Spiller, MD in 1925.[7] Approximately 5% of all patients with cancer develop MSCC, while as many as 20% of patients with spinal metastases suffer MSCC4.[8] Breast, lung, prostate, and renal cancer are responsible for the majority of MSCC.[9,10] The thoracic spine (60%) is the most commonly implicated region, followed by the lumbar spine (25%), and cervical spine (15%).[4,9] When MSCC occurs, the culprit lesion is located within the vertebral body itself in about 85% of cases, whereas paravertebral spaces are the origin in 15% of cases.[4] As with spinal metastases in general, the overall incidence of MSCC has increased, which likely also is due to the increasing longevity of patients with cancer.[11]

CLINICAL PRESENTATION

The most common symptom of spinal metastases and MSCC is new or worsening back pain.[4,9,10] Bone metastasis is the most common cause of cancer-associated pain and represents multifactorial pathophysiology, including osteolysis, tumor-induced growth factor production, nerve infiltration, and periosteal distension.[4,6] The characteristics of this pain typically are somatic, neuropathic, or both. Somatic pain is localized and worsened by movement or manipulation of the affected region, while neuropathic pain typically radiates, burns, and worsens at night.[4,6] In high risk patient populations, sudden and severe worsening of pain should raise suspicion for a pathological fracture, which may result from either osteolytic or osteoblastic lesions.[4,5]

Neurological injury in MSCC is due to compression-mediated demyelination and axonal damage, along with vascular compromise leading to vasogenic edema, ischemia, and ultimately infarction of the spinal cord4. The incidence of focal extremity weakness due to MSCC ranges from 35% to 75% and represents the most common focal neurological manifestation.[4,12] It is often associated with ambulatory dysfunction, though the degree of impairment varies greatly. Sensory deficits are less common, typically preceded by pain and motor impairment, progress distally to proximally, and may be associated with more severe neurological injury[4, 12]. Bowel and bladder dysfunction are grave features of MSCC and are seen in 50-60% of cases.[4] When present, sphincter dysfunction (tested by digital rectal examination and measurement of urinary post-void residuals) represents a poor prognostic indicator and reduces the likelihood of complete functional neurological recovery.[4,13] While the characteristic syndrome of MSCC includes the above manifestations, many patients present with more general signs and symptoms, such as nonspecific pain and ambulatory dysfunction.[4,12]

CLINICAL PRESENTATION AND EVALUATION OF METASTATIC SPINAL CORD COMPRESSION

Metastatic spinal cord compression is a medical and surgical emergency requiring immediate evaluation and intervention to prevent paralysis and other irreversible neurological injury.[4,14] It is paramount that clinicians maintain a high index of suspicion and promptly evaluate symptoms that raise the possibility of spinal metastatic disease or MSCC, particularly in patients with an established diagnosis of malignancy.[6,15] Poor prognostic factors include prolonged duration of neurological deficit, severe neurological compromise, prior radiation treatment of metastatic lesions, and metastases located in the thoracic spine (although there are only few and low-quality studies to establish these prognostic features).[16] Patients who are unable to lift their legs against gravity and those who have been non-ambulatory for greater than 48 hours are at greatest risk of poor functional recovery.[16]

Ambulatory status at the time of diagnosis carries the greatest power of prognostication, as multiple studies demonstrate improved post-treatment outcomes and functional capacity for patients who were able to ambulate at the time of intervention.[10,12,17] There is insufficient standardization in the assessment of pre-treatment functional capacity and inadequate tools for quantifying the post-treatment prognosis, but experts agree that pre-treatment ambulation is strongly linked to better outcomes and reduced rates of morbidity and mortality.[16-19]

Given the preceding prognostic considerations, early detection, diagnosis, and intervention in cases of MSCC is crucial to improving patients' outcomes.[14,18] The gold-standard imaging modality to diagnose MSCC is magnetic resonance imaging (MRI), which confers a high diagnostic sensitivity (93%) and specificity (97%).[2,4,8] MRI offers detailed visualization of the spinal cord and its surrounding structures and is useful not only for surgical planning, but also for identifying targets in cases when emergent radiation treatment is necessary,[1, 2,4,8] Experts recommend MRI evaluation of the entire spine, as up to 30% of patients with MSCC have more than one metastatic lesion in the spine.[15,20]

Fortunately, data suggest that patients with MSCC today are more likely to experience significant functional recovery. A study in 2010 showed that 62% of patients with MSCC were ambulatory at the time of their diagnosis and intervention, whereas only approximately one-third of patients in the 1990s remained ambulatory by the time of intervention.[14,21,22] In addition to early diagnosis, multiple studies have demonstrated that early surgical intervention (in appropriate candidates) plus radiation therapy improves outcomes in comparison to radiation therapy alone.[2, 6,14,17,9,10,12,23,24,25]. Historically, laminectomy alone was the standard method of surgical intervention, but more recent studies and surgical advances support decompression and fusion for stabilization over decompression alone.[2,16,17,21, 23]

Overall median survival rates for patients with MSCC range between 6 to 9 months.[18,19,21,25,26] In addition to patients' functional and ambulatory condition, survival rates are greatly influenced by the type and features of the primary malignancy.[25] Lung cancer and cancer of unknown primary causing MSCC bear the worst prognoses, while prostate and myeloma are associated with more favorable outcomes.[18,19,25,26]

NEUROIMAGING IN THE DIAGNOSIS OF SPINAL METASTASES

Historically, plain film radiographs were the first imaging test used for the diagnosis of spinal metastatic disease. With the advent of more sophisticated imaging modalities, however, radiographs are no longer routinely utilized for this purpose. Radiographs require a minimum mass diameter of 1 cm and a bone density of 50% or greater to achieve adequate visualization, resulting in a very high rate of false negative tests. The development of computed tomography (CT) scans presented a significant advancement, as they can detect bony metastatic lesions up to 6 months before they are reliably identified on radiograph. Nevertheless, though excellent for detecting bony abnormalities, CT is far inferior to MRI when it comes to delineation of soft tissues and the diagnosis of spinal cord compression.

Standardized use of MRI in the evaluation of spinal metastatic disease has greatly impacted the management and outcome expectations for patients. In addition to its superior visualization of the spinal cord and surrounding soft tissue, MRI remains the only modality capable of evaluating the bone marrow and its constituent elements with high resolution. T1-weighted MR scans are particularly useful for the evaluation of bone marrow due to the hyperintense signal generated by its high fat content, which enables detection of focal hypointense lesions relative to the surrounding normal tissue. In contrast, T2-weighted MR images show metastatic lesions as hyperintense compared to bone marrow, due to their relatively high water content. The addition of intravenous contrast further aids detection of lesions in the epidural space, as well as MSCC. A limitation of MRI, however, is its inability to differentiate conclusively between changes resulting from tumor versus those from surgery.

Biopsy is the gold standard test to determine the primary origin of any metastatic lesion. Neuroimaging can play a role in identifying the tissue of origin during the early stages of a metastatic evaluation, as many malignancies cause either lytic (osteoclast-predominant) or sclerotic (osteoblast-predominant) bony lesions (though some are characterized by mixed features). Primary cancers of the lung, breast, thyroid, adrenal glands, and melanoma (among others) cause lytic bony metastases. In contrast, prostate, bladder, and nasopharyngeal cancers cause sclerotic metastases. Cancers of ovarian, cervical, testicular, and occasionally lung etiology may cause mixed—lytic and sclerotic—patterns. Both lytic and sclerotic lesions involving the posterior cortex may cause destruction of the cortex and pedicles. An important sign of diffuse bone marrow infiltration is a hyperintense appearance of the vertebral discs in comparison to bone on a T1-weighted MRI. A systematic grading of spinal cord compression proposed by Bilsky and colleagues is commonly used to stratify the severity of MSCC.[27]

Other imaging modalities that have proven useful in screening for bone metastases are bone scintigraphy and single-photon-emission computed tomography (SPECT). These are nuclear medicine scans that operate by injection of a radioactive tracer that accumulates in newly formed bone at the site of a metastatic lesion. Neoplastic lesions appear "hot" (indicative of increased bone turnover, including degradation and formation), but this effect may not be seen in cases where the cancer has caused excessive tissue destruction and consequently impaired blood flow to the site. One of the best modalities for visualization of bone marrow involvement is the [18F] fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) scan, which measures glucose metabolism and thus preferentially highlights areas of increased bone cell turnover. This is particularly useful for when evaluating for multiple myeloma.[28]

MANAGEMENT OF SPINAL METASTASTIC DISEASE

General considerations of treatment

Metastatic malignancy generally is an incurable disease. Whether and how to pursue treatment requires careful consideration of several patient and disease-specific determinants. Physicians should proactively seek to understand each patient's perceptions, expectations, and preferences. In their 2017 report, the International Spine Oncology Consortium proposed a number of factors to consider prior to initiating treatment, beginning with a thorough assessment of the patient's baseline functional status.[29] The Karnofsky performance scale and the Eastern Cooperative Oncology Group (ECOG) scale are commonly used in general oncology as functional performance evaluators. Patients with 'poor functional status' are generally defined as those with a Karnofsky performance score of less than 40.

The overall burden of disease also plays a significant prognostic role, even following treatment of spinal lesions. Extensive extra-spinal metastatic disease denotes a poor prognosis for survival after spinal radiation. Some tumor types (for example, hormone-sensitive breast cancer and lung cancer with target-sensitive genomic alterations) have more favorable prognostic profiles, and this must also be factored into spine-specific treatment paradigms. Hematological cancers affecting the spine generally have well-established systemic treatment protocols that may be favored over surgery or local radiation, at times even when cord compression is present. Similarly, tumor histology is important in predicting whether conventional external beam radiation therapy (cEBRT) can achieve durable local response, as some histologies are more radiosensitive than others. Finally, mechanical stability of the spine, commonly assessed by the Spine Instability Neoplastic Score (SINS), will greatly influence treatment options as the primary goal in mechanically unstable spines is to restore structural stability.[30] SINS incorporates both clinical and radiological features and scores range from 0 to 18, with higher numbers signifying a higher degree of instability.

Radiation therapy

The two most common forms of radiation therapy for spinal metastases are external beam radiation therapy (EBRT) and stereotactic body radiation therapy (SBRT). The former is most frequently employed, while the latter often is reserved for specifically indicated circumstances. The primary goal of EBRT is palliation and it is the preferred treatment for radiosensitive tumors (e.g. lymphoma, myeloma, germ cell tumors). Practice guidelines, informed by multiple randomized controlled trials, favor shorter fractionated regimens of EBRT over more protracted ones, as they have been shown to be noninferior in their primary outcome (pain control) and associated with fewer acute post-treatment adverse effects.[31,32]

SBRT utilizes confocal beams of radiation to precisely target a specific site, while avoiding collateral radiation damage to important adjacent structures. It is particularly useful for the treatment of relatively radioresistant tumors like sarcoma, melanoma, and renal cell carcinoma. It is also used in patients who have persistent pain despite treatment with EBRT.[33] SBRT is associated with a higher risk of vertebral compression fractures. It is worth noting, however, that SBRT and EBRT have not been compared directly in prospective randomized controlled trials.

Surgery

The two main indications for surgical consultation in spinal metastatic disease are spinal instability and MSCC. Surgical consultation (by a neurosurgeon or specialized orthopedic spine surgeon) generally is recommended for any patient with a SINS greater than 72.[34,35] MSCC is a medical emergency and surgery is a critical component in the care of patients with MSCC. Surgical intervention typically is pursued in conjunction with medical and radiation therapy, as multiple clinical trials involving MSCC have demonstrated significantly better outcomes in patients treated with surgery plus radiation in comparison to radiation therapy alone.[36] These findings have led to expansion of the surgical role in the management of MSCC and advancements in surgical technique. A trial by Patchell et al. found that more patients in the surgical group (84%) were able to ambulate after treatment versus the radiation monotherapy group (57%), and they remained ambulatory for a longer duration (median 122 days versus 13 days).[37] Minimally invasive techniques like cement augmentation of vertebral bodies are increasingly used and have proven effective in the management of certain disease presentations, such as pathological fractures.[2,38]

Another benefit of surgical intervention is to facilitate safe delivery of postoperative radiation therapy. Spine separation surgery is one such procedure which creates a gap access to the tumor, allowing radiation to be administered, while sparing the spinal cord and the cauda equina from direct exposure and potential radiation damage.[39-41]

Medical management

The aspect of medical management that is most directly relevant to the hospitalist or general internist is analgesia, since pain is the most common symptom in spine metastasis. Mild bone pain is usually managed well with scheduled acetaminophen, with or without a nonsteroidal anti-inflammatory drugs (NSAID). As pain becomes more severe, the addition of an oral opioid agent

may be necessary. In the hospital, this approach can be combined with intravenous opioids for breakthrough pain, titrated to therapeutic efficacy while at the same time avoiding neurological and respiratory side effects. Glucocorticoids are frequently used to improve outcomes when there is MSCC, but they are also a useful adjunct for analgesia.[42]

Osteoclast inhibitors reverse or delay the progression of bone metastases and reduce the likelihood of skeletal-related events (SREs). Denosumab and zoledronic acid (a bisphosphonate) are the most frequently utilized agents.[43] Denosumab has been shown to have a benefit over zoledronic acid in reducing overall bone tumor burden, but comes with a significant additional cost, resulting in the more common use of the latter.[43,44] The well-known adverse effects of these agents include jaw necrosis, hypocalcemia, increased risk of atrial fibrillation and stroke (bisphosphonates), and a higher risk of infection (denosumab).

Depending on the primary tumor identified on biopsy, systemic chemotherapy and more recently developed targeted therapy or immunotherapy may play a role in controlling systemic disease burden.[29,45] Systemic chemotherapy regimens generally come with a significantly increased risk of toxicity, and the treating hospitalist should be cognizant of possible adverse effects during the course of therapy.

ROLE OF THE HOSPITALIST PHYSICIAN IN THE MANAGEMENT OF PATIENTS WITH SPINAL MASS

The medical complexity of hospitalized patients has increased substantially over time, making multidisciplinary care increasingly necessary and common. In addition, patients with disseminated cancer are likely to be older, and are thus more likely to have multiple medical comorbidities that complicate their pre- and postoperative care. Much like the primary care physician in the outpatient setting, the hospitalist physician today serves an important role in coordinating treatment plans among multiple care teams and is vital to managing medical comorbidities.

Hospitalists are often called upon to evaluate patients for their overall risk for surgery, therefore today's hospitalist needs a deep understanding of perioperative medicine, and must be well versed in the utilization of the multiple risk stratification tools. For a risk assessment of major adverse cardiac and cerebrovascular events (MACCE) the hospitalist needs to be familiar with the Gupta Score and the Revised Cardiac Risk Index (RCRI).[46,47] They also need to understand the current AHA/ACC guidelines for perioperative assessment,[48] as well as ASA classification.[49] Although the risk of MACCE is a central part of preoperative assessment, there are other tools to aid with risk stratification, such as the risk of postoperative respiratory failure estimated by ARISCAT.[50] The risk of postoperative venous thromboembolism is defined using the Caprini score.[51] Understanding which patients can proceed to surgery without delay and which patients need further testing for enhanced risk stratification is an integral skill for the current hospitalist.

In the postoperative period the hospitalist continues to play an important role, as they are often consulted to manage postoperative sequelae. In the postoperative period the hospitalist may be called upon to manage metabolic complications and electrolyte disturbances, or to manage hyperglycemia in steroid-treated patients and diabetics. Prevention, early detection and treatment of postoperative venous thromboembolic disease (VTE) are also critical management skills for the hospitalist, as are the detection and management of postoperative infections. Additionally, the hospitalist must feel comfortable managing acute postoperative pain, and working collaboratively with dedicated pain medicine services. Lastly, the hospitalist must frequently assess goals of care, and involve palliative care when indicated, after careful consultation with their surgical colleagues.

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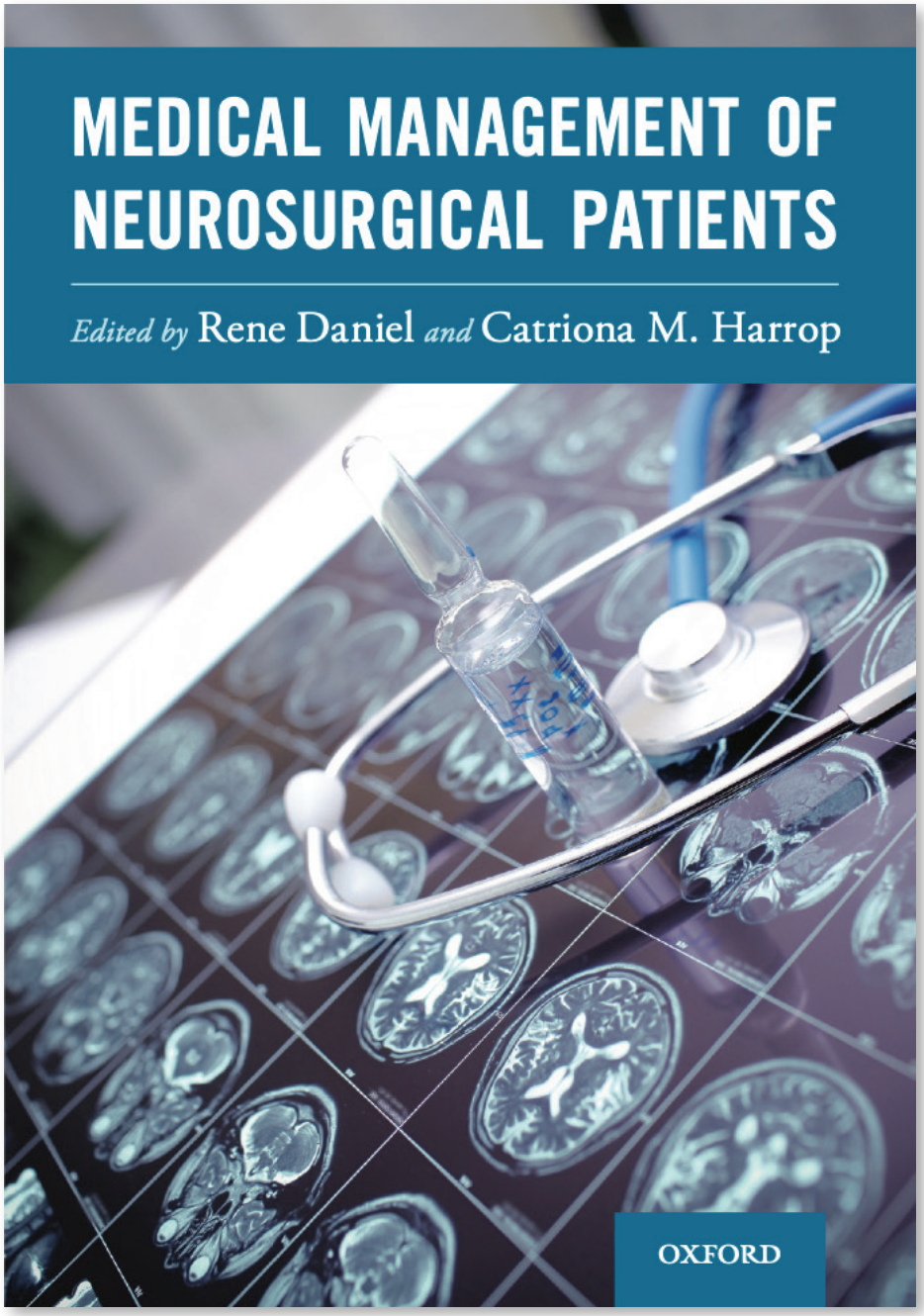
Textbook Spotlight



Modern management of neurosurgical patients requires close cooperation between neurosurgeons and other specialists. The latter include internists, nurse practitioners and physician assistants. This textbook aims to provide a guide for these professionals to the challenges associated with medical management of these patients. It gives an overview of neurosurgical operations and procedures, seizure management, and preoperative risk stratification. It further discusses the intricacies of the management of fever, infection, electrolytes, bleeding disorders and endocrine problems in the context of central nervous system injury. A particular emphasis is placed on the management of pressure injuries, pain management, and physical and occupational therapy, which are critical areas in the care of the neurosurgical patient. Finally, it reviews the types of contributions palliative care can make to the care of the neurosurgical patient. The book's objective is to provide a practical tool, and where appropriate its chapters include algorithms and tables to increase the efficiency of medical decision making when taking care of these patients.

Management of Hyperglycemia in the Neurosurgery Patient

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ABSTRACT

Hyperglycemia is associated with adverse outcomes in patients who are candidates for or underwent neurosurgical procedures. Specific concerns and settings that relate to these patients are preoperative glycemic control, intraoperative control, management in the neurological intensive care unit (NICU), and postoperative control. In each of these settings, physicians have to ensure appropriate glycemic control to prevent or minimize adverse events. The glycemic control is usually managed by a neurohospitalist in co-management with the neurosurgery team pre- and postoperatively, and by the neurocritical care team in the setting of NICU. In this review article, we outline current standards of care for neurosurgery patients with diabetes mellitus and/or and hyperglycemia and discuss results of most recent clinical trials. We highlight specific concerns with regards to glycemic controls in these patients including enteral tube feeding and parenteral nutrition, the issues of the transition to the outpatient care, and management of steroid-induced hyperglycemia. We also note lack of evidence in some important areas, and the need for more research addressing these gaps. Where possible, we provide suggestions how to manage these patients when there is no underlying guideline.

Keywords: *neurosurgical patient, hyperglycemia, hypoglycemia, glycemic control, management, standard of care*

INTRODUCTION

In the general inpatient population, both high blood glucose levels and low glucose levels are associated with unfavorable outcomes.[1,2] This is also true for neurosurgical patients. Both prospective and retrospective studies showed that hyperglycemia is a risk factor for poor outcomes in traumatic brain injury, and increases both short and long-term mortality in patients with primary intracerebral hemorrhage and wound infections following spinal procedures.[3-7] It is also associated with increased risk for vasospasm following aneurysmal subarachnoid hemorrhage and poor functional outcome after acute ischemic stroke.[8,9] A retrospective study of 918 patients undergoing craniotomy and spine-related neurosurgical procedures demonstrated that preoperative hyperglycemia [defined as blood glucose (BG) exceeding 120 mg/dL] was associated with increased risk of postoperative complications at all levels of care.[10] Similarly, hyperglycemia in diabetes patients (defined as blood BG over 200 mg/dL) was an independent predictor of morbidity after brain biopsy in a retrospective study.[11]

Surgical procedures themselves are known to induce intraoperative hyperglycemia.[12] On the other hand, anesthetics moderate glucose and glucose metabolism.[13,14] For example, volatile anesthetics inhibit secretion of insulin in response to glucose, and thus inhibit the stress-induced hyperglycemia.[13] Clinical and animal studies suggest that hyperglycemia exacerbates neurological damage due to brain ischemia.[15,16] These results, in addition to those outlined above, emphasize the deleterious effects of poor glycemic control.

Increase in complications due to hyperglycemia among neurosurgical patients has also been reported for systems other than the central nervous system (CNS): genitourinary (acute renal injury and urinary tract infections), digestive (paralytic ileus), the peripheral nervous system (PNS, peripheral nerve root lesions) and cardiovascular (cardiac arrhythmias).[17,19] Electrolyte abnormalities were also associated with hyperglycemia in neurosurgical patients.[17,19]

Finally, another factor that often induces hyperglycemia in the neurosurgery patients is the use of glucocorticoids. Risk factors for steroid induced hyperglycemia include traditional risk factors for type 2 diabetes mellitus, along with dose and duration of steroid usage.[20] Other risk factors are concurrent immunosuppression, hypomagnesemia and hepatitis C virus infection.[20] Glucocorticoids can induce hyperglycemia in non-diabetics and worsen glucose control in established diabetic patients, with negative consequences outlined above.

Similar to hyperglycemia, hypoglycemia was also associated with complications in neurosurgical patients, including increased mortality.[18] This is due to the crucial role of glucose for the brain metabolism.[21] In addition, the glucose

metabolism in brain in controlled by glucose transfer, and the glucose levels in blood thus may not reflect the glucose levels in brain cells, which could be lower than expected based on blood glucose levels.[22] The case thus can be made for careful glycemic control at any point of management of a neurosurgical patient.

In this article, we review glycemic goals and management practices for patients, which were admitted for a neurosurgical procedure. For practical purposes, we have subdivided the management into six steps. Each step has its own specific features and concerns. We will proceed chronologically, starting with admission, preoperative management, continuing with intraoperative glycemic control, postoperative care in intensive care unit setting and on the floor, and finishing with discharge and transition into outpatient care.

ADMISSION

The neurosurgical procedures can be divided into elective and emergent. Depending on the procedure, patients can be admitted on the day of surgery, or if need be, prior to surgery (for example, if extensive surgery is anticipated and patient needs pre-operative optimization under close supervision). The management of BG in emergent procedures is described below in the section 4 (Intraoperative control). In this section, we concentrate on elective and thus scheduled procedures.

Prior to admission, the patient will likely undergo preoperative testing at an outpatient clinic. At present, there is no consensus with the respect to the glycemic goal of patients with a planned neurosurgical procedure. A review article suggests that the goal should be consistent with the goals as outlined for outpatient population by then American Diabetes Association[1,23] According to the latest ADA guideline, the pre-meal glucose targets are 80-130 mg/dL and hemoglobin A1C levels less than 7%. The A1C goal can be relaxed to 8% in selected patients {e.g. patients with history of severe hypoglycemic episodes, and/or limited life expectancy, see ADA guideline for details.[1,23] In the absence of evidence to the contrary, we suggest that these targets are likely appropriate for patients planning to have a neurosurgical procedure.[1] Hemoglobin A1C level should be checked during the preoperative testing visit unless there is one available within last 3 months.[1,24] Admission orders should clearly state whether the patient is a Type 1, Type 2 or a non-diabetic.

PREOPERATIVE GLYCEMIC CONTROL

Prior to admission, patients with diabetes mellitus type 2 are likely treated with either oral diabetic medications or with insulin. Oral medications may have unpredictable pharmacokinetics and/or pharmacodynamics during surgery, and are known to have a number of undesirable side effects.[25] For these reasons, we suggest oral medications should be held the day of surgery.[25] This is consistent with the general ADA recommendations [1]. Given the half-life of metformin, some authors suggest holding it 24 hours prior to surgery, and 48-72 hours is suggested for sulfonylureas.[23] However, there is no recent clinical evidence suggesting better outcomes with these strategies.[23]

For insulin-dependent diabetes mellitus type 2, many studies suggest to continue the full dose of the long acting insulin (e.g. glargine).[1,23] However, a recent observational study in type 2 diabetic patients undergoing ambulatory surgery showed that the optimal dosing of glargine is 60-87% of the daily dose, which is our recommendation.[26]

Some type 2 diabetics are on premixed insulin (long and short acting components). In this situation, there appear to be two options: if the surgery is not scheduled for a very near future, we suggest that patient can be transited, in collaboration with their PCP or endocrinologist, to a regimen including long acting and meal insulin. The meal insulin then can be held prior to surgery. This appears to be a preferable solution, since premixed insulin regimen on the floor results in more hypoglycemic episodes than a regimen including long acting and meal insulin.[27] Alternatively, ADA guidelines recommend that the patient can take ½ the dose of the premixed

Table 1. Preoperative Adjustment of Diabetic Medications

Medication	DM Type 1	DM Type 2	Reference
Re			
Oral	–	Stop	25
Basal insulin (long acting, one dose daily)	Full dose	Decrease to 60-87% dose	12,26
Basal Insulin (split dose)	–	Full dose the night, decrease as above in am	24
Meal insulin	Stop	Stop	11
Mixed Isulin	–	½ intermediate component in am	1
Correction dose (q6h)	Start	Start	1, 12
Insulin pump	Continue*	–	26 26-30

*Stop pump and start insulin infusion if emergent or a long procedure

insulin dose, which corresponds to the long acting component. For example, if a patient is taking 50 units of 70/30 before breakfast, 70% of this dose is conceptually intermediate acting insulin and would be 35 units. One could give ½ (17 units) of that amount in the form of NPH or longer acting insulin the AM of surgery.[1]

Type 1 diabetics should receive their full dose of basal insulin preoperatively. A common mistake is to stop basal insulin when a patient is made NPO. This could lead to rapidly elevating BG that could precipitate DKA. Type 1 diabetics thus should continue their basal insulin.[12]

Insulin pumps are becoming a more popular insulin delivery method in both type 1 and type 2 diabetics. In general, insulin pumps can be left in place for shorter elective procedures. They have been shown to be safe in several studies[28-32] If the patient demonstrates decompensated metabolic control, the patient should be started on an insulin infusion and the pump be removed. In general, the infusion should be in place for ½ hour before the pump is discontinued. It is optimal to have the patient test their basal rates before surgery. Patients should also change their insertion site and reservoir the day before surgery and bring extra pump supplies with them.

Post-operatively, the pump can be continued as long as the patient is awake, alert and oriented and is capable of managing the pump. If the patient is not capable of appropriate self- management, the pump should be discontinued after a subcutaneous basal/bolus regimen is started.

Insulin pumps should be discontinued for emergent or longer neurosurgical procedures.

Finally, if a patient is NPO following admission and waits for the procedure for an extended period of time, correction dose (sliding scale) insulin should be added to the long-acting insulin regimen (see above), with point of care glucose checks every 6 hours.[1,12] ADA guidelines propose the inpatient glycemic goals to be 140-180 mg/dL.[1] There is no evidence suggesting that these goals should be different for neurosurgical patients. Therefore, we think these goals are appropriate in this patient population.

The proposed adjustments in insulin regimen for patients with insulin-dependent diabetes mellitus are summarized in **Table 1**.

INTRAOPERATIVE CONTROL

Recent results (see above in Introduction) suggest that close and careful glucose control during a procedure is critical for a successful outcome.[13-16] A very recent observational study showed that severe intraoperative hyperglycemia (defined as BG > 180 mg/dL) is associated with postoperative composite infections after craniotomy.[33]

These results suggest that the intraoperative glycemic goals should be BG less than 180 mg/dL for neurosurgical procedures. In the absence of direct evidence, we suggest that the lower end of the range should be glucose no lower than 140 mg/dL, which is the target of ADA for hospitalized patients.[1] We note that a retrospective study on patients undergoing a cardiac surgery suggested that blood BG less or equal to 140 mg/dL was associated with worse outcomes.[34]

Oral glucose-lowering agents are to be stopped prior to procedure (see above). However, the last time when they were taken should be taken into consideration. Assuming their effect wore off, the glucose levels during the procedure are dependent on the intrinsic control by the patient's body, and on insulin doses given during the procedure. Point of care glucose checks can be used to monitor BG during procedure. For patients who were only on oral medications at home, correction insulin doses appear to be an acceptable approach.

There are two options for BG control in patients who already are treated with insulin at home: long acting insulin together with the correction dose insulin, and continuous intravenous insulin infusion. There is no evidence suggesting which of these methods leads to better outcomes in neurosurgical patients.

Table 2. Management of BG in patient receiving enteral tube feeding (TF) or parenteral nutrition.

Situation	Basal Insulin	Bolus Insulin	Comments
Continuous TF	Continuous IV insulin infusion until patient reaches goal TF. This will be TDD* of insulin for that TF rate. Basal insulin will be 30-40% of the TDD* in the form of glargine daily or NPH/detemir BID	Bolus: Regular insulin q 6 hours with regular insulin correction.	Patients with DM1 always require basal insulin. ADA recommends basal insulin plus rapid acting correctional insulin every 4 hours.
Nocturnal TF	NPH and regular insulin given before TF	Can use correction dose rapid acting insulin during TF	Give an AM dose of NPH as well in insulin requiring DM2, SM1 and patients on glucocorticoids
Bolus TF	Add regular insulin to TPN bottle.	Rapid acting insulin with the TF bolus	
Parenteral	Add regular insulin to TPN bottle.	Rapid acting correction dose insulin	
Interrupted enteral	Run D5 or D10 if insulin was given. Reduce basal dose.	Hold bolus doses	Continue basal insulin for DM1

References: [1], [33]; *TDD - total daily dose

Multiple factors could be involved in selection of a method to control BG. These include the type of diabetes and the length of procedure. Given all the factors that could influence BG levels, we suggest that the continuous insulin infusion is a better option for the type I diabetics undergoing a long procedure and prevents strong fluctuations in the BG levels. The same applies to the type II diabetics that have a highly insulin-dependent diabetes mellitus and had a poor BG control prior to procedure. For non-insulin requiring type 2 diabetics, long acting insulin with correction dose insulin seems to be an appropriate option. For emergency procedures in patients with hyperglycemia with or without type 2 diabetes, intravenous insulin infusion seems to be an appropriate option, since it can enable better control if unexpected variations in BG levels occur.

POSTOPERATIVE GLYCEMIC CONTROL IN THE NEUROLOGICAL INTENSIVE CARE UNIT SETTING

Following a procedure, neurosurgical patients often spend a significant period of time in the neurological intensive care unit (NICU). Given the stress-induced hyperglycemia, hyperglycemia associated with SAH, ICIH and TBI, and the effect on anesthetics on glucose control, it is not surprising that hyperglycemia is common among critically ill patients.[35,36] What should be the glycemic goal in this setting? A meta-analysis of sixteen randomized clinical trials by Kramer et al. analyzed protocols that used tight glycemic targets (70-140 mg/dL) versus protocols that kept the glucose levels below 144-300 mg/dL.[35] A few conclusions were drawn. First, tight glucose control resulted in better neurological outcomes, but had no effect on mortality. However, hypoglycemic episodes were far more common than in the tightly controlled group. Second, although the "loose control" protocols were associated with worse neurological outcomes, these were observed only when glucose levels were above 200 mg/dL. The outcomes for the range between 140-180 mg/dL were not worse than in the tight glucose control group. Similar results were obtained by Ooi et al, who performed a meta-analysis of outcomes of tight glucose control versus conventional glucose control in critically ill neurological and neurosurgical patients.[37] Nine studies were included in the analysis, five of which were restricted to neurosurgical patients and four included neurological patients. The results showed that tight glucose control improved the neurological outcomes and reduced rates of infection. Again, mortality was not affected by the tight glucose control, but it did result in more hypoglycemic events. These results did not enable the authors to determine the optimal glucose targets, which means the question of appropriate glycemic targets remains , to a certain degree open.[37] Nevertheless, the available evidence suggest that the glycemic goal between 140-180 mg/dL appears to be appropriate for critically ill neurosurgical patients.[35-37]

Critically ill patients immediately post-procedure are either managed with intravenous insulin infusion or long-acting insulin with correction dose insulin. Nutrition is usually restarted as early as possible post-procedure. Patients can be transitioned from intravenous insulin infusions to subcutaneous regimens when they are clinically stable. It is imperative to remember that there should be an overlap of 1-2 hours between the first subcutaneous insulin dose and the discontinuation of the insulin infusion.[23]

A significant percentage of critically ill patients require enteral tube feeding, either due to being intubated or to dysphagia. In these cases, there is a paucity of data regarding the optimal method of glucose management with enteral nutrition. We follow the ADA guidelines with some modifications depending on the situation,[1,23,38] (**Table 2**). If a patient is capable of oral intake, he or she can be then restarted on a long acting and meal insulin. We note that the doses of the subcutaneous insulin should be calculated from the insulin does that were given during the insulin infusion, using standard protocols. Oral home diabetic medications are not restarted the critical care setting. Instead, these patients are treated with an insulin-based regimen, as outlined above.

Per the ADA guidelines, glucose monitoring for patients who can eat should be performed before meals.[1] In the patient who do not eat, glucose monitoring is advised every 4–6 h.[24] If patients are managed with intravenous insulin infusion, BG testing is should occur in more frequent intervals, from every 30 min to every 2 h.[1]

POSTOPERATIVE GLYCEMIC CONTROL ON THE FLOOR

BG levels are usually managed in our practice and in many neurosurgical practices after transition from NICU or directly from the postoperative unit by a team of neurohospitalist and the neurosurgical primary team.

Observational studies in general surgery patients have concluded that perioperative hyperglycemia is associated with poor outcomes such as delayed wound healing, increased chances of infection, prolonged length of stay and increased health care costs.[39-41]

ADA guidelines recommend for general inpatient population the BG goal 140-180 mg/dL, and in the absence of contrary evidence, this appears to be an appropriate goal for neurosurgical patients on general floor.[1] When BG falls below this goal, therapeutic regimen should be adjusted. However, for patients who have history of successfully maintaining tight glycemic control in the outpatient setting and are clinically stable, the glycemic goal can be lower than 140 mg/dL.[1] The glycemic goal is usually achieved by a combination of basal and bolus insulin.[1] A randomized clinical trial of insulin therapy in the management of general surgical patients demonstrated the superiority of basal-bolus insulin when compared to the correction dose insulin in achieving glycemic goals.[39] One caveat of the trial is that the BG goal was 100-140 mg/dL, which is lower than the BG goal recommended above.

Finally, a recent trial suggests that sitagliptin, either alone or in combination with basal insulin, was as efficient in achieving BG goals as a basal-bolus insulin regimen.[42] However, more studies will be needed to compare efficacy and safety of sitagliptin-based regimen with the standard therapy.[1,42]

As noted in Introduction, glucocorticoids are commonly used in the neurosurgical patient. They pose a significant challenge to the achievement of glucose goals.

Steroids induce mainly post-prandial hyperglycemia, with peaks occurring usually in the afternoon and evening.[43-45] Checking a baseline fasting BG or hemoglobin A1C prior to the procedure helps predict patients at risk for developing hyperglycemia while on steroids.[20]

Several approaches have been proposed for the treatment of glucocorticoid-induced hyperglycemia, but no published studies have investigated the efficacy of these approaches. Our suggestions are as follows. Bedside glucose testing should be initiated for patients with or without a history of diabetes. Another important factor is a carbohydrate consistent diabetic diet. Insulin therapy should be initiated for patients whose blood sugars exceed established glucose goals. Patients already on basal-bolus therapy will need increases in their insulin doses, particularly in the prandial component. Occasionally, patients will require a continuous IV insulin infusion for severe and persistent elevations in BG despite subcutaneous insulin[24]

It is very important that insulin dosing be adjusted during glucocorticoid tapers. Insulin should be proactively adjusted to avoid hypoglycemia.

GLYCEMIC CONTROL DURING TRANSITION TO OUTPATIENT CARE

The discharge is the next critical step in managing neurosurgery patients and their BG levels. While there are clinical studies for management of inpatient hyperglycemia (see above), little is known about management of hyperglycemia in neurosurgical patients after discharge.

The admission A1C can be helpful in formulating an appropriate treatment regimen. A recent discharge algorithm for glycemic medication adjustment based on admission A1C found the average A1C reduction decreased from 8.7% on admission to 7.3% three months after discharge.[46]

In the case of patients who do not continue steroids as outpatients, it is usually possible to discharge them on their home diabetic medications.[1] Patients who were not well controlled prior to admission will require necessary adjustments to their regimen to optimize glucose control. This often necessitates the utilization of insulin. Insulin naïve patients need training in self-injection technique and diabetes education. This includes the prevention and correction of hypoglycemic episodes. The insulin requirements are based on the inpatient insulin requirements. PCP should be informed of the changes in the patient's medications.

If patients continue to be treated with glucocorticoids upon discharge, BG management becomes a complex process. Elderly patients and debilitated neurosurgical patients are even more

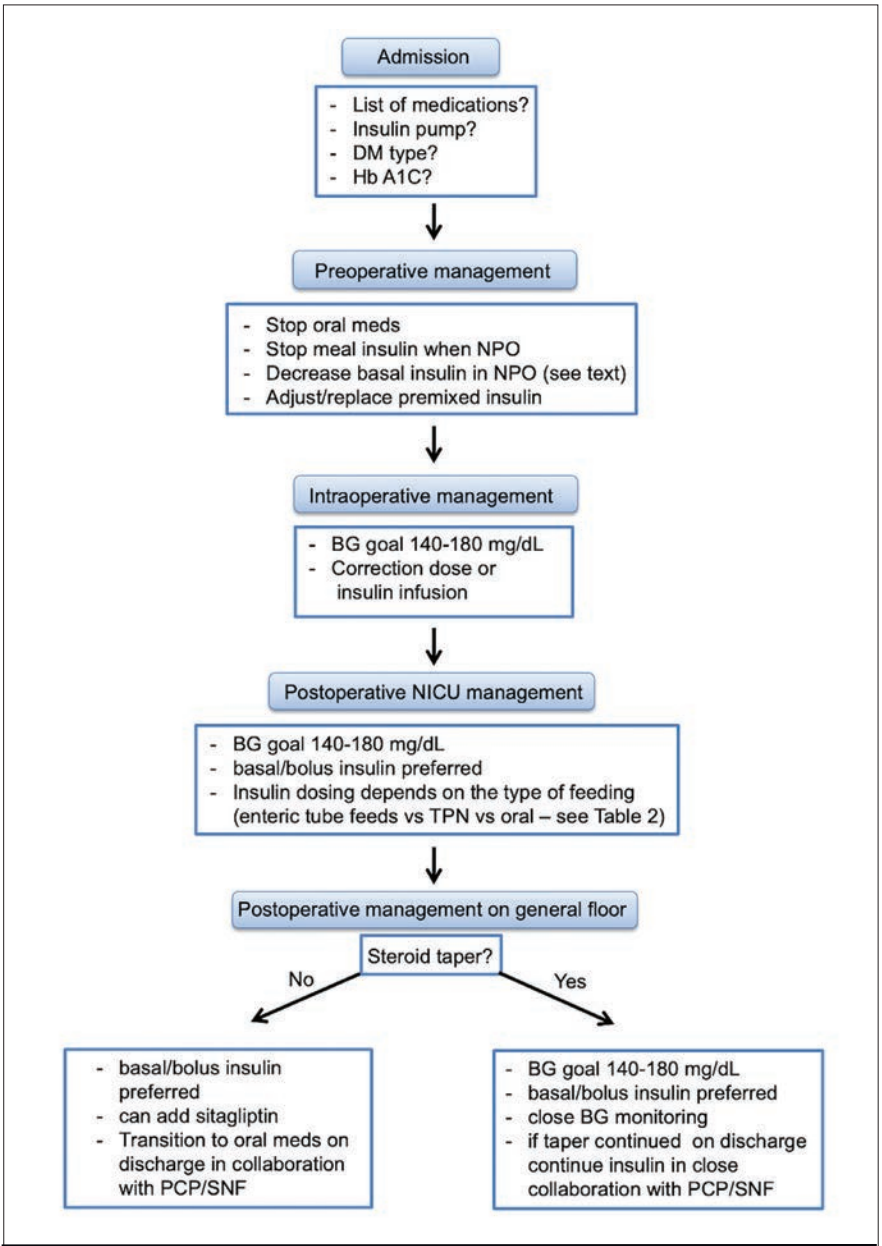

Figure 1.

Algorithm for management of hyperglycemia in neurosurgery patient.

challenging when it comes to self-adjusting insulin doses at home. There is no "standard steroid taper" and different neurosurgery practitioners use different steroid tapers depending on the clinical scenario. Hence, as of now there is no standard protocol for management of hyperglycemia at home while on steroid taper. We thus believe that it is critical that the patient monitors their BG before meals and at bedtime. The must also be in contact with the health care provider who is managing their glucose levels.

A survey of patients discharged on insulin that included a high proportion of patients on glucocorticoids showed that 49% of patients reported BG level over 300 mg/dL.[47] A survey done in a diabetic center at Massachusetts General Hospital between 2011 and 2013, showed the incidence of hypoglycemia (BG <60 mg/dl), among a diabetic population discharged on glucocorticoids was up to 46%.[48] Given the risks of hyper- and hypoglycemia, development of standard protocols for management of BG in patients on steroid taper outside of hospital setting is highly desirable.

If blood sugars are below 70 mg/dl, patients in our practice are advised to reduce insulin dose by 20%. If blood sugars are above 300 mg/ dl, the insulin dose should be increased by 20%. These are arbitrary adjustments and need to be tapered according to the dose of steroids and BG levels at home, in conjunction with PCP. Given the lack of supporting studies, we categorize these suggestions and those below as expert opinion-level recommendations.

Taken together, we suggest that close follow-up with PCP, ideally within 1 week is essential. For newly diagnosed diabetics while in the hospital or steroid induced hyperglycemia requiring insulin, the PCP should be sent a copy of the hospitalization record or a brief discharge summary including a list of the discharge medications. The neurohospitalist should contact the PCP and convey the information to make sure they are aware for the need for a close follow-up.

SUMMARY AND DISCUSSION

In this article, we review management of hyperglycemia in the neurosurgical patient. Neurosurgery patients pass through several levels of care, necessitating careful adjustment in the management of their hyperglycemia. These include the preparation for the neurosurgical procedure (including the NPO regimen), intraoperative management, postoperative management (including possible stays in neurological intensive care units), and finally the transition to outpatient care. Our suggested approach to the management of BG levels in neurosurgery patients is outlined in the **Figure 1**.

Several major points bear repeating:

1. Outpatient oral anti-hyperglycemia medication should be held prior to the procedure.
2. For insulin-requiring type 2 diabetics, basal long-acting insulin should be taken at a decreased dose and the meal insulin held prior to procedure (see above). If the patient is being treated with premixed insulin, the long-acting component of the premixed insulin should be taken at a decreased dose (see above).
3. Insulin pumps do not have to be discontinued prior to a short procedure. If the BG control decompensates, the patient undergoes a longer or an emergent procedure, or is unable to control the insulin pump, the pump should be stopped and replaced by an insulin infusion during the procedure.
4. The available evidence suggests that a relaxed blood BG control, with a glycemic goal of 140 mg/dL to 180 mg/dL leads to better outcomes for neurosurgery patients than a tight BG control with a goal less than 140 mg/dL. This result is consistent with the BG management goals proposed in the ADA guideline for general inpatient population.
5. Given the significant role that enteric tube feedings play in the management of neurosurgery patients, the attending physician needs to be aware of the BG management methods.
6. After transition out of the neurological intensive care unit, glycemic goals are usually achieved by treatment with insulin. The combination of a basal insulin (e.g. glargine) and bolus insulin (meal and correction dose) yields significantly better outcomes that management with the correction doses only, or management with premixed insulin.[27,39] However, very recent evidence suggests that addition of sitagliptin leads to an improved glucose control.[42]
7. Use of steroids significantly impacts BG management. Patients often require higher doses of insulin, particularly in the prandial component. BG levels need to be followed closely, particularly with decreasing glucocorticoid dosages to prevent hypoglycemia.
8. Neurosurgery patients discharged to home or to a skilled nursing facility (SNF) need close follow up in order to maintain appropriate glycemic goals. The transition of care plays a crucial role at discharge. An early appointment with the primary care physician is a must. Interaction between patient's primary care physician and inpatient attending physician is necessary to ensure smooth transition of care, and appropriate glycemic control. If the patient is being discharged to an intermediate care facility, it is advisable that the attending physician prepares detailed instructions and contacts the facility physician to ensure the appropriate glycemic control.

The summary which is listed above and our suggested management guidelines are based on differing levels of evidence. There is a new clinical study, which supports the decrease of basal insulin (glargine) prior to procedure.[26] On the other hand, outside of the ADA guideline, we did not identify any studies that would support that management of the premixed insulin as suggested in our review, although it appears to be somewhat consistent with the management of long-acting basal insulin. We rely here on the expert opinion. The Rabbit 2 Surgery trial, which compares management of hyperglycemia with basal vs correction dose only insulin, was a double blinded, randomized trial and thus provides a high level of confidence to the proposal that basal insulin should be included in the management of inpatient neurosurgery

patients.[39] Additionally, premixed insulin should be avoided in the inpatient setting. There are multiple studies that support the relaxed insulin control in the neurological intensive unit (see above). In addition, there is an ongoing clinical trial addressing intensive versus non-intensive insulin therapy for hyperglycemia after traumatic brain injury, which may shed more light on this issue.[49]

An important and developing issue is whether preadmission diabetes mellitus should impact glycemic goals in hospitalized patients. A growing body of literature suggests that in general ICU patients, while tight glucose control is associated with decreased mortality in the nondiabetic population, diabetics may benefit from higher glucose goals.[50,51] Similar, a very recent observational study reported that chronic pre-morbid hyperglycemia increase the risk of hypoglycemia and modifies the association between acute hypoglycemia and mortality.[52] It remains to be established whether these conclusions can be extended to neurocritical patients. If so, the glycemic goals will have to differ for patients with preadmission diabetes and nondiabetics. We hope this issue will be addressed in near future by researchers in the field.

Unfortunately, there is no evidence-based algorithm for the management of the steroid taper. Here, we again rely on the expert opinion. There is, however, an ongoing clinical trial addressing the treatment of inpatient diabetes on steroids. Unfortunately, no results are available at the time of this publication.[53]

A crucial issue with regards to glycemic control is the development and management of hypoglycemia in neurosurgical patients. In this article, we have concentrated on the management of hyperglycemia, and did not approach systematically the issue of hypoglycemia, We note that hypoglycemia issue in general inpatient population has been addressed in the ADA guideline.[1] Nevertheless, hypoglycemia in neurosurgical patients is a topic that deserves an extensive analysis and warrants a different article.

Taken together, there is need for more evidence addressing management of hyperglycemia in neurosurgery patients. Existing gaps in our knowledge include glycemic goals in the presence vs. absence of preexisting diabetes mellitus, evidence-based protocols for management of steroid taper, and use of oral diabetic medications in inpatient setting. Nevertheless, the current level of knowledge allows us to propose an approach to the hyperglycemia management that we hope neurohospitalists find helpful and informative (**Figure 1**). We also hope that our review will stimulate research in the areas that need high quality of evidence to improve outcomes of neurosurgery patients.

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Statement of Conflict of Interest

The authors declare no competing interests.

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Opportunities And Challenges – The Next 5 Years of a Service Dedicated to the Medical Management of Neurosurgical Patients

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ABSTRACT

Neurosurgery hospitalists will continue to be closely involved in the management of patients which undergo neurosurgery. In the first article, we discuss the tremendous potential of the service for improving the care for neurosurgical patients at Jefferson. We highlight the interactions with other services and the areas for potential growth. Further, we emphasize the need for constant feedback, which is necessary to improve the care provided by FHS.

In the second part of the article, we highlight the potential impact of FHS beyond the Jefferson Hospitals in Center City of Philadelphia, to other hospitals within the Jefferson network, and beyond Jefferson. We re-emphasize the educational opportunities FHS is able to provide for other neurosurgery hospitalists nationwide and on international level, and the future research and education program.

We hope that this article will increase understanding of other physicians of FHS work, and that it will open new interactions with other services both at Jefferson and beyond.

MANUSCRIPT

Over last 5 years, FHS became closely integrated part of the Department of Neurological Surgery, proving both preoperative and postoperative care for neurosurgical patients, as well as orthopedic spine patients of the Department of Orthopedics. In addition to consulting services, FHS also serves as the primary team for many neurosurgical patients, particularly those with multiple medical comorbidities. FHS role as the primary team is appreciated by other services, as reflected in increasing preferences for patients to be placed on the FHS service. In taking care of neurosurgical patients as a primary team, FHS helps surgical teams to increase the number of procedures performed at Jefferson. Recently, FHS was also tasked by Jefferson with providing consultative and co-management care for the ophthalmology services at the Wills Eye Hospital and the Jefferson Hospital of Neuroscience, as the need for the hospitalist support for ophthalmology became apparent.

The increasing demand placed on the service is appreciated, but at the same time strains the service resources. This is due to the above stated fact – FHS is an attending-run service, which until very recently did not utilize NPs or residents. Thus, patient care, from admission to discharge, is provided by the attending physician only, although with the support from other consulting services, which is of course highly appreciated. FHS is working to address the situation on multiple ways, with the objective to deliver the highest possible patient care: First, FHS is working closely with other services which admit similar patients, i.e. neurosurgery, orthopedic spine, general medicine and trauma as well as the Emergency Department, to coordinate admission criteria in order to place patients onto appropriate services, and to avoid inappropriate admissions. A continuous feedback from neurosurgeons is necessary. Second, FHS was pleased to welcome this year its first nurse practitioner (NP). Greater Involvement of NPs is expected to help with appropriate management of resources and will ultimately lead to increased number of patients accepted by FHS. Third, close interactions with the nursing staff is crucial to the FHS success. Thus, training and education of the nursing staff by FHS will become an important aspect of the FHS work (more on that below).

After establishment of the FHS, other Jefferson departments, following its example, established their own services. These include Medical Oncology and Gastroenterology, both who now have dedicated Hospitalist services. FHS is always willing to share the practical experience and help in establishment of this care model, in order to ensure high quality patient care.

In the Jefferson network outside of the Center City, there is no FHS-like dedicated service. Likewise, hospitalist services for neurosurgeons around the country and internationally are usually provided at a consulting or co-management level, and dedicated primary services like FHS to our knowledge do not exist. The situation is aggravated by a scarcity of guidelines how to manage medical problems in neurosurgical patients. Given the overall positive experience with FHS at Jefferson, it would seem reasonable to initiate cooperation and collaborations with other hospitals at Jefferson and beyond with the objective to standardize patient care and decrease inefficiencies, thus decreasing length of stay, mortality, complications and readmissions. Indeed, FHS took the fist step by producing, together with neurosurgery and many other services of Jefferson, the first textbook in the field.[1] We hope this text will become a standard of care at Jefferson and beyond when it comes to medical management of these patients.

Table 1. Mortality of patients with epidural abscess at Jefferson.

Mortaility, FHS vs. Other Services				
	N total cases	N total cases		Overall Mortality
FHS	48	0	0.0%	p=0.026
Other	48	6	12.5%	

In summary, the previous paragraph outlines a set of challenges and opportunities for neurosurgery hospitalists both at Jefferson and nationwide. The standardization of guidelines and patient care across multiple hospitals is paramount. The published textbook is only the first step in this direction and needs to be build upon. In addition to increasing awareness of the book by presentations at national and international meetings, the textbook should be updated in a timely manner, and a second edition may be needed in not-so-distant future. Involvement of non-Jefferson physicians in its creation may be also possible. In addition, other educational opportunities arise on the heels of the book. At present, there is no symposium which is dedicated to the education of neurosurgery hospitalists. Organization of this type of event at Jefferson would improve education and confirm the leading role of FHS in this process. Finally, education does not stop at once a year event and a book. An attractive option currently being explored is the creation of an online course for neurosurgery hospitalists, which could be accessed worldwide. FHS, together with other Jefferson departments have the resources to perform this highly useful service and create new education opportunities worldwide. Last but not least, educational resources should be present "at one's fingertips". Following this rule, FHS created its own smart phone application, which address the questions which arise from day to day work, from preoperative risk stratification to admissions to treatment protocols. Further improvement of the application and validation of thereof should again lead to improvement in patient care.

Patient care always brings to light many areas where clinicians run into the limits of human knowledge. It is the duty of any academic service to increase our understanding of the human body, its diseases and the diagnostic and treatment options available. Generally, there are two approaches to do so. First, it is always desirable to evaluate retrospectively the failures and processes in patient management. FHS here engages statisticians and is in the process of evaluating the impact of FHS physicians on the patient care, starting with mortality, length of stay and readmissions. Interestingly, our early data suggest that the mortality of patients with epidural abscess is strikingly lower when under care of FHS as a primary team, when compared to other services (**Table 1**). The statistical analysis is ongoing, and it is hoped it will point for us areas of potential improvement, which can be addressed.

Second, new, prospective research studies can address new hypothesizes, which were created on the back of newly available technologies and knowledge. Thus, new clinical studies in preoperative care, currently also ongoing, and collaboration with other services such as infectious diseases will keep FHS at the cutting edge of the field. At the same time, it is crucial to exchange experiences and results with other similar services nationwide. Thus, FHS will work toward collaboration with other similar services across the country. Incorporation of new approaches from other services should be implemented efficiently, such as, for example, improvement of preoperative risk stratification based on the Canadian guidelines.[2]

Taken together, neurosurgery hospitalist work in general and FHS work in particular is a continuously changing process, which is influenced by interactions with with and requests for help from other services, as well as by new data, either coming in from its own research or from other physicians' studies. However, the strive for the highest quality patient care remains constant.

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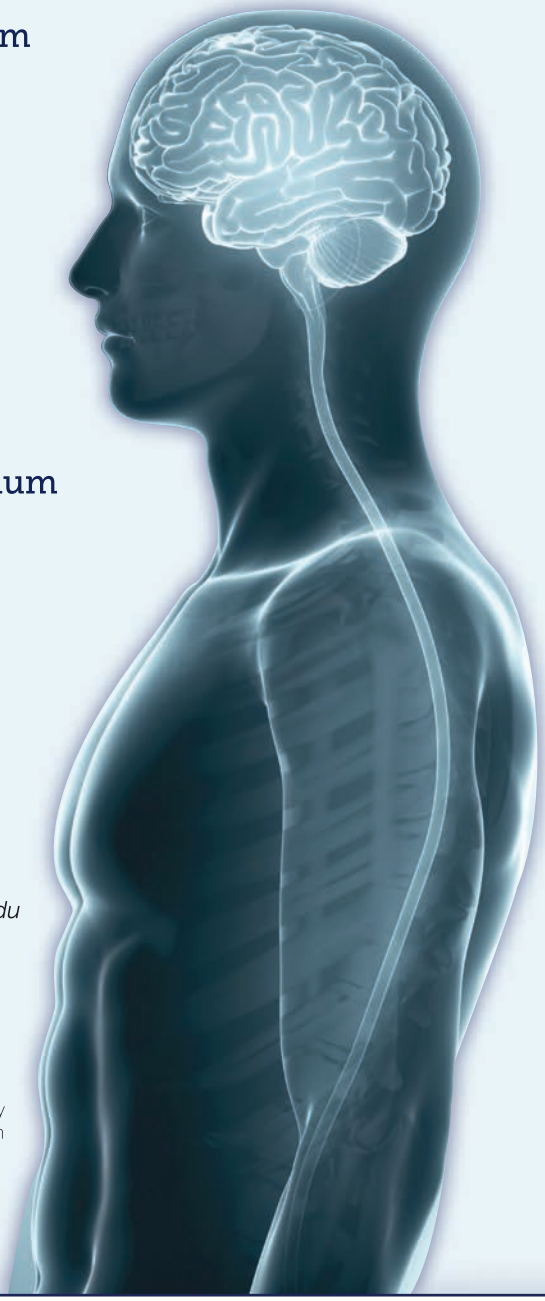

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