# Exploring MIMIC to learn from practice variation

Leo Anthony Celi MD, MS, MPH

Beth Israel Deaconess Medical Center

Harvard-MIT Health Sciences & Technology Division

# Collaborative Ecosystem

- Beth Israel Deaconess Medical Center
  - Department of Medicine
  - Surgical ICU
  - Division of Cardiothoracic Anesthesia
  - Division of Dermatology
  - Department of Pharmacy
  - Division of Infectious Disease

# Collaborative Ecosystem

Various logos have been removed due to copyright restrictions, including Mount Sinai School of Medicine,
Escuela de Ingeniera de Antioquia, Mount Auburn Hospital, University of Oxford, NHS, MIT Portugal, among others.

# Goals

- Present an overview of clinical research in progress

- Provide a unifying theme as regards the motivation behind the projects

- Introduce a vision of an empiric data-driven day-to-day practice

# Evidence-Based Medicine

- Multi-center PRCTs and systematic reviews are gold standard

- PRCTs provide aggregated outcomes – difficult to apply to individual patients

- Benefits may not translate into the real world – efficacy vs. effectiveness

- Errors and biases abound: 41% of the most cited original clinical research later refuted (Ioannidis, JAMA 2005)

# Evidence-Based Medicine

- 2007 analysis of >1000 Cochrane systematic reviews
  - 49%: current evidence does not support either benefit or harm
  - 96%: additional research is recommended
- Most of what clinicians do has never been formally put to the test

# Evidence-Based Medicine

- Large-scale evidence impossible to obtain for the millions of questions posed in day-to-day practice

- Is there a role for highly granular clinical databases such as MIMIC?

# Collective Experience

- Aggregation of knowledge extractable from actual patient care of numerous clinicians

- Capture clinician heuristics mathematically : predicting fluid requirement (Celi *et al., Crit Care* 2008)

- Build patient subset-specific models: mortality prediction (Celi *et al., J Healthcare Eng* 2011)

- Examine areas with significant care variability

# Practice Variation

- Variability in care not explained by patient or contextual factors
- Up to 85% variation in care (Millenson, *Health Aff* 1997)
  - Provider training
  - Provider knowledge base and experience
  - Local culture
- Treatment variation: Does it translate to variation in clinical outcomes?

# What Matters During a Hypotensive Event? Fluids, Vasopressors, or Both?

Kothari R, Lee J, Ladapo J, Celi LA

# Practice Variation

- Hypotension in the ICU: assess fluid responsiveness and optimize cardiac preload , + vasopressors

- Variable opinion among clinicians as regards harm from excess fluid and risk of vasopressor use

# Methods

- Definition of hypotensive episode
- Interventions: fluid rate, use of vasopressors
- Primary outcomes: Mortality
- Secondary outcomes
  - Duration of hypotensive episode
  - ICU length-of –stay
  - Rise in creatinine within 3 days after the hypotensive event

# Methods

- Control variables or confounders:
  - SAPS
  - Average MAP 3 hours prior to the hypotensive event
  - Minimum MAP during the hypotensive event
  - Average MAP during the hypotensive event
- Multivariate regression analysis
- Propensity score analysis: pressors vs. mortality

# Results

Table 1. Interventions given during HE according to ICU type

| Interventions Given During HE According to ICU Type | | | | |
| --- | --- | --- | --- | --- |
| | MICU | SICU | CCU | Total |
| Fluids only | 69 (26%) | 115 (31%) | 25 (18%) | 209 (27%) |
| Pressors only | 147 (54%) | 171 (46%) | 82 (61%) | 400 (51%) |
| Fluids & Pressors | 54 (20%) | 87 (23%) | 28 (21%) | 169 (22%) |
| Total | 270 | 373 | 135 | 778 |

# Results

## Table 2. Type of vasopressor used according to ICU type

| Type of Vasopressor Used According to ICU Type | | | | |
|---|---|---|---|---|
| | MICU | SICU | CCU | Total |
| Dobutamine | 5 (2%) | 4 (2%) | 8 (7%) | 17 (3%) |
| Dopamine | 50 (25%) | 31 (12%) | 52 (47%) | 133 (23%) |
| Epinephrine | 2 (1%) | 2 (1%) | 4 (4%) | 8 (1%) |
| Norepinephrine | 113 (56%) | 133 (52%) | 47 (43%) | 293 (51%) |
| Phenylephrine | 69 (34%) | 120 (47%) | 30 (27%) | 219 (38%) |
| Vasopressin | 12 (6%) | 9 (3%) | 10 (9%) | 31 (5%) |
| Total patients | 201 | 258 | 110 | 569 |

# Results

Figure 1. Fluid rate during hypotensive event
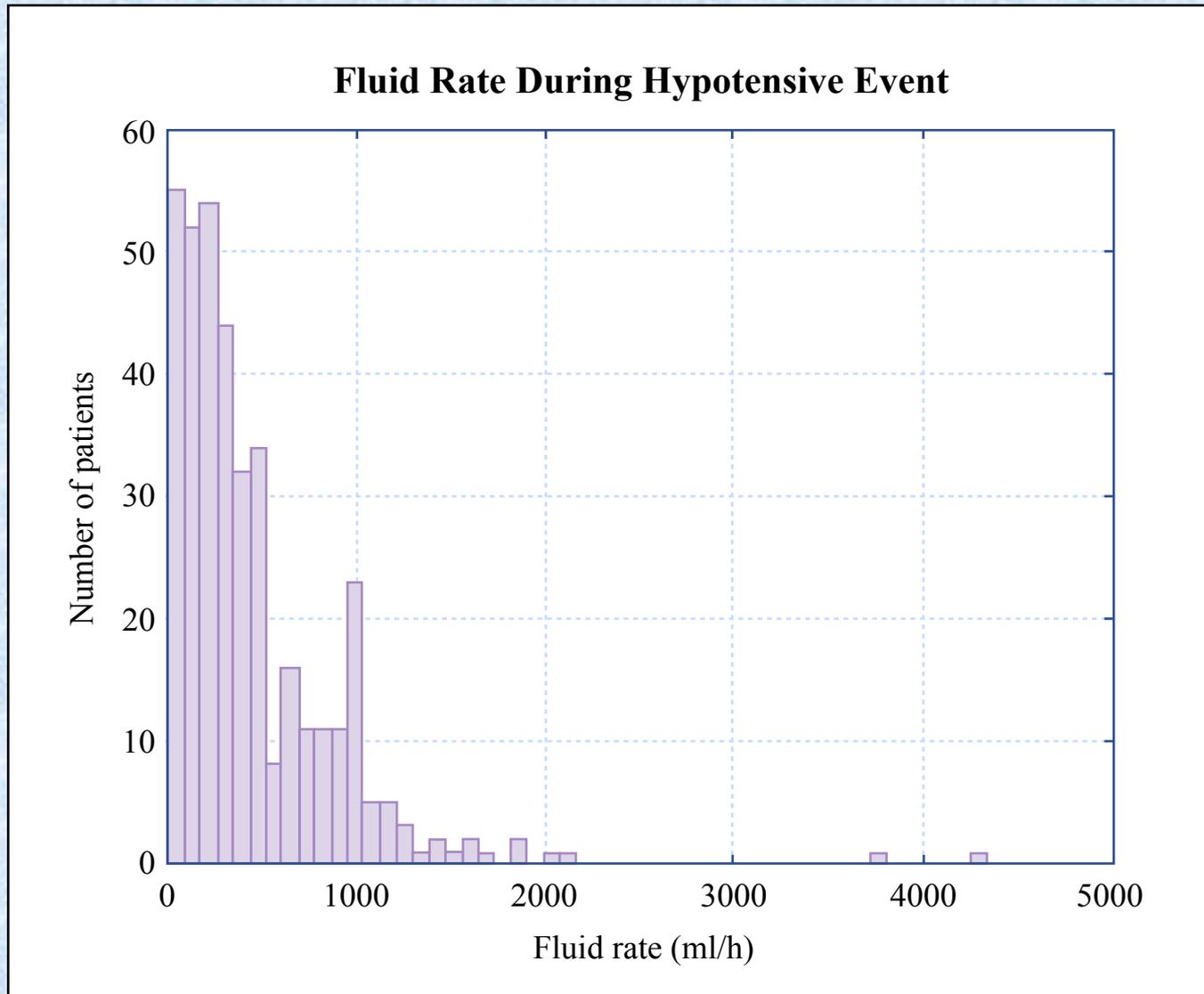
# Results

Table 3. Multivariate analysis for HE duration (N=730, Hosmer-Lemeshow p=0.906)

| | Odds Ratio | 95% CI | P Value |
|---|---|---|---|
| Fluid rate ≤ 500 ml/hr but > 250 ml/hr | 1.261 | 0.803-1.981 | 0.314 |
| Fluid rate > 500 ml/hr | 0.876 | 0.562-1.366 | 0.560 |
| Vasopressor use | 0.444 | 0.818-2.532 | $< 10^{-5}$ |
| Average MAP prior to HE | 0.978 | 0.310-0.635 | 0.002 |
| SAPS | 1.018 | 0.965-0.992 | 0.214 |
| SICU (vs. MICU) | 0.600 | 0.428-0.842 | 0.003 |
| CCU (vs. MICU) | 0.686 | 0.442-1.065 | 0.093 |

# Results

Table 4. Multivariate analysis for hospital mortality (N=730, Hosmer-Lemeshow p=0.678)

| | Odds Ratio | 95% CI | P Value |
|---|---|---|---|
| Fluid rate ≤ 500 ml/hr but > 250 ml/hr | 1.057 | 0.666-1.679 | 0.813 |
| Fluid rate > 500 ml/hr | 0.647 | 0.408-1.028 | 0.065 |
| Vasopressor use | 1.934 | 1.340-2.791 | $< 10^{-3}$ |
| Average MAP prior to HE | 0.985 | 0.971-0.999 | 0.03 |
| Average MAP during HE | 1.005 | 0.973-1.038 | 0.768 |
| Minimum MAP during HE | 0.997 | 0.970-1.024 | 0.821 |
| SAPS | 1.121 | 1.086-1.158 | $< 10^{-11}$ |
| SICU (vs. MICU) | 0.670 | 0.473-0.949 | 0.024 |
| CCU (vs. MICU) | 0.636 | 0.403-1.005 | 0.052 |

# Results

Table 5. Propensity score model (N=730, Hosmer-Lemeshow p=0.845)

| | Odds Ratio | 95% CI | P Value |
|---|---|---|---|
| Fluid rate $\leq$ 500 ml/hr but > 250 ml/hr | 0.217 | 0.139-0.338 | $< 10^{-10}$ |
| Fluid rate > 500 ml/hr | 0.333 | 0.211-0.526 | $< 10^{-5}$ |
| Average MAP prior to HE | 1.011 | 0.995-1.027 | 0.166 |
| SAPS | 1.050 | 1.015-1.086 | <0.005 |
| SICU (vs. MICU) | 0.750 | 0.511-1.100 | 0.141 |
| CCU (vs. MICU) | 1.375 | 0.789-2.394 | 0.261 |

# Results

## Figure 3. Calibration of the propensity score model



**Calibration of the Propensity Score Model**
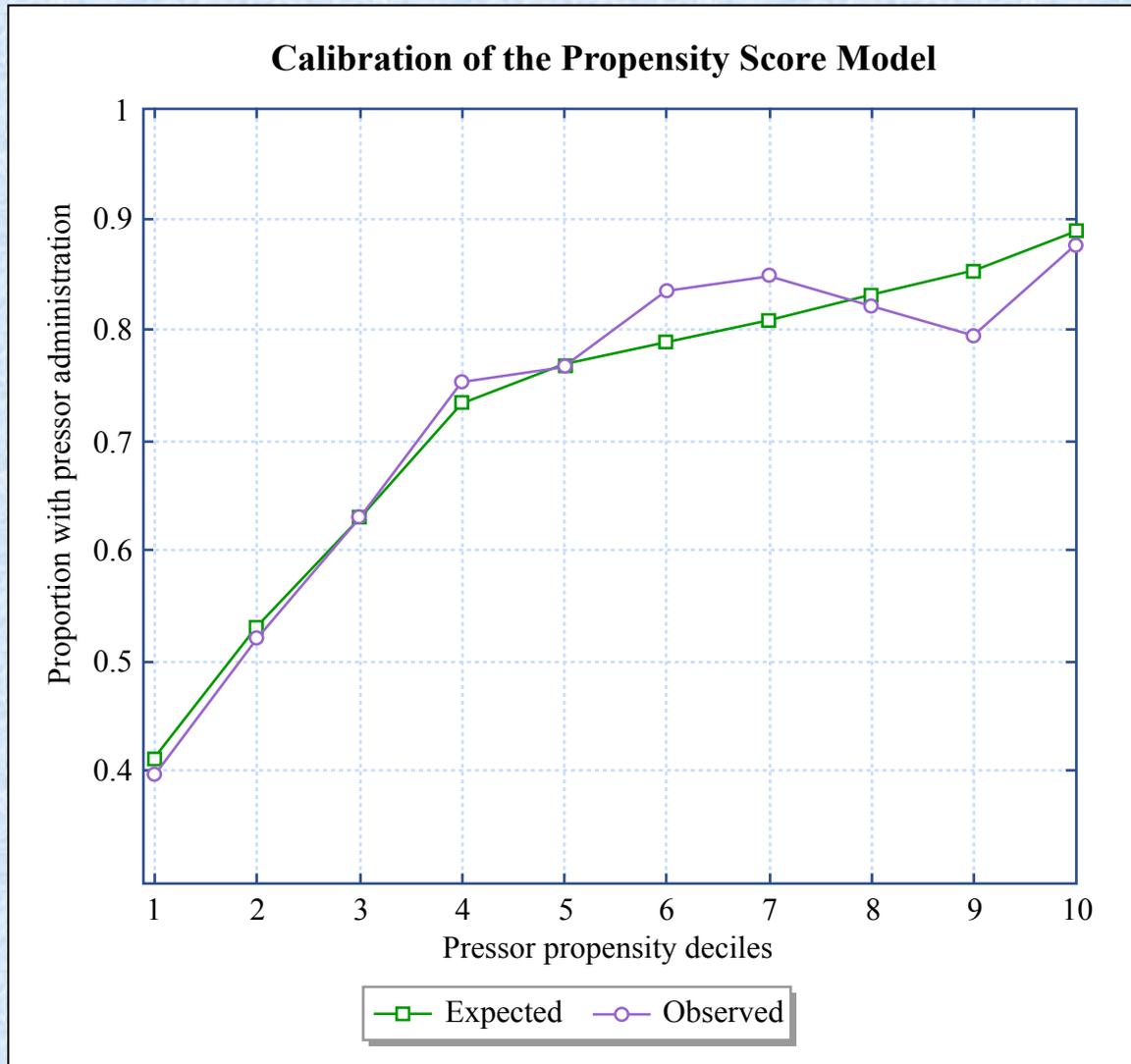
# Results

Table 6. Vasopressor use vs. hospital mortality after adjustment for propensity score (N=730, Hosmer-Lemeshow p=0.345)

|  | Odds Ratio | 95% CI | P Value |
|---|---|---|---|
| Vasopressor use | 1.820 | 1.282-2.584 | 0.001 |
| Propensity score | 4.858 | 1.670-14.131 | 0.004 |

# Results

Table 4. Multivariate analysis for ICU length-of-stay among survivors
(N=347, Hosmer-Lemeshow p=0.291)

| | Odds Ratio | 95% CI | P Value |
|---|---|---|---|
| Fluid rate ≤ 500 ml/hr but > 250 ml/hr | 1.000 | 0.432-2.314 | 1.000 |
| Fluid rate > 500 ml/hr | 2.957 | 0.836-10.453 | 0.092 |
| Vasopressor use | 1.490 | 0.743-2.987 | 0.262 |
| Average MAP prior to HE | 1.013 | 0.982-1.044 | 0.424 |
| Average MAP during HE | 0.953 | 0.888-1.023 | 0.185 |
| Minimum MAP during HE | 0.988 | 0.923-1.058 | 0.726 |
| SAPS | 1.125 | 1.043-1.213 | 0.002 |
| SICU (vs. MICU) | 1.082 | 0.517-2.263 | 0.835 |
| CCU (vs. MICU) | 1.95 | 0.673-5.651 | 0.218 |

# Results

Table 4. Multivariate analysis for creatinine rise (N=618, Hosmer-Lemeshow p=0.745)

| | Odds Ratio | 95% CI | P Value |
|---|---|---|---|
| Fluid rate ≤ 500 ml/hr but > 250 ml/hr | 0.734 | 0.455-1.185 | 0.206 |
| Fluid rate > 500 ml/hr | 0.744 | 0.457-1.210 | 0.233 |
| Vasopressor use | 1.060 | 0.725-1.550 | 0.763 |
| Average MAP prior to HE | 0.992 | 0.997-1.007 | 0.281 |
| Average MAP during HE | 0.984 | 0.951-1.019 | 0.365 |
| Minimum MAP during HE | 0.974 | 0.945-1.003 | 0.077 |
| SAPS | 1.030 | 0.998-1.064 | 0.068 |
| SICU (vs. MICU) | 0.870 | 0.606-1.251 | 0.453 |
| CCU (vs. MICU) | 1.072 | 0.667-1.724 | 0.773 |

# Discussion

- Vasopressor use during a hypotensive event is an independent predictor of mortality
  - Multivariate logistic regression
  - Propensity score analysis
- Mean vasopressor load associated with increased risk of 28-day mortality (Dunser, *Crit Care* 2009)
- Side effects
  - impaired microcirculation
  - increased metabolic demands
  - altered immune response

# Incorporating Dynamic Information during a Hypotensive Episode to Improve Mortality Prediction
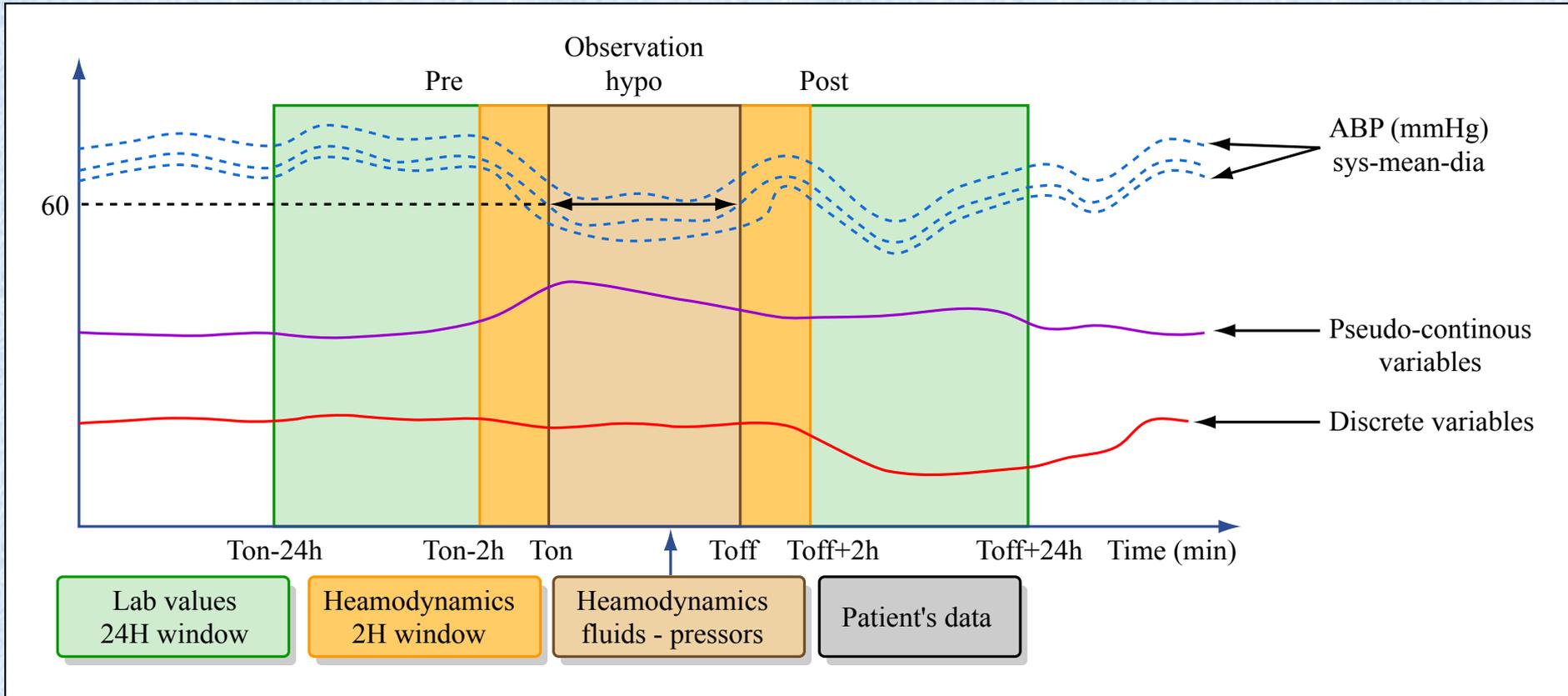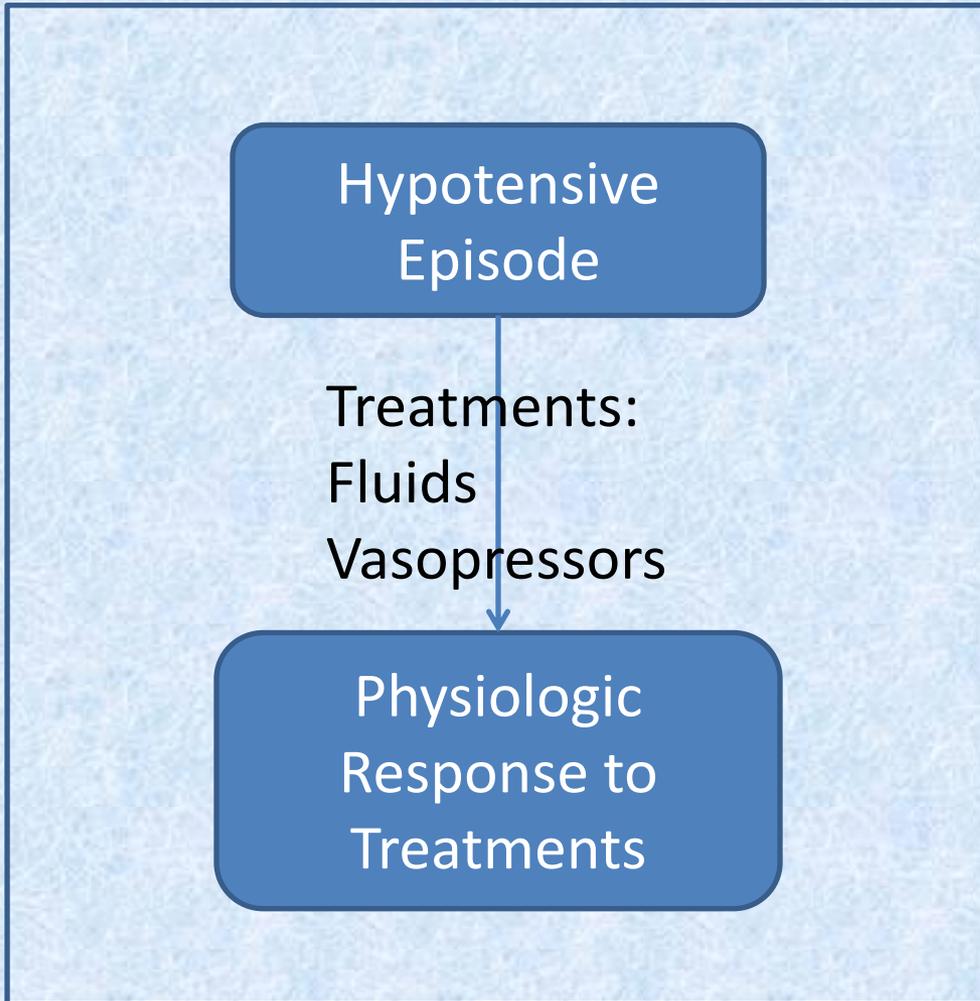## Mayaud L, Celi LA, Kothari R, Clifford G, Tarrasenko L, Annane D

Hypotensive Episode

Treatments:
Fluids
Vasopressors

Physiologic Response to Treatments

Initial Presentation

Event -> Treatment -> Response

Outcome Prediction

Images by MIT OpenCourseWare.

Images by MIT OpenCourseWare.

# Transfusing the Non-Bleeding Patient
## Samani S, Samani Z, Malley B, Celi LA

- Compare survival curves of transfused and non-transfused non-bleeding patients with hemoglobin between 7 and 10 g/dL

- Control variables:  age, severity score, co-morbidities, hemoglobin

- Cox regression model to calculate hazards ratio

- Propensity score analysis and instrumental variable analysis to confirm findings

# Impact of 24/7 Intensivist on Clinical Outcomes
Celi LA, Stevens J, Lee J, Osorio J, Howell M

- Nocturnal intensivist program initiated in MICU in 2002, SICU in 2010

- Control for potential confounding by other ICU quality improvement  projects by comparing adjusted clinical outcomes of MICU and SICU patients

- Perform analysis on patients admitted at night as day admissions may dilute treatment effect

# Quantifying the Risk of Unnecessary Broad-Spectrum Antibiotics

Snyder G, Pho M, Golik M, Celi LA

- Antibiotic use is the main driver of antimicrobial resistance in the hospital
- Vancomycin/Cefepime for every healthcare facility-associated fever & leukocytosis
- Streamlining rarely happens despite negative cultures
- Difficult to distinguish infectious vs. non-infectious SIRS

# Predicting Whether a Laboratory Test will be Significantly Changed from the Previous Determination

Cismondi F , Celi LA

- Frequency of laboratory testing very ad hoc
  - Hematocrits for GI bleed
  - Chem 7 for Hyperglycemic Hyperosmolar State, DKA
  - ABG for status asthmaticus
- Can we predict whether a test will give us additional information?
- Reduce iatrogenic anemia, false positives

# Other Works in Progress

- Developing mortality prediction models for elderly patients undergoing open heart surgery
- Cost effectiveness of CABG vs. PCI among elderly patients
- Looking at coupling/uncoupling of physiologic variables using information transfer among different patient subsets
- Influence of MELD scores on Kaplan-Meier curves among patients with cirrhosis admitted to the ICU
- Impact of troponin leaks during critical illness on long-term survival
- Epidemiology of rash in the ICU
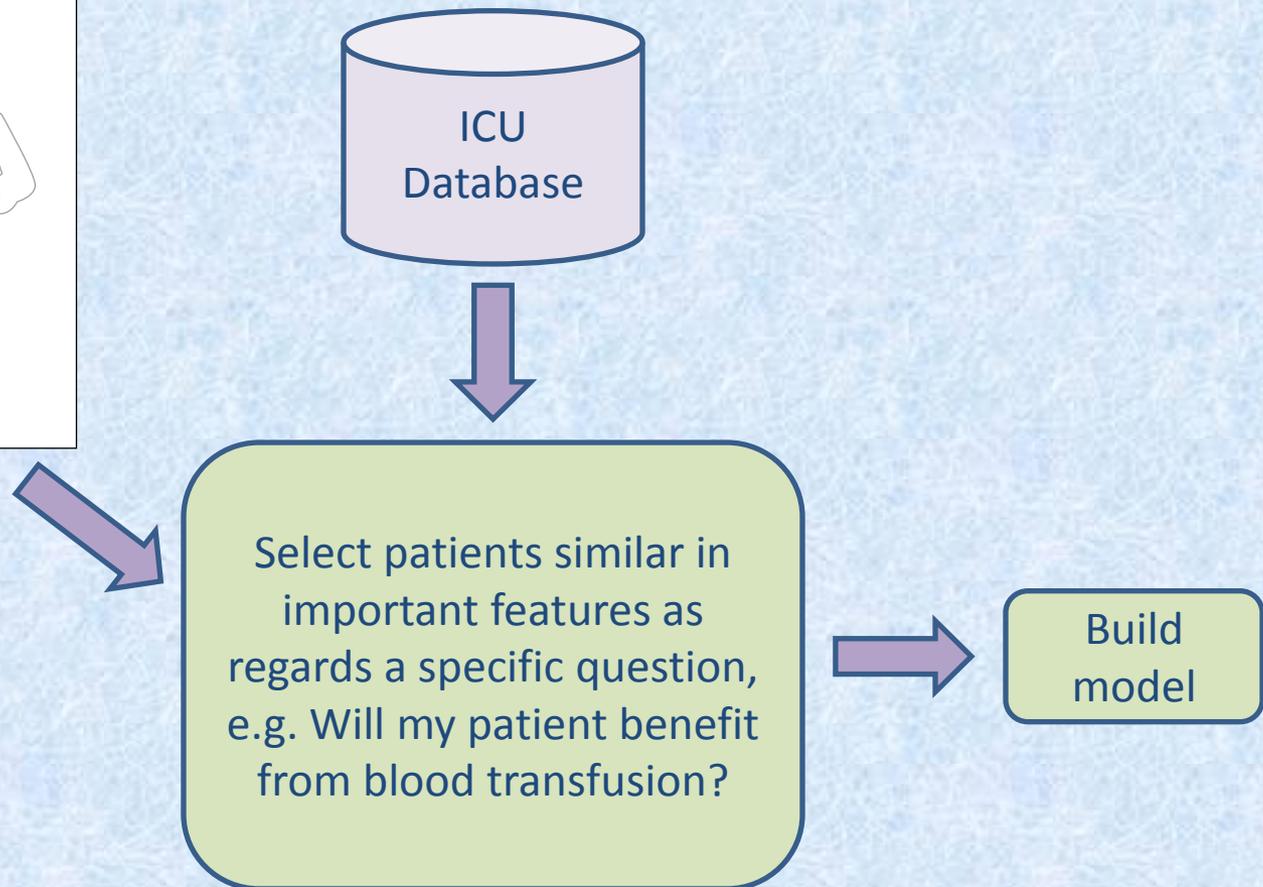- Are there racial disparities in resource utilization at the end-of-life at BIDMC?

# Conclusions

- Clinical databases such as MIMIC present an opportunity to study areas where practice variation exists

- Large-scale evidence impossible to obtain for the millions of questions posed in day-to-day practice - impractical, expensive, "unethical"

- Data mining might allow us to catch-up with a century of non-evidence-based medicine

# The MIMIC Vision



Images by MIT OpenCourseWare.

ICU Database

Select patients similar in important features as regards a specific question, e.g. Will my patient benefit from blood transfusion?

Build model

**"Our vision is the creation of a learning system that aggregates and analyzes day-to-day experimentations, where new knowledge is constantly extracted and propagated, and where practice is driven by outcomes, and less so by heuristics and gut instinct."**

HST.950J / 6.872 Biomedical Computing
Fall 2010