A high-pressure situation: decompressing the evidence regarding management of traumatic brain injury

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Learning Objectives

Define the pathophysiology of traumatic brain injury (TBI) in relation to its resulting complications.

Evaluate common agents used for appropriately managing severe TBI in adults.

Discuss the current evidence regarding treatment modalities surrounding severe TBI.

Review the TBI pharmacotherapy recommendations as outlined in the 2016 Brain Trauma Foundation guidelines and 2015 ACS TQIP guidelines.
Content Outline

Background
- Types and categorization
- Pathophysiology
- Complications
- Guidelines introduction

Acute management
- Intracranial hypertension management

Post-acute management
- Prophylaxis considerations
- Neuropsychiatric rehabilitation
Background

Taylor A. Roberson, PharmD
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“Disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury.”
Traumatic Brain Injury

- Open
  - Focal
  - Diffuse
- Closed
  - Focal
  - Diffuse

Traumatic Brain Injury

Primary mechanical damage

- Occurs at moment of impact
  - Direct trauma
  - Acceleration/deceleration & rotational forces

Secondary insult

- Delayed, non-mechanical damage
- Cerebral ischemia, intracranial hypertension

Direct tissue damage

Systemic insults
- Cerebral ischemia
- Metabolic failure

Transient neuronal depolarization
- NT release & neuronal excitation
- Cell energy failure & membrane disruption
- Cellular edema & microanatomic disruption
- Cerebral edema

Intracranial lesion
- Impaired autoregulation & altered CBF

Cerebral autoregulation maintains a constant cerebral blood flow (CBF) over a wide range of cerebral perfusion pressure (CPP) from 50 to 140 mmHg (solid line) by altering vascular resistance (represented by circles). Following brain injury autoregulation may be completely lost resulting in a linear relationship between CPP and CBF (dashed line).
Monro-Kellie Hypothesis

The Monro–Kellie doctrine dictates that once auto-regulatory mechanisms for keeping intracranial pressure (ICP) within tight limits are exhausted, decompensation occurs and ICP rises exponentially (red asterisk). CSF, cerebrospinal fluid.
Cerebral Perfusion Pressure

**MAP** - **ICP** = **CPP**

≥ 60 mmHg
# Goals of Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal Value</th>
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<tbody>
<tr>
<td>Pulse Oximetry</td>
<td>≥ 95%</td>
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<tr>
<td>ICP</td>
<td>20 - 25 mmHg</td>
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<tr>
<td>Serum sodium</td>
<td>135-145 mEq/L</td>
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<tr>
<td>( \text{PaO}_2 )</td>
<td>≥ 100 mmHg</td>
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<tr>
<td>( \text{PbtO}_2 )</td>
<td>≥ 15 mmHg</td>
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<tr>
<td>INR</td>
<td>≤ 1.4</td>
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<tr>
<td>( \text{PaCO}_2 )</td>
<td>35-45 mmHg</td>
</tr>
<tr>
<td>CPP</td>
<td>≥ 60 mmHg*</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 75 x 10³ / mm³</td>
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<tr>
<td>( \text{SBP} )</td>
<td>≥ 100 mmHg</td>
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<tr>
<td>Temperature</td>
<td>36.0-38°C</td>
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<tr>
<td>Hemoglobin</td>
<td>≥ 7 g/dL</td>
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<tr>
<td>pH</td>
<td>7.35-7.45</td>
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<tr>
<td>Glucose</td>
<td>80-180 mg/dL</td>
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# Devices for Monitoring ICP

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<thead>
<tr>
<th>Intraparenchymal bolt</th>
<th>External ventricular drain (EVD)</th>
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<tbody>
<tr>
<td>• Diagnostic</td>
<td>• Diagnostic</td>
</tr>
<tr>
<td>• Monitoring capabilities include temperature and PbtO₂</td>
<td>• Therapeutic</td>
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</table>
Management Guidelines

Brain Trauma Foundation: Guidelines for the Management of Severe Traumatic Brain Injury, 4th Edition
- Class 1, 2, 3 studies
- Level of recommendations

ACS TQIP: Best Practices in the Management of Traumatic Brain Injury

Acute Management
<table>
<thead>
<tr>
<th>Glasgow Coma Score</th>
<th>Best eye response</th>
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<td></td>
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<tr>
<td></td>
<td>To sound</td>
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<tr>
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<td>Spontaneous</td>
<td>4</td>
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<td>Reason:</td>
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<th>Best motor response</th>
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<td>Extension</td>
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<tr>
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<td>Abnormal flexion</td>
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<tr>
<td></td>
<td>Normal flexion</td>
<td>4</td>
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<td>Localizing</td>
<td>5</td>
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<tr>
<td></td>
<td>Obey commands</td>
<td>6</td>
<td></td>
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<tr>
<td></td>
<td>Untestable</td>
<td>Reason:</td>
<td></td>
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</tbody>
</table>

Glasgow Coma Scale

- ≥ 13: • Mild brain injury
- 9-12: • Moderate brain injury
- ≤ 8: • Severe brain injury

Rapid Sequence Intubation (RSI)

- Endotracheal intubation for severe TBI
  - Airway protection
- Intubation can transiently increase ICP
- RSI with medications including paralysis can ameliorate ICP rise
- Many clinical controversies on which medications should be used for RSI in TBI

Fluid Resuscitation

- Avoid hypotension
- 0.9% sodium chloride preferred
- Avoid hypotonic & hypoosmolar solutions
  - D5W
  - 0.45% or 0.225% NaCl
  - D5/0.45% NaCl or D5/0.225% NaCl
  - Lactated Ringer’s
- Colloids associated with higher mortality vs NS

Steroids

Brain Trauma Foundation

- The use of steroids is not recommended for improving outcome or reducing ICP
- In patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated
- Level I recommendation

Intracranial Hypertension

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Approach to Management

Tier One
- Head of bed
- Sedation & analgesia
- Ventricular drainage

Tier Two
- Hyperosmolar therapy
- Hyperventilation

Tier Three
- Neuromuscular paralysis
- Barbiturate coma
- Craniectomy
- Hypothermia

• If ICP remains ≥ 20 - 25 mmHg proceed to next tier
Sedation & Analgesia

**Pros**
- Prevention of agitation
- Treatment of pain
- Facilitation of ventilation
- Induction of anxiolysis
- Minimization of seizures
- Potential neuroprotective effects of propofol

**Cons**
- Arterial hypotension
- Interference with neurological exam
- Propofol-related infusion syndrome

Sedation & Analgesia

• Kelly et al, 1999
  – Double blind RCT, propofol vs morphine
  – Daily ICP & CPP similar, ICP lower on day 3 in propofol group (p<0.05), no difference in mortality or overall GOS

• No convincing evidence that one sedative is more efficacious than another for improvement of patient outcomes
  – Additional trials are Class III or not included in guidelines
  – Most trials demonstrate improved ICP and CPP with varying sedative agents vs baseline

• High doses of opioids have potentially deleterious effects on ICP and CPP

Sedation & Analgesia

Brain Trauma Foundation

- Propofol is recommended for the control of ICP
- Not recommended for improvement in long-term outcomes
- Level IIB recommendation

ACS TQIP

- Use short-acting agents (e.g. propofol, fentanyl, midazolam)
Ventricular Drainage

Option One  Closed drain
  • Continuous ICP measurements with intermittent drainage

Option Two  Open drain
  • Continuous drainage with intermittent ICP measurements

Option Three  Drain + Monitor
  • Continuous drainage with EVD and ICP measurements with additional monitor

Hyperosmolar Therapy - Mechanism

1. Osmotic Gradient

- Increased osmotic gradient
- Water extraction from brain tissue
- Reduction in brain volume

2. Rheological Effect

- Reduction in blood viscosity
- Increased initial cerebral blood flow and oxygen
- Reflex cerebral vasoconstriction
- Reduction in cerebral blood volume

# Hyperosmolar Therapy - Agents

## Mannitol
- Osmotic diuretic
- Preparation: 25% 50 mL vial, 20% 500 mL bag
- Dose: 0.25 – 1 g/kg IV bolus
- Administration: Peripheral or central, filter
- Main monitoring parameter: Serum osmolality

## Hypertonic Saline (HTS)
- Concentrated NaCl
- Preparation: 3%, 7.5%, 23.4% intravenous solution
- Dose: IV bolus
  - 250 mL of 3%
  - 75 mL of 7.5%
  - 30 mL of 23.4%
- Administration: Central line
- Main monitoring parameter: Serum sodium

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Mangat, 2014

Study Design

- Retrospective cohort
- HTS vs mannitol in patients with severe TBI
- N = 73

Outcomes

- 2-week mortality, ICP burden

Results

- Mortality not different, Cumulative ICP burden 15 vs 36% (p=0.003), Daily
  ICP burden 0.3 vs 1.3 hours/day (p=0.001)
- Conclusion: HTS was more effective in lowering ICP burden but did not
  effect mortality
Hyperosmolar Therapy

• Evidence comparing agents is low quality, has significant limitations, and is conflicting
  – Most studies demonstrate a similar or greater reduction in ICP with hypertonic saline when compared to mannitol

• Continuous vs. intermittent bolus HTS
Hyperosmolar Therapy – Practical Considerations

Mannitol

- Diuresis
- Crystallization
- Rebound intracranial hypertension

Hypertonic Saline

- Volume expansion
- Extravasation
- Hypernatremia

Hyperosmolar Therapy - Overview

- Equimolar boluses of mannitol and HTS act in similar manners to reduce ICP
- Both appear to be effective for ICP reduction in severe TBI
- Mannitol is considered the “gold standard” due to historical use but with no demonstrative superiority
- Distinct agents may be preferred in different clinical contexts
Hyperosmolar Therapy

Brain Trauma Foundation

- Mannitol is effective for control of elevated ICP
- *Re-stated recommendations from the 3rd edition which are not supported by evidence meeting current standards*

ACS TQIP

- Hyperosmolar therapy (mannitol or hypertonic saline) should be given intermittently as needed for ICP elevation and not on a routine schedule
Neuromuscular Paralysis

Theoretical benefits

- Limited evidence

Facilitation of ventilation

Limitation of ICP surges

Prevention of shivering

Reduction in ICP

Decrease in energy expenditure

Sanfilippo et al. Neurocrit Care. 2015.
# Neuromuscular Blocking Agents (NMBA)

## Depolarizing
- Succinylcholine
- Potential ICP surge

## Non-Depolarizing
- Rocuronium, vecuronium, atracurium, cisatracurium, pancuronium
- Vecuronium used as “test-dose”
- Atracurium or cisatracurium used if “responder” as continuous infusion
Sanfilippo, 2015

Design

• Systematic review evaluating effects of neuromuscular paralysis on TBI and elevated ICPs

• Lack of evidence to support or reject the use of neuromuscular blockage in patients with TBI

• Nondepolarizing NMBAs could be safer than succinylcholine (short-term effects on the ICP)

Conclusion

• Confirmed the lack of strong evidence about the effect of NMBAs on long-term outcome in patients with TBI
Neuromuscular Paralysis

ACS TQIP

• Neuromuscular paralysis using a bolus “test dose” should be considered if previous measures fail

• If there is a positive response, continuous infusion of a neuromuscular blocking agent should be employed (Tier 3)

• The infusion should be titrated to maintain a train of four of at least two twitches
Barbiturate Coma

- The only non-surgical strategy for refractory intracranial hypertension

Decreased cerebral metabolism

Decreased cerebral blood volume

Lowered intracranial pressure

**Eisenberg, 1988**

**Design**
- To evaluate effect of pentobarbital on refractory ICP
- RCT, five centers
- Pentobarbital vs standard, crossover, N=73

**Outcomes**
- Mortality, ICP

**Results**
- ICP control two-times greater with pentobarbital, Responders had higher likelihood of survival (92% vs 17%), 6-month mortality: 36% responders vs 90% non-responders
- Conclusion: High-dose pentobarbital is an effective adjunctive therapy
Barbiturate Coma

Pentobarbital infusion

- 10 mg/kg over 30 minutes
- 5 mg/kg every hour for 3 doses
- 1 mg/kg/hour
- Titrated to burst suppression

- Maximum reduction in cerebral metabolism with burst suppression of 3 – 6 bursts/min (10 – 20 sec suppression)

Barbiturate Coma

Pentobarbital
Barbiturate Coma

• Poor correlation between pentobarbital levels and benefit or complications
  – Sedation: 1 – 5 ug/mL
  – Coma: 30 – 40 ug/mL

• Presence of pentobarbital in the blood precludes pronouncement of brain death
  – <5 ug/mL
  – T_{1/2} = 15 – 50 hours

Barbiturate Coma Concerns

- Hypotension
- Auto-induction
- Drug interactions
- Feeding intolerance
- Constipation
- Infection

Barbiturate Coma

Brain Trauma Foundation

- High-dose barbiturate is recommended for elevated ICP refractory to maximum standard medical and surgical treatment
- Level IIB recommendation

ACS TQIP

- Barbiturate or propofol coma may be used for those who have failed aggressive measures
- It should only be used if a test dose results in a decrease in ICP, thereby identifying the patient as a “responder”
Decompressive Craniectomy

- Surgical procedure in which a large section of the skull is removed and the underlying dura mater is opened
Post-Acute Management

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Post-Acute Complications

- Post-traumatic seizures (PTS)
- Venous thromboembolism (VTE)
- Infection
- Neuropsychiatric disturbances
Post-Traumatic Seizures

- Occurs in up to 12% of patients with severe TBI

- Definitions:
  - Early: within 7 days of injury
  - Late: after 7 days of injury
  - Post-traumatic epilepsy: recurrent seizures more than 7 days following injury
Seizure Prophylaxis

• Utilized for the prevention of early PTS

• Potential benefits of preventing seizures:
  – Limiting physiological disturbances
  – Preventing the development of chronic epilepsy
  – Preventing herniation and death

• Phenytoin is considered the “gold standard”
  – Increasing use of levetiracetam due to side effect profile
Study Design

• Prospective observational study in blunt head trauma
• Levetiracetam 1000 mg IV Q12H vs. phenytoin 20 mg/kg IV loading dose then 5 mg/kg/day IV divided every 8 hours

Outcomes

• Early PTS in patients on levetiracetam (n=406) vs. phenytoin (n=407)

Results

• No difference in seizure rate (1.5% vs. 1.5%, p=0.997)
• No significant difference in adverse drug reactions (7.9% vs. 10.3%, p=0.227)
• No significant difference in mortality (5.4% vs. 3.7%, p=0.236)
Seizure Prophylaxis

Brain Trauma Foundation

- Phenytoin is recommended to decrease incidence of early PTS when benefits outweigh risks
  - Insufficient evidence to recommend levetiracetam over phenytoin
- Not recommended to prevent late PTS
- Level IIA recommendation
Venous Thromboembolism

- Patients with TBI have a high risk for VTE
  - Up to 54% incidence of deep venous thrombosis (DVT) without prophylaxis
  - 20-30% incidence of DVT with mechanical prophylaxis
- VTE risk increases with severity of TBI
VTE Risk Factors in TBI

- Trauma
- Elderly age
- Reduced mobility
- Motor deficits
- Multi-system trauma

## Modified Berne-Norwood Criteria

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No moderate or high risk criteria</td>
<td>• Subdural or epidural hematoma &gt; 8 mm</td>
<td>• ICP monitor placement</td>
</tr>
<tr>
<td></td>
<td>• Contusion or intraventricular hemorrhage &gt; 2 cm</td>
<td>• Craniotomy</td>
</tr>
<tr>
<td></td>
<td>• Multiple contusions per lobe</td>
<td>• Evidence of progression at 72 hours</td>
</tr>
<tr>
<td></td>
<td>• Subarachnoid hemorrhage with abnormal CT angiogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Evidence of progression at 24 hours</td>
<td></td>
</tr>
<tr>
<td>Initiate pharmacologic prophylaxis if CT stable at 24 hours</td>
<td>Initiate pharmacologic prophylaxis if CT stable at 72 hours</td>
<td>Consider placement of an IVC filter</td>
</tr>
</tbody>
</table>
VTE Prophylaxis

Brain Trauma Foundation

• Low molecular weight heparin (LMWH) or low-dose unfractionated heparin may be used in combination with mechanical prophylaxis
  • Increased risk for intracranial hemorrhage with pharmacologic therapy
• Level III recommendation

ACS TQIP

• VTE prophylaxis should be considered within the first 72 hours following TBI in most patients
• Earlier initiation of pharmacologic prophylaxis (<72 hours) appears to be safe in patients who have a low risk for progression of intracranial bleeding and have a stable repeat head CT
Infection

- TBI increases risk for ventilator-associated pneumonia and ventriculostomy-related infections
- Infection rates are as high as 27% in patients undergoing ICP monitoring
- Infection prophylaxis includes:
  - Systemic antimicrobial prophylaxis
  - Antimicrobial-impregnated catheters (AIC)
Systemic Antimicrobial Prophylaxis

- Correlation between length of time EVD is in place and infection risk

- Two approaches to systemic prophylaxis:
  - Periprocedural
  - Continue for duration EVD is in place

- Goal: reduce infection rates without increasing the risk for multidrug-resistant pathogens or adverse effects
Study Design

- Prospective performance analysis
- Periprocedural vs. extended use of antibiotics in patients with EVD

Outcomes

- Rates of catheter-related ventriculitis and nosocomial infections over 4 years with periprocedural (n=135) vs. extended use of antibiotics (n=410) in patients with EVD

Results

- No significant difference in rates of ventriculitis (1.1% vs. 0.4%, $p=0.22$)
- Significantly increased risk for nosocomial infections with extended antibiotic use (2.0% vs. 0.0%, $p=0.026$)
- Cost savings of $162,516 in periprocedural group
Dellit, 2014

Study Design

- Retrospective review
- Cefazolin for duration EVD in place vs. periprocedural cefazolin

Outcomes

- Rates of *Clostridium difficile* and positive cerebrospinal fluid cultures 12 months before and after protocol change
  - Cefazolin 1 g IV Q8H while EVD in place (n=352) → periprocedural cefazolin only (n=369)

Results

- No significant difference in positive cerebrospinal fluid cultures (12.8% vs. 10.3%, p=0.29)
- Increased rate of *C. difficile* in patients with extended antibiotic use (19 cases vs. 9 cases, p=0.04)
Infection Prophylaxis

**Neurocritical Care Society**

- Suggest one dose of antimicrobials prior to EVD insertion
- Recommend against the use of antimicrobials for the duration of EVD placement

**Infectious Diseases Society of America**

- Periprocedural prophylactic antimicrobial administration is recommended for patients undergoing EVD placement (strong, moderate)
- Prolonged antimicrobial prophylaxis for the duration of the EVD is of uncertain benefit and not recommended (strong, moderate)

Neuropsychiatric Disturbances

Arousal

Sympathetic storm

Agitation & aggression

Executive function

Attention

Memory
## Adjunctive Therapy

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<th>Category</th>
<th>Treatments</th>
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<tr>
<td><strong>Attention</strong></td>
<td>- Neurostimulants&lt;br&gt;- Amantadine and other dopaminergics&lt;br&gt;- Donepezil</td>
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<td><strong>Arousal</strong></td>
<td>- Neurostimulants&lt;br&gt;- Amantadine and other dopaminergics&lt;br&gt;- Modafinil</td>
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<tr>
<td><strong>Memory</strong></td>
<td>- Neurostimulants&lt;br&gt;- Donepezil/Dopaminergics</td>
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<tr>
<td><strong>Executive function</strong></td>
<td>- Dopaminergics</td>
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<td><strong>Agitation &amp; aggression</strong></td>
<td>- Propranolol&lt;br&gt;- Amantadine&lt;br&gt;- Atypical antipsychotics&lt;br&gt;- Antidepressants&lt;br&gt;- Methylphenidate&lt;br&gt;- Carbamazepine/Valproate&lt;br&gt;- Lithium</td>
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Summary

• Management of TBI remains a controversial topic
  – High quality studies are limited

• Guideline recommendations are not all-inclusive

• Understanding the pathophysiology of TBI is key to properly manage its complications
References


BELIEVE IN WE™ OhioHealth

A FAITH-BASED, NOT-FOR-PROFIT HEALTHCARE SYSTEM
RIVERSIDE METHODIST HOSPITAL + GRANT MEDICAL CENTER + DOCTORS HOSPITAL
GRADY MEMORIAL HOSPITAL + DUBLIN METHODIST HOSPITAL + HARDIN MEMORIAL HOSPITAL
MARION GENERAL HOSPITAL + REHABILITATION HOSPITAL + O’BLENESS HOSPITAL + MANSFIELD HOSPITAL
SHELBY HOSPITAL + WESTERVILLE MEDICAL CAMPUS + HEALTH AND SURGERY CENTERS
PRIMARY AND SPECIALTY CARE + URGENT CARE + WELLNESS + HOSPICE
HOME CARE + 28,000 PHYSICIANS, ASSOCIATES & VOLUNTEERS