Examples of Respiratory Compromise

Conference on Respiratory Insufficiency
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Introduction

• Describe clinical presentation of common subsets of respiratory compromise
• Discuss pathophysiology
• Discuss epidemiology and risk factors for poor outcomes
• Offer examples of predictive models / tools
• Propose gaps on knowledge
Control of breathing and airway protection

• 33 yo male presents to the emergency department with severe lower back pain after an MVA. His evaluation includes normal vitals & basic blood work. His toxicology reveals only benzodiazepine which he is prescribed. There is no evidence of fracture on radiography or CT.

• He is given fentanyl in the ER and the trauma service is called
• He is admitted to the general medical ward for pain control and an MRI
• He is prescribed ATC morphine and prn doses IV for severe / breakthrough pain in addition to NSAIDs.

• Four hours later he is found apneic and pulseless.
• ACLS is performed and he is intubated. The CXR shows a new infiltrate.
Control of breathing and airway protection

• Hallmarks
  • Central depression of respiratory drive
  • Loss of tone in upper airway
  • Blunting of airway clearance mechanisms

• Results
  • Impaired gas exchange (hypercapnia and hypoxemia)
  • Aspiration of upper pharyngeal contents into lower airways
  • Inability to clear lower airways of debris

→ Respiratory failure → cardiopulmonary arrest → death
Central respiratory depression – Opiates as paradigm

- 1.3% risk of developing critical respiratory event post-op
- 1% of those receiving fentanyl experienced adverse event including respiratory depression in ED
- Use of PCA with lock-outs lowers risks to 0.2 – 0.5%
- Fatal events occur in the setting of inadequate and adequate monitoring
Overview of control of respiration

- Chemoreceptors (O₂, CO₂, pH)
- Baroreceptors
- Pulmonary stretch reflexes
- Respiratory pump muscles
- Upper airway dilator muscles
Mechanism of CNS opiate respiratory depression

• MEDULLA: Neurokinin 1 receptors (NK-1 R) expressing neurons in pre-Botinger complex mediate inspiration, inhibited by opiates
• CORTEX: Reduced sensitivity of chemoreceptors to changes in pCO2 are well described among opiate addicted patients
• PONS: Suppression of acetyl-choline release in medial pontine reticular formation → “sleep-like” state
Mechanisms of central depression

- **Pons**
- **Cortical regions**
- **RTN/pFRG**

**Neuronal Interactions**
- **pre-Bötzinger**
  - $I_{CAN}$
  - $I_{NaP}$

**Muscle Groups**

**Respiratory Pump Muscles**
- Intercostal muscles
- Abdominal muscles
- Accessory muscles

**Upper Airway Dilator Muscles**
- Pharyngeal constrictor muscles
- Laryngeal muscles
- Genioglossus muscle

**Opioid Pathways**
- Cranial and spinal nerves

**Central Depression Mechanisms**
Forces controlling patency of upper airway

**Forces controlling patency of upper airway**

**COLLAPSING FORCES**
- Negative inspiratory pressure
- External compressive forces

**Upper Airway**

**MAINTAINING FORCES**
- Pharyngeal muscle dilators
- Laryngeal muscles
- Tongue muscles
- Longitudinal lung traction

**Inspiratory Air Flow**
Other effects

- Opioid receptors on bronchioles
  - Bronchoconstriction → increase in Raw

- Abdominal and chest wall rigidity
  - Especially at high doses (e.g. Stiff chest in fentanyl boluses)
  - Reduced phrenic nerve and diaphragm activity
    → Reduced Vt
Central depression by opiates: Biological factors

• Age – lower rates of clearance
• Gender – females - up to 25 % higher levels of oxycodone
• Ethnicity – some groups have enhanced clearance (allelic variants in CYP2D6); rapid metabolizers run greater risk of respiratory depression than poor metabolizers
• Co-morbidities – Hepatorenal impairments affect clearance (fentanyl and methadone minimally effected by liver or renal impairment)

• Drug interactions
  • Potentiation: Buprenorphine and opiates or benzos and opiates
  • Opiates and cardiac meds
Opiate induced resp failure: patient characteristics / profile

- Sleep disordered breathing
- Morbid obesity
- Snoring
- Older age
- Opioid naïve
- Post-surgical (esp. upper abdominal, chest wall or upper airway)
- Increased opioid dose need
- Prolonged anesthesia
- Use of additional sedating drugs
- Prior cardio-pulmonary disease, other major organ dysfunction (liver, renal)
- Smoker
Risk factors for respiratory failure / death

• Upper airway obstruction
• Chronic use of opioids (chronic blunting of chemoreceptors)
• Abnormal metabolism (e.g. mutation in CYP2D6 causing rapid metabolism of codeine to active metabolite)
• Joint Commission (Sentinel event alert, August 2012)
  • 11% Excessive dosing (esp. opioid naïve), drug-drug interactions, adverse reactions
  • 47% medication errors
  • 29% inadequate monitoring
Monitoring for central depression

• High frequency of nursing assessments at outset
  • Level of conscientiousness
  • Vitals
  • Pain scores
• Sudden death can occur despite monitoring
  • Can we identify susceptible individuals up front?
  • Is this more related to aspiration which is more difficult to detect and more common than we believe?
  • How do we monitor outside of ICU / recovery room?
  • Do we need more objective methods of monitoring outside of ICU / PACU?
Acute lung injury / ARDS

• Berlin Definition – JAMA 2012
  • Onset with 1 week
  • Bilateral opacities
  • Not explained by cardiac failure (objective assessment – TTE for example)
  • Poor oxygenation
    • Mild – P/F 200 – 300 on >= PEEP 5
    • Moderate – P/F 100 - 200 on > = PEEP 5
    • Severe – P/F < 100 on > = PEEP 5
Causes of ARDS in the Medical ICU

- Sepsis: 32% (n=33)
- Pneumonia: 40% (n=43)
- Aspiration: 9% (n=10)
- Other: 19% (n=21)
Risks Factors for Mortality in ARDS/ALI

<table>
<thead>
<tr>
<th>Risk</th>
<th>Coefficient</th>
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<tbody>
<tr>
<td>Age &gt;65</td>
<td>1.98</td>
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<tr>
<td>Cirrhosis</td>
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<td>HIV</td>
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<td>Transplant</td>
<td>3.67</td>
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<tr>
<td>Sepsis</td>
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</table>
Pneumonia as model for Acute lung injury

- Comprise large fraction of patients with ARDS
- Some are admitted and progress to insufficiency and failure
- Many tools to predict progression – not perfect
PNA - pathophysiology

- V/Q mismatch
- Airway obstruction – secretions, bronchospasm
  - Increased resistive W.O.B.
- Restrictive physiology – consolidation, effusion, atelectasis
  - Increased elastic W.O.B.
- Diffusion impairment
- Severe multi-lobar PNA → ARDS
  - Physiological shunt (severe hypoxemia)
  - Severe restrictive physiology / reduced lung compliance (markedly increased WOB)
  - Increased dead-space ventilation (hypercapnia)
Shunt Physiology in ARDS
Hydrostatic & Non-hydrostatic Pulmonary Edema
Lung Compliance in ARDS

\[ C_L = \frac{\Delta V}{\Delta P} \]
PNA – Progression / stages

• Clinical signs and symptoms
  • Cough
  • Dyspnea
  • Pleuritic chest pain
  • Fever / chills / sweats / hypothermia
  • Headache
  • Malaise

• Progression
  • Systemic Illness
    • Sepsis
    • Severe sepsis / septic shock / ARDS
  • Pulmonary
    • Respiratory insufficiency
    • Respiratory failure
    • Complications: ARDS, empyema, necrotizing pna, abscess, BP fistula, fibrosis, bronchiectasis
<table>
<thead>
<tr>
<th>CRIT CARE 2012</th>
<th>PSI</th>
<th>CURB 65</th>
<th>CRB-65</th>
<th>CURB</th>
<th>CORB</th>
<th>ATS/IDSA</th>
<th>SMART-COP</th>
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<td>Urea / Albumin</td>
<td>X (U)</td>
<td>X (U)</td>
<td>X (U)</td>
<td>X (U)</td>
<td>X (ALB)</td>
<td>X (U)</td>
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<td>WBC / PLT</td>
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<td>X</td>
<td>X (WBC)</td>
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Pooled discriminative performance

- Newer rules (ATS/IDSA 2007, SCAP and SMART-COP) better at predicting ICU admission
- High NPV is hallmark, however

Figure 4 Pooled discriminative performance of the principal scores for severe CAP compared with Pneumonia Severity Index (PSI) and CURB-65 ROC curve.

Marti et al Crit Care 2012
PNA - Summary

• Many prediction rules exist – likely under-utilized?
• Often designed to predict 30 day mortality
  • Prediction of shorter term progression is more useful
  • Newer models focus on shorter term escalation of care as end-point
• Lack PPV needed to confidently identify those for closer monitoring
• High NPV - can identify those with low risk of progression to respiratory insufficiency, respiratory failure, ARDS, severe sepsis, shock
  • Helpful with triage
• Do we need to incorporate biomarkers or more physiologic data?
• Do these rules apply to non-bacterial forms of pna?
Bronchospasm – COPD and Asthma admissions

For Asthma admissions:
• Approximately 500,000 admissions annually
• 1.7 – 2.0 % of all ICU admissions
  • Approximately 30 % require intubation
  • Mortality rate once intubated ranges between 6 and 42%
  • Mortality much higher in intubated patients (to be avoided)
• 5000 deaths annually
Mortality risk factors for patients with SA

- Prior intubation
- Frequent hospitalizations
- Prior ICU admission

- Predicting mortality
  - Less than 50% of asthma mortalities possess these features
  - Risk stratification difficult
  - Few formal tools exist that predict in-hospital deterioration
Pathophysiology of acute severe asthma

• Three hallmarks
  • Inflammation
  • Bronchoconstriction
  • Mucus production

• Results in:
  • Increased airway resistance
    → Increased resistive WOB
  • Air trapping (unable to empty to baseline FRC)
    → Dynamic hyperinflation
    → Increased elastic recoil
    → Increased elastic WOB
    Reduced Vt
    → Increased dead-space → hypercapnia
  • Mucus plugging of small airways
    → V/Q mismatch → hypoxemia
Dynamic hyperinflation

With each respiratory effort:
- More air is trapped and there is increased end exp volume
- Vt is smaller → increased dead-space ventilation
- The elastic recoil of the lung is increased
- *Also increase in intra-thoracic pressures = Auto-PEEP*
Extra-pulmonary consequences

• Lactic acidosis
  • Increased WOB (resistive and elastic)
  • Anaerobic metabolism in the setting of hypoxemia
  • Side-effect of high doses of SABA

• Reduced Cardiac output, hypotension
  Dynamic hyperinflation $\rightarrow$ auto-PEEP (increased intra-thoracic pressures)
  • Reduce venous return to RV
  • Rapid RV filling during exaggerated inspiratory efforts $\rightarrow$ septal displacement into LV, impaired LV filling / reduced SV
  • Increased RV afterload due to auto-PEEP $\rightarrow$ worsening of IV septal displacement
  • Clinical manifestation = Pulsus paradoxus
    • Exaggerated reduction in SBP during inspiration (> 12 – 15 mmHg)

• Myocardial ischemia
  • Increased WOB
  • Rapid HR due to SABA, reduced SV, anxiety
  • Hypotension
<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe Exacerbation*</th>
<th>Imminent Respiratory Arrest</th>
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</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
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<tr>
<td>Dyspnea</td>
<td>At rest</td>
<td>Unable to speak</td>
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<tr>
<td>Speech</td>
<td>Single words, no phrases</td>
<td>Lethargic, confused, Obtunded</td>
</tr>
<tr>
<td>Alertness</td>
<td>Agitated</td>
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<tr>
<td><strong>Signs</strong></td>
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<tr>
<td>Respiratory rate</td>
<td>&gt;30/min</td>
<td>&lt;10 breaths/min</td>
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<tr>
<td>Heart rate</td>
<td>&gt;120/min</td>
<td>&lt;60/min</td>
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<tr>
<td>Pulsus paradoxus</td>
<td>&gt;25 mm Hg</td>
<td>Normal/low</td>
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<tr>
<td>Use of accessory muscles</td>
<td>Evident</td>
<td>Paradoxical</td>
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<tr>
<td>Wheeze</td>
<td>Present—loud</td>
<td>“Silent chest”</td>
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<td><strong>Functional assessment</strong></td>
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<tr>
<td>PEF</td>
<td>&lt;40% predicted</td>
<td>&lt;25% predicted</td>
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<tr>
<td>paO₂</td>
<td>&lt;60 mm Hg</td>
<td>N/A</td>
</tr>
<tr>
<td>paCO₂</td>
<td>&gt;42–45 mm Hg</td>
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<tr>
<td>SaO₂</td>
<td>&lt;91%</td>
<td>N/A</td>
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NHBLI, Guidelines for the diagnosis and management of asthma
<table>
<thead>
<tr>
<th>TABLE 2. Risk Factors for Death From Asthma</th>
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</thead>
<tbody>
<tr>
<td><strong>Asthma History</strong></td>
</tr>
<tr>
<td>Previous severe exacerbation (intubation or ICU admission)</td>
</tr>
<tr>
<td>Two or more hospitalizations in last year</td>
</tr>
<tr>
<td>Three or more emergency department visits in last year</td>
</tr>
<tr>
<td>Hospitalization or emergency department visit within past month</td>
</tr>
<tr>
<td>Greater than 2 canisters of short-acting beta agonist per month</td>
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<tr>
<td>Difficulty perceiving asthma symptoms or severity of exacerbations</td>
</tr>
<tr>
<td>Other risk factors: lack of action plan, sensitivity to alternaria</td>
</tr>
<tr>
<td>Previous severe exacerbation (intubation or ICU admission)</td>
</tr>
<tr>
<td>Two or more hospitalizations in last year</td>
</tr>
<tr>
<td><strong>Social History</strong></td>
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<tr>
<td>Low socioeconomic status</td>
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<tr>
<td>Illicit drug use</td>
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<tr>
<td>Major psychosocial problems</td>
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<tr>
<td>Inner-city residence</td>
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<td><strong>Comorbidities</strong></td>
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<tr>
<td>Cardiovascular disease</td>
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<tr>
<td>Other chronic lung disease</td>
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<tr>
<td>Chronic psychiatric disease</td>
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</table>

NHBLI, Guidelines for the diagnosis and management of asthma
Evaluation

- History
- HR, RR, Pulse
- Peak flow, FEV1
- Pulsus paradoxus
- Oxygen saturation
- ABG
- Assessment of breathing pattern
- Assessment of volume status
- Assessment of mental status
- Response to initial therapy
Asthma exacerbations - Summary

- Risk factors for poor outcomes exist but are inconsistently present in those who deteriorate / die
- Extra-pulmonary manifestations suggest poor outcomes
- Deterioration can be sudden / rapid
- Mechanical ventilation of patients with asthma adds to their risk
- Should a formal tool for be developed to predict decline?
- Could enhanced monitoring of these patients impact mortality / outcomes?
Pulmonary embolus

• Cardiovascular and respiratory deterioration possible
• In those without overt hemodynamic instability in can be difficult to know who is “sick”
• Management / monitoring of the hemodynamically stable patient is not straightforward
The PE story we all have heard

• 70 yo male with a h/o HTN and COPD presents to the ED with pleuritic chest pain and dyspnea for two days.
• P105, BP 110/65, RR 22  O2 sat 92% r/a, Afebrile
• No adventitious sounds on lung exam, heart exam tachy, extremities cool with no edema
• Trop-I 0.5 → ?, EKG – sinus tach, inv T-waves across precordium
• CTA – RUL lobar embolus; IV flattening
• He is admitted to a monitored bed
• TTE – mild RV HK with RA and RV enlargement; IV septal flattening
  • A second TTE on HD # 2 is unchanged
• He is placed on LMWH immediately and given Coumadin on HD #2
• Discharged with 4 days of LMWH on HD #2
• Within 12 hours he is brought back to the hospital by EMS after a PEA arrest and expires in the ED
Epidemiology

• 600,000 PE’s per year in the US

• Accounts for 100,000 to 200,000 deaths

• Mortality rates:
  • 13.0 - 17.5 % at 3 months across all severities

• Most deaths within 60-90 minutes
Recognized Groups by Risk

- **High risk (Massive) - hemodynamic compromise: 22%**
  - In *past*,
    - Massive used to describe angiographic score for occlusion
    - V/Q obstruction score (Miller Index)
    - 35 – 75% mortality

- **Intermediate risk (Sub-massive) = RV dysfunction, no hemodynamic compromise: 31%**
  - 5 – 25% mortality
  - Difficult to distinguish clinically from Low risk

- **Low risk PE: 47%**
  - Often asymptomatic
  - Incidental finding; small clots in distal vessels
  - 1 – 4% short term mortality

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- **Major PE = Intermediate and High risk PE**

Grifoni et al; Circulation, vol 101, 2000; ICOPER, Lancet 1999; Circulation 2011 v123
Outcomes in Pulmonary Embolism

Mortality

Sudden Death

Cardiac Arrest

Shock

Hemodynamically Stable - RV Normal

Hemodynamically Stable - RV Dysfunction

Stratification by RV dysfunction?

Emboli Size

Severity

Cardiopulmonary Status

Wood, Chest 121(3), 2002
Hemodynamics

OBSTRUCTION
- Decreased RV CPP
- Ischemia
- Decreased CO / MAP

Elevated PVR / Pressure Load
- RV Decompensation
- Increased RV Volume
- Septal Shift Pericardial Restriction
- Reduced LV Distensibility
- Decreased LV Pre-load

NEUROHORMONAL
- Decreased RV Output

Wood, Chest 121(3), 2002
IMPAIRED GAS EXCHANGE

• V / Q mismatch

• Reduced mixed-venous saturation

• Impaired diffusion

• Right – to – left shunt

• Dead space ventilation → hypercapnia?

- Hypoxia adds to increases in PVR
Marketers used to assess severity

- **Vital signs**: BP, HR, (RR)
- **Troponin** released in response to low CPP & myocardial injury
  - CPP = MAP – RV intra-cavitary pressure
  - Others = HFABP
- **Oxygen saturation**
- **Co-morbidities**
- **Clot burden**: Especially co-existing DVT
- **RV strain**:
  - **BNP** released in response to RV pressure load / dilation
  - TTE
  - EKG
  - CTA

--> Ideally we want to detect deterioration prior to drop in BP
**PE Severity Index (PESI)**

- Weighted variables (11)
- Easy to obtain

> Prospectively validated
> Elevated risk possible w/out hemodynamic compromise
> Most helpful for triage decisions (Low risk = I & II; High risk = III, IV and V)

<table>
<thead>
<tr>
<th>Class</th>
<th>Points</th>
<th>Mortality (30 day)</th>
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<tbody>
<tr>
<td>I</td>
<td>0 - 65</td>
<td>0 – 1.6</td>
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<tr>
<td>II</td>
<td>66 - 85</td>
<td>1.7 – 3.5</td>
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<td>III</td>
<td>86 - 105</td>
<td>3.2 – 7.1</td>
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<td>IV</td>
<td>106 - 125</td>
<td>4.0 – 11.4</td>
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<td>V</td>
<td>&gt; 125</td>
<td>10 – 24.5</td>
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Table 1. Original and Simplified Pulmonary Embolism Severity Index (PESI)

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<th>Simplified PESI</th>
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<td>Age &gt;80 y</td>
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<tr>
<td>Male sex</td>
<td>+10</td>
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<tr>
<td>History of cancer</td>
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<tr>
<td>History of heart failure</td>
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<td>History of chronic lung disease</td>
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<td>+1c</td>
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<tr>
<td>Pulse ≥110 beats/min</td>
<td>+20</td>
<td>+1</td>
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<tr>
<td>Systolic blood pressure &lt;100 mm Hg</td>
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<td>+1</td>
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<td>Respiratory rate ≥30 breaths/min</td>
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<tr>
<td>Temperature &lt;36°C</td>
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<tr>
<td>Altered mental status</td>
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<tr>
<td>Arterial oxyhemoglobin saturation level &lt;90%</td>
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<td>+1</td>
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- Predicts 30 Day Mortality
- 11 variables to 6

SPESI
Score of 0 = Low risk → 1.1%
Score 1 or greater = High risk → 8.9%

PESI
Low risk → 2.1%
High risk → 14%

Jimenez et al, Arch Int Med 2010
ROC curves of SPESI and PESI (30 day mortality)

- SPESI has greater sensitivity (96 v. 88)
- PESI and SPESI have similar NPV (97 v. 99)
- PESI and SPESI have similar PPV (10.9 v. 10.9)

- SPESI has similar operating characteristics yet is easier to use

- Does not tell us about in-hospital decline

Jimenez et al, Arch Int Med 2010
PE Risk Score: Identification of Intermediate-risk patients with acute symptomatic PE

Goal: Identify normotensive patients at higher risk for complications (consideration of aggressive therapy?)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP 90 – 100</td>
<td>2</td>
</tr>
<tr>
<td>Elevated Troponin</td>
<td>2</td>
</tr>
<tr>
<td>RVD (TTE or CTA*)</td>
<td>2</td>
</tr>
<tr>
<td>HR &gt; 110</td>
<td>1</td>
</tr>
</tbody>
</table>

*PROTECT criteria for CTA

<table>
<thead>
<tr>
<th>Stage</th>
<th>Points</th>
<th>30 day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0 - 2</td>
<td>4.2 %</td>
</tr>
<tr>
<td>II</td>
<td>3 - 4</td>
<td>10.8 %</td>
</tr>
<tr>
<td>III</td>
<td>&gt; 4</td>
<td>29.2 %</td>
</tr>
</tbody>
</table>

**Cumulative incidence of 30 Day PE related complications (PE related death, recurrent PE, hemodynamic collapse, mechanical ventilation)

Bova et al Eur Resp J v44 2014
PE Risk Score: Identification of Intermediate-risk patients with acute symptomatic PE

30 day cumulative complication rate for symptomatic PE stratified by stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>In Hosp</th>
<th>30 day**</th>
<th>30 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.6</td>
<td>4.2</td>
<td>1.7</td>
</tr>
<tr>
<td>II</td>
<td>9.7</td>
<td>10.8</td>
<td>5.0</td>
</tr>
<tr>
<td>III</td>
<td>28.0</td>
<td>29.2</td>
<td>15.5</td>
</tr>
</tbody>
</table>

In-hospital events contribute greatly to events at 30 days

Bova et al Eur Resp J v44 2014

Did not account for bleeding risk or for thrombotic burden (i.e. presence of DVT)
PE predictors of poor outcome / clinical deterioration

- Validated models / scoring systems exist
- Models have good NPV but poor PPV so, by themselves, can not efficiently inform decisions about aggressive therapy or enhanced monitoring
- Models allow us to classify patients as low risk with reasonable certainty
  - Allows outpatient management of PE
- Models often not applicable to the in-hospital setting (outcomes at 30 days)
- PE risk score (Bova et al, Eur Resp J 2014) alludes to in-hospital events but requires prospective validation for this end-point
Afferent inputs from chemo receptors, stretch receptors and baroreceptors

**NTS** – nucleus tractus solitarius – relays info on pO2 from carotid sinus

**RTN** – retrotrapezoid nucleus – main site of cerebral chemoreception

**MRN** – Medullary raphe nucleus – senses changes in pH and pCO2