Articles that Changed the Practice of Emergency Medicine

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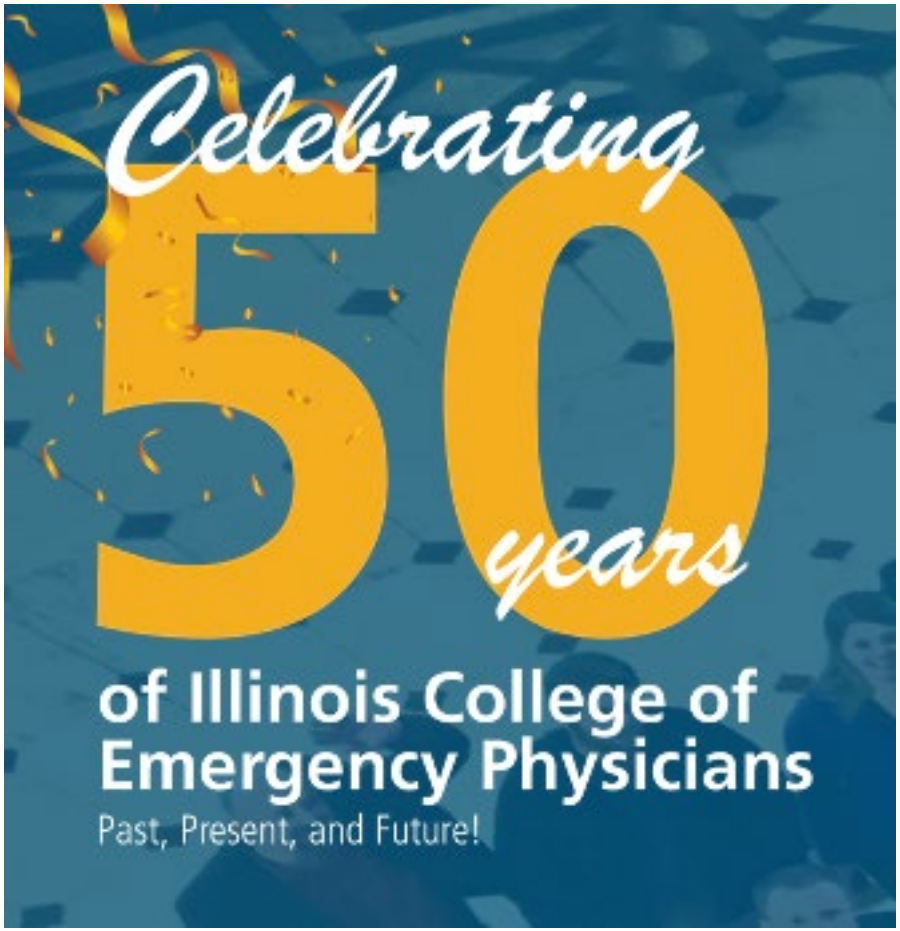
Disclosure

- My presentation will at times involve comments or discussion concerning unapproved or off label uses of a medical device or pharmaceuticals. When any unapproved or off-label uses of products is discussed, disclosure must be made.
- Sadly, I have no financial relationships or interest with industry or manufacturers represented in the presentation.

Objectives

- Review the cumulative literature over the past 50 years to outline those that most impacted advances in emergency medicine.
  - Look at the most important “game changers” (IMHO) over the tenure of ICEP.
- Analyzing the implications and limitations of the studies on the practice of clinical emergency medicine.
  - EM was changed forever after their publication.

Happy Golden Anniversary ICEP!



Notable 1970's

- 1973: The Heimlich maneuver is introduced as first aid for choking victims.
- 1975: Lyme disease, a disease transmitted by ticks to humans, is identified in Lyme, Connecticut.
- 1976: A swine-flu epidemic threatens to sweep the USA. Millions are vaccinated, but the warning turns out to be a false alarm.
- 1978: The novel *The House of God* is published, and sold >2 million copies.

The Times they are a Changing

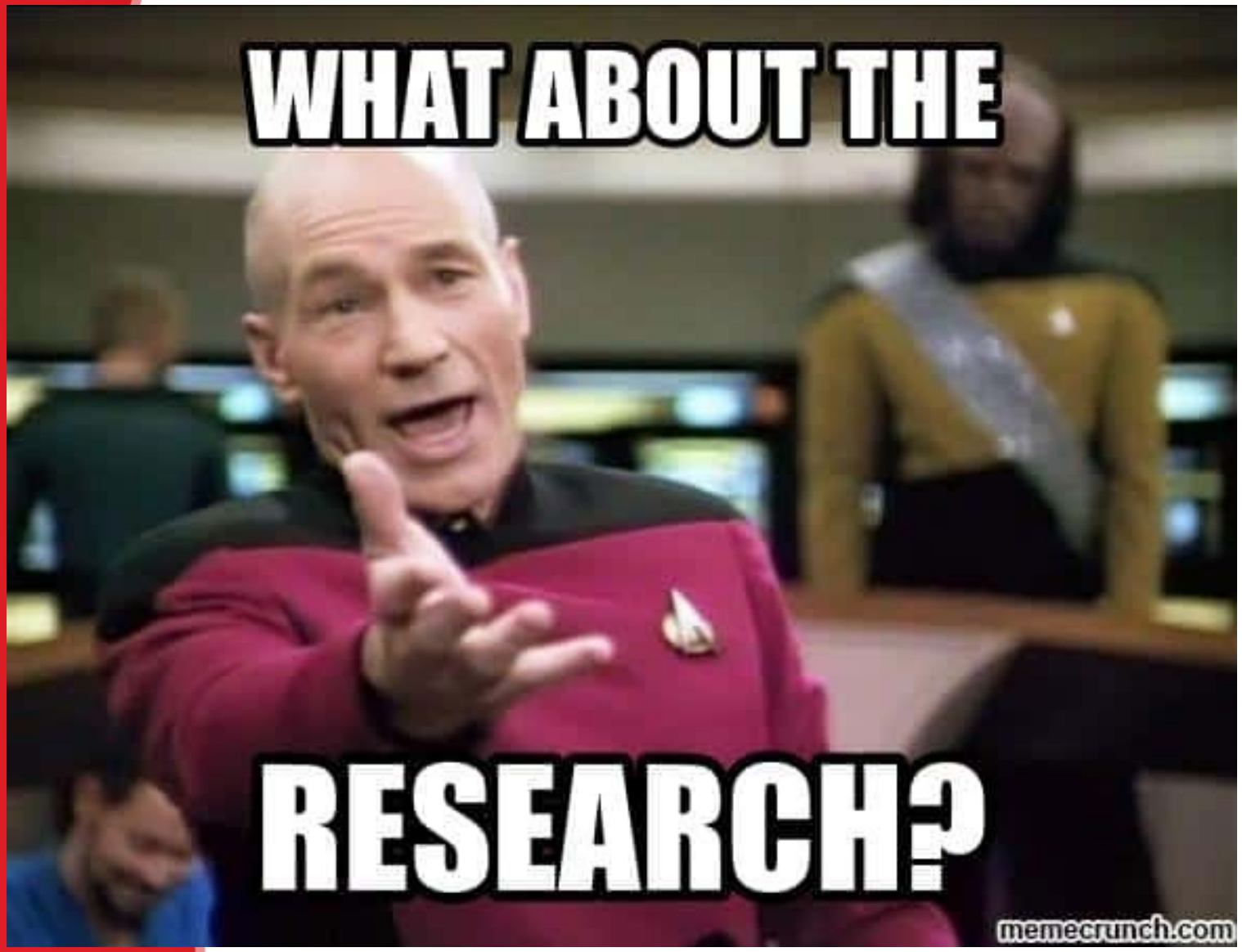
- Until the advent of specialty training in the 1970s, EDs were generally staffed by hospital physicians on a rotating basis.
  - American Board of Emergency Medicine was recognized in 1979.
- Ambulance services where often run by funeral directors, because they had vehicles that could transport people horizontally.

1970's TV Physicians

You've Come a Long Way Baby!







WHAT ABOUT THE
RESEARCH?
memecrunch.com

The Articles

- Large trials that are impactful
  - Changed EM forever
- Represent my opinion as to those that are most important
- From reputable journals
- Really hard to choose only 5!

1987: This is your brain on drugs
2023: You can't afford the egg, the gas stove is being outlawed, the only thing you can get is the drugs.

Need for Paradigm Shift

- Before 1995, the standard for patients with stroke was to be evaluated in the ED without speed
  - No need to perform urgent brain imaging as no change in management for ICH or ischemic stroke.
- The acute treatment involved anticoagulation (heparin), prolonged bed rest, prophylactic antibiotics, and extended oral anticoagulation.
- Stroke mortality was high
  - 214,000 US stroke deaths in 1973.

Tissue Plasminogen Activator for Acute Ischemic Stroke

NIH Neurologic Disorders and Stroke r-TPA Stroke Study Group. *NEJM*.

December 14 1995; 333 (24) 1581-1587.

NINDS TPA for Stroke Trial

- 400,000 annual strokes with the majority due to arterial occlusions (80%).
- Early work on t-PA and stroke centered on rescuing the penumbra and limiting hemorrhage.
  - Safety had been tested on 2 open label, dose escalation studies treating within 90-180 minutes of the stroke.
  - Utilized doses <0.95 mg of t-PA.
- Needed a larger, randomized, placebo-controlled trial.

NINDS TPA for Stroke Trial

- Double-blinded, randomized, placebo-controlled trial.
- Study divided into two parts:
  - Part 1 tested tPA activity, indicated by complete resolution or improvement in NIHSS by ≥4 points within 24h. Groups divided by time from symptom onset to tPA delivery:
    - 0-90 mins
    - 91-180 mins
    - 0-180 mins
  - Part 2 investigated benefits of tPA at 90 days based upon several indices:
    - Bartel index; Modified Ranking scale; Glasgow outcome scale; NIHSS scale.

NINDS TPA for Stroke Trial

- Clearly defined time of onset; deficit measurable on NIHSS; baseline CT scan of brain that showed no evidence of ICH.
- Randomized to placebo or intravenous alteplase (0.9 mg/kg up to maximum 90 mg; 10% as bolus, then remaining 90% as 60-minute infusion).
- No anticoagulants or antiplatelets to be given for 24 hours after treatment.
- N=624
  - Part 1: N=291, tPA (n=144) vs. placebo (n=147).
  - Part 2: N=333, tPA (n=168) vs. placebo (n=165).

NINDS TPA for Stroke Trial

- Improvement by >4 points on NIHSS or complete resolution at 24 hours:
  - 47% vs. 39% (RR 1.2; 95% CI 0.9-1.6; P=0.21)
- Proportion after stroke with favorable outcomes at 90 days:
  - Barthel index: 50% vs. 38% (OR 1.6; 95% CI 1.1-2.5, P=0.026)
  - Modified Rankin scale: 39% vs. 26% (OR 1.7; 95% CI 1.1-2.6; P=0.019)
  - Glasgow outcome scale: 44% vs. 32% (OR 1.6; 95% CI 1.1-2.5; P=0.025)
  - NIHSS: 31% vs. 20% (OR 1.7; 95% CI 1.0-2.8; P=0.033)
- 90-day mortality:
  - 17% vs. 21% (P=0.30)

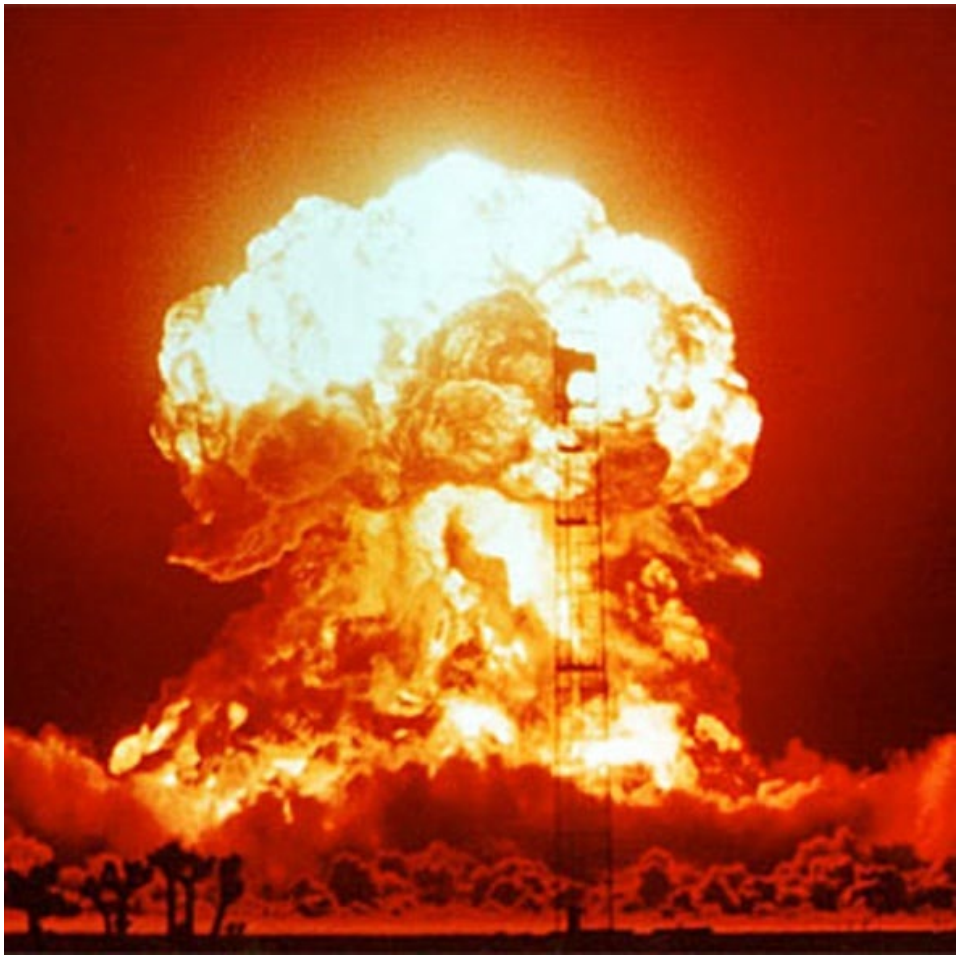
NINDS TPA for Stroke Trial

- Subgroup Analysis
  - t-PA improved all outcome measures at 90 days regardless of age, stroke subtype, severity of stroke, and use of aspirin before stroke.
- Adverse Events:
  - ICH within 36 hours of stroke treatment:
    - 6.4% vs. 0.6% (P<0.001), of which 45% were fatal.
  - ICH within 3 months of stroke treatment:
    - 7.7% vs. 1.3% (P<0.001), of which 61% were fatal.
  - New ischemic strokes:
    - 5.8% vs. 5.4% (P not stated).

NINDS TPA for Stroke Trial

- Recommendations
  - The NINDS tPA trial demonstrated that tPA was an effective treatment for acute stroke if given within 3 hours of stroke symptom onset.

NINDS TPA for Stroke Trial



NINDS TPA for Stroke Trial

Table 1

Percentage of patients (N = 320) in the 91 to 180-minute subgroups with a specific baseline National Institutes of Health Stroke Scale (NIHSS)score*

Baseline NIHSS score	*tPA-treated patients, % (n = 153)*	*Patients given placebo, % (n = 167)*
0-5	19.0	4.2
6-10	24.2	27.5
11-15	17.0	21.0
16-20	21.6	19.8
>20	18.3	27.5

tPA = tissue plasminogen activator

NINDS TPA for Stroke Trial

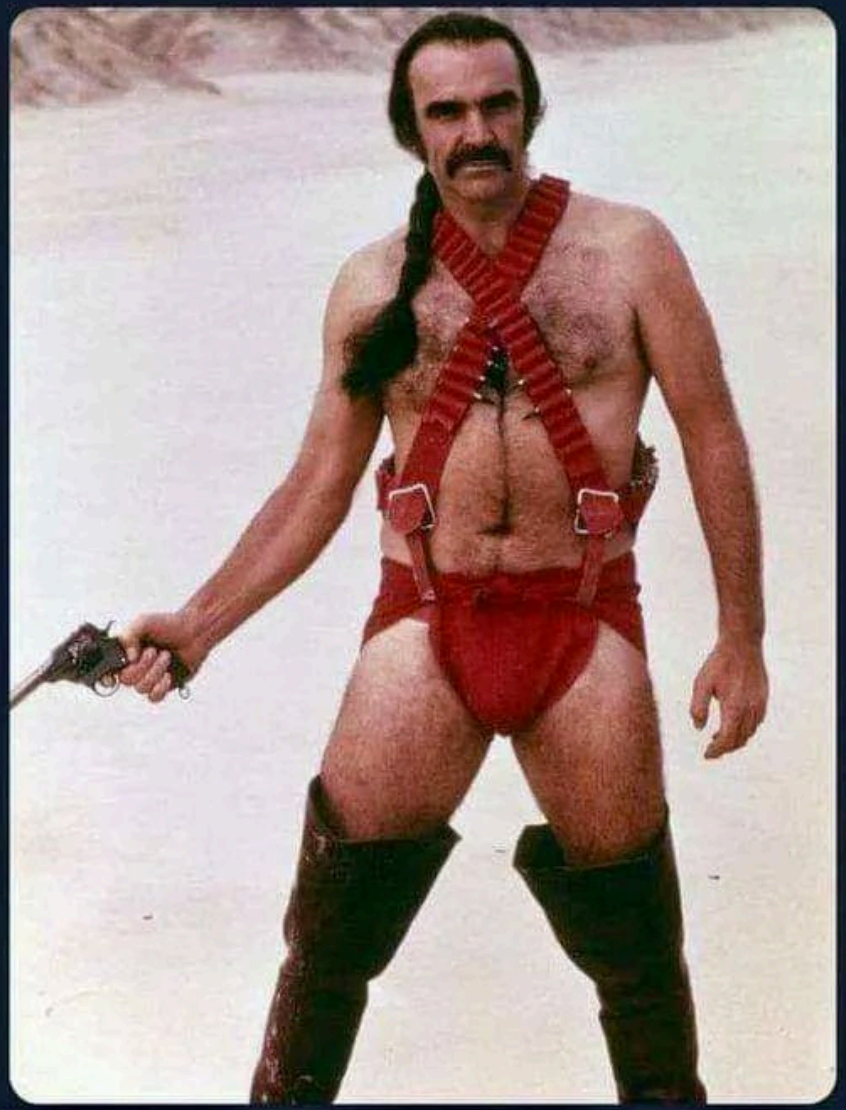
Jerome Hoffman

- *An important methodologic concern about the NINDS trial is that it selectively enrolled patients with less than 90 minutes of symptoms… the study showed an overall 11%-13%absolute benefit with tPA treatment; however, a recent report by the NINDS authors[2] clarified that the benefits were greater than this in the "very early" (0-90min) group, which means that they had to be less than this in the"early" (90-180 min) [sic] group. This is extremely important because, in real clinical practice, "very early"patients are almost non-existent.*

NINDS TPA for Stroke Trial

- NINDS was a touchstone for modern stroke care:
  - Brain Attack Coalition and American Heart Association guidelines
  - Stroke fellowships
  - Tele-neurology
  - Primary and Comprehensive Stroke Centers
  - Endovascular treatment strategies
  - CT Perfusion/Diffusion weighted MRI/Rapid MRI
- In most western industrialized countries, death from stroke declined by 30-50% from 1975 to around 2005
- In the United States, about 85% of stroke victims now survive
  - Age-standardized death rates among adults aged ≥35 years declined from 315.7 deaths per 100,000 in 1968 to 73.3 per 100,000 in 2015.

The movie “Zardoz” takes place in 2023, so get ready for everyone to start dressing like this



Need for Paradigm Shift

- 1970: The link between gram-negative bacteremia, endotoxemia, and manifestations of sepsis was established.
- 1991: the first sepsis conference was held and defined sepsis.
- 1991: 700,000 cases of sepsis occurred with a mortality of 47%.
- 1970-1991: No established specific care algorithm or accepted universal guidelines.

Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

Rivers E, et al.

Cochrane Database of Systematic Reviews. 2022, Issue 5. Art. No.: CD013506.

Sepsis Goal Directed Therapy

- Within 6 hours of presentation to the ED intensive monitoring of specific circulatory parameters with the aggressive management of 5 key parameters to specified targets to optimize oxygen delivery to tissues.

Sepsis Goal Directed Therapy

- The rationale for EGDT is that early optimization of O2 delivery will improve outcome in sepsis.
- Interventions:
  1. Reduce work of breathing by early use of mechanical ventilation.
  2. Fluid resuscitation.
  3. Use of vasoactive agents: noradrenaline, dobutamine.
  4. Transfusion.

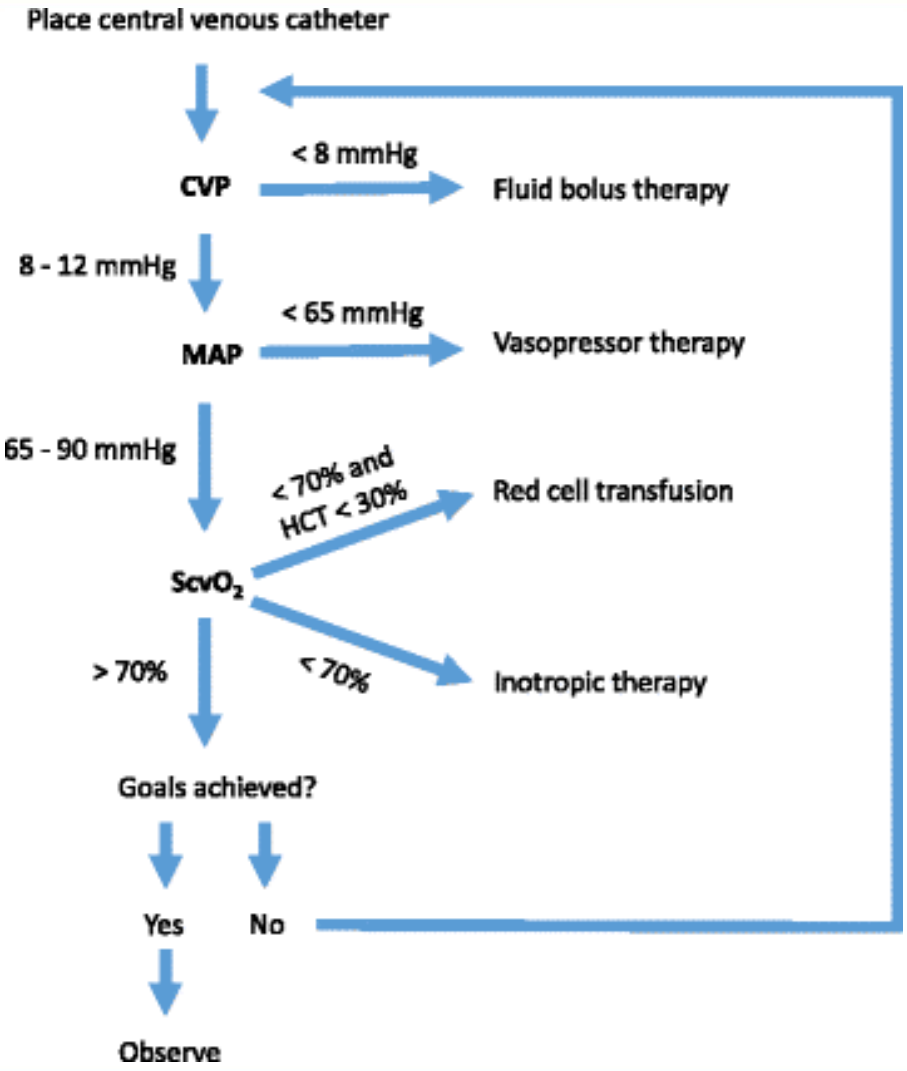
Sepsis Goal Directed Therapy

- Rivers et al randomized ED patients with severe sepsis or septic shock at a single urban Detroit ED to a protocol of early goal-directed therapy (EGDT) vs. standard therapy.
- In the EGDT arm, patients received an arterial line and a central line with continuous central venous oxygen saturation ($ScvO_2$) monitoring:
  - Parameters:
    1. CVP 8-12 mmHg
    2. MAP 65 – 90 mmHg
    3. Urine output >0.5 ml/kg/hr
    4. Mixed venous oxygen saturation >65% / ScvO2 >70%
    5. Hematocrit >30%
  -

Sepsis Goal Directed Therapy

- N=263 patients with severe sepsis or septic shock
  - Early-goal directed therapy (n=130).
  - Standard therapy (n=133).
  - Included ED patients with signs of sepsis, severe sepsis, or septic shock (SIRS plus SBP <90mmHg despite 20-30ml/kg crystalloid challenge over 300 minutes or blood lactate >4mmol/L).
  - Primary outcome: In-hospital mortality.

Sepsis Goal Directed Therapy



Sepsis Goal Directed Therapy

TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

Sepsis Goal Directed Therapy

- Criticisms:
  - ED staff was not blinded to treatment group.
  - It is impossible to determine which interventions were most important.
  - The use of ScvO2 and pressure monitoring had not been tested in this population prior.
  - The study was single-center.
  - The control group had an above-average mortality.
  - Transfusion red blood cells to increase $ScvO_2$ is controversial.

Sepsis Goal Directed Therapy

- EGDT was a touchstone for modern sepsis care:
  - Surviving Sepsis Campaign.
  - It is now “routine” to treat sepsis patients by aggressive resuscitation practices.
  - Despite all the controversies, it is agreed that early volume resuscitation, antibiotics, support with vasopressors, and source control remain the cornerstones of treatment in the septic patient.


ICU
OR
Wards
Outpatient
Emergency Department
ifunny.co

Need for Paradigm Shift

- 1966: Opening of the second trauma unit at Cook County by Dr. Freeark and Dr. Baker.
- Illinois created the first stateside trauma system in the early 1970s.
  - Model for the nation; ICEP helps lead the way.
- The Emergency Medical Services Act of 1973 gave $300 million for the development and operation of statewide EMS systems.
- 1976: The American College of Surgeons Committee on Trauma published criteria to categorize hospitals according to resources to provide trauma care.
- Nationwide, needed change was slow.

Trauma Mortality in Orange County: The Effect of Implementation of a Regional Trauma System

Cales RH, et al. *Annals of Emergency Medicine*. 1984; 13; 1-10.

Orange County Regional Trauma System

- OC in 1984 had a population of 2 million, 6 base station hospitals, 37 paramedic units and 31 hospitals.
- Prior to the trauma system, critically injured patients were brought to the closest hospitals.
- June 1980 – implemented a regional trauma system was implemented:
  - Level 1: UC Irvine
  - Level 2: 4 hospitals
  - Non-trauma hospitals

Orange County Regional Trauma System

- OC had no trauma designation in 1979 and trauma patients were taken to the closest hospital.
- A study comparing San Francisco, a city that directed critical trauma patients to a single level1 trauma center, demonstrated 73% of non-CNS trauma deaths in OC were preventable.
- With the help of local government, a trauma system was implemented in 1980.

Orange County Regional Trauma System

- Orange County MVC mortality cohort comparison for 1977-1978 (pre-implementation) and 1980-1981 (post-implementation).
- MVCs outside of the county, isolated burns and prehospital cardiac arrests were excluded, then a stratified randomized sample for each cohort was reviewed (by hand).
  - 58 deaths for the 1977-78 cohort and 60 deaths for the 1980-81 cohort.
  - ISS scores assigned
  - Surgeons reviewed each blinded case to assess potential salvageability of the patient if treated with “optimal trauma care”.

Orange County Regional Trauma System

- 39/118 (33%) deaths were judged potentially salvageable.
- Salvable mortality decreased from 34% pre-implementation to 15% post-implementation ($p < 0.2$).
- For patients dying of non-CNS deaths, it dropped from 86% to 40% ($p < 0.03$).
  - No change in CNS deaths.
- Following implementation, 4% of deaths occurring in trauma facilities were judged potentially salvable compared to 54% in non-trauma facilities.
- No difference in cohort's mean ISS scores.
- Increased transport times by 2.5 minutes.

Orange County Regional Trauma System

- Regional Trauma Centers were a touchstone for modern trauma care:
  - Injury in America: A Continuing Public Health Problem.
  - Center for Injury Control at the CDC.
  - Trauma Care Systems and Development Act 1990.
  - HEMS integration.
  - 1992 Model Trauma Care System Plan.
  - EMS Field Triage Criteria and training.
  - Twiage/video conferencing technology.

Mike Primavera
@primawesome

I like how every time a doctor pulls some medicine into a syringe they squirt a little bit out for their fallen homies.

Emergency!

Emergency!

- Emergency!
  - First aired in January 1972, the TV show brought emergency medical services into the mainstream.
  - John Gage and Roy DeSoto, who work as paramedics and firefighters in Los Angeles County.
    - Brought the *idea* of paramedicine into homes throughout the United States.
  - It was an idea most of the country had no experience with until then.
  - Two of the 12 EMS units that existed in the US happened to be in Los Angeles.
  - Personally – I wanted to be Johnny Gage and had a crush on Dixie.

Emergency!

- What was Station 51's call sign after each radio call?

Emergency!

- What was Station 51's call sign after each radio call?

- "KMG 365"

Need for Paradigm Shift

- Mid 1960s: CPR was accepted and closed chest defibrillation was perfected by Zoll.
- First Mobile Cardiac Care Unit (with physicians) was established in Belfast in 1960s and featured mobile cardioversion. 1967 Lancet: 10 VF cardiac arrest victims treated with ROSC, 50% were discharged.
- 1968: St. Vincent Hospital NY with similar program.
- Multiple cities (Seattle, LA, Miami) changed from physicians to paramedics.
- It was clear a unified encompassing system approach was needed.

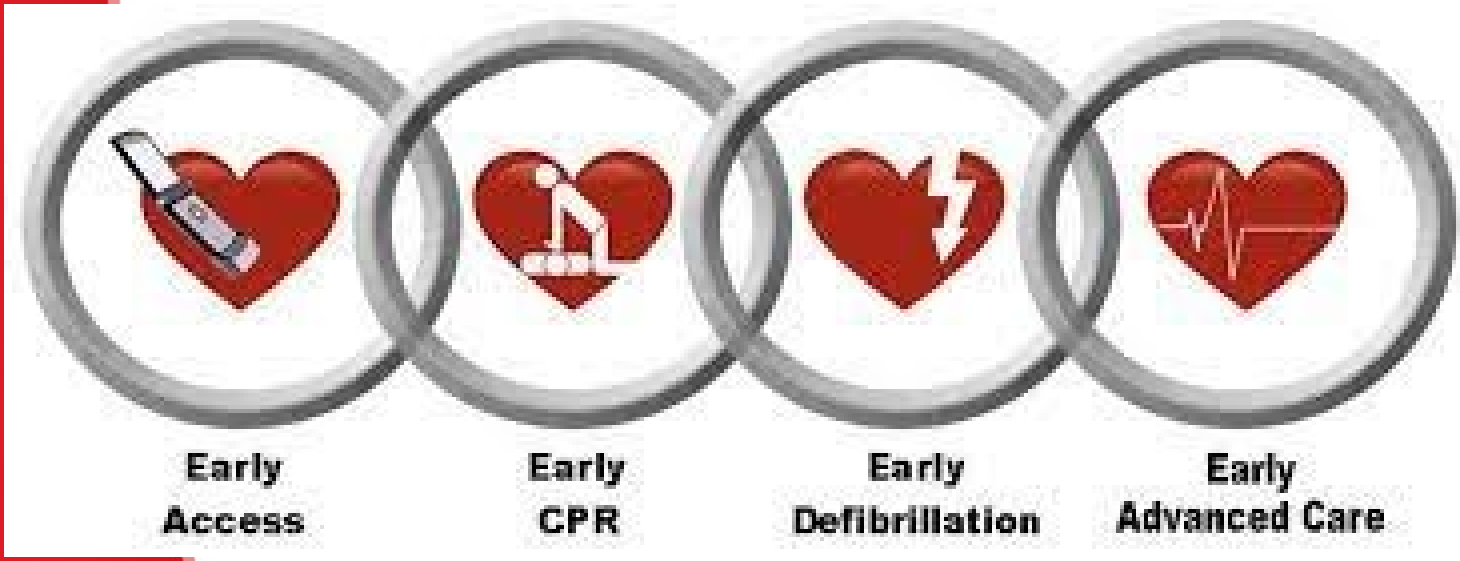
Improving Survival from Sudden Cardiac Arrest: The “Chain of Survival” Concept

Cummins RO, et al. *Circulation.* May 1991; 83(5):1832-1847.

“Chain of Survival” Concept

- Survival from cardiac arrest when certain events occur rapidly:
  1. Recognition of warning signs.
  2. Activation of EMS.
  3. Basic CPR.
  4. Defibrillation.
  5. Intubation.
  6. IV Medications.
- These events make the “chain of survival”.
- Most EMS systems has defects in the “chain” at some point/event.

“Chain of Survival” Concept



“Chain of Survival” Concept

- Early Access Link:
  1. Public education.
  2. Increased numbers of EMS/ambulances.
  3. Uniform adoption of 911.
- Early CPR
  1. Early “citizen initiated’ CPR.
  2. Community training of CPR.
  3. ?? Use of dispatcher-assisted CPR??

“Chain of Survival” Concept

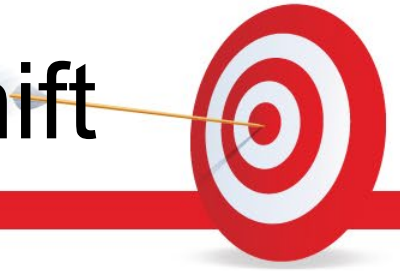
- Early Defibrillation:
  1. Early defibrillation is highly effective.
  2. Allow non-paramedics to defibrillate?
  3. Automated defibrillators are helpful to first responders and paramedics to identify shockable rhythms.
- Early CPR
  1. Early “citizen initiated’ CPR/Community training of CPR.
  2. ?? Use of dispatcher-assisted CPR??
  3. ?Home defibrillators for high-risk patients.
- ACLS
  1. EMT-D vs. Paramedic systems.
  2. Intubation in the field.

“Chain of Survival” Concept

- “The Chain of Survival” concept was a touchstone for modern OHCA care:
  - Data from a large, population-based cohort demonstrate a continuous increase in OHCA survival after implementing the chain of survival.
  - Over the years since its introduction, multiple new interventions have occurred, and others have decreased in importance.
  - The American Heart Association has also added two new links to the chain: post-resuscitation care in 2010, and physical and emotional recovery in 2020.
  - In 2020 the American Heart Association issued a new pediatric chain of survival for infants, children, and adolescents.


Every doctor has interesting cases to discuss
But an emergency physician has stories to tell !

Need for Paradigm Shift



- 1976: first experience with the administration of streptokinase for STEMI by Chazov in Russia.
- 1980: Still did not feel definitively that coronary artery thrombosis was the actual cause of STEMIs.
- 1986: GISSI-1 trial was the first large-scale randomized trial to prove a reduction in mortality with i.v. administration of a fibrinolytic agent
- Standard fibrinolytic regimens induced incomplete recanalization slowly and bleeding complications, especially intracranial hemorrhage, were a concern.

A Comparison of Coronary Angioplasy and Fibrinolytic Therapy in Acute Myocardial Infarction

Henning R, et al. *New Engl J Med.* August 21, 2003; 349(8):733-42.

PCI vs. Thrombolytics in STEMI

- PCI, at the time of the article, was only offered to a limited number of STEMI patients admitted to hospitals with interventional capability.
- Transportation to a primary PCI center was a major limitation.
- Community-wide trail to compare the transfer of patients for primary angioplasty with the use of on-site fibrinolysis.

PCI vs. Thrombolytics in STEMI

- Randomized STEMI patients to either fibrinolysis or to primary angioplasty.
- Danish study, enrolled between 1997-2001 at 24 referral hospitals without angioplasty capability and 4 hospitals with interventional capability.
  - If randomized to angioplasty at a referral hospital, the transfer had to be completed within 3 hours.
  - A physician accompanied the patient directly to the cath lab.
- Primary outcome was a composite of death, clinical reinfarction, or stroke at 30 days.

PCI vs. Thrombolytics in STEMI

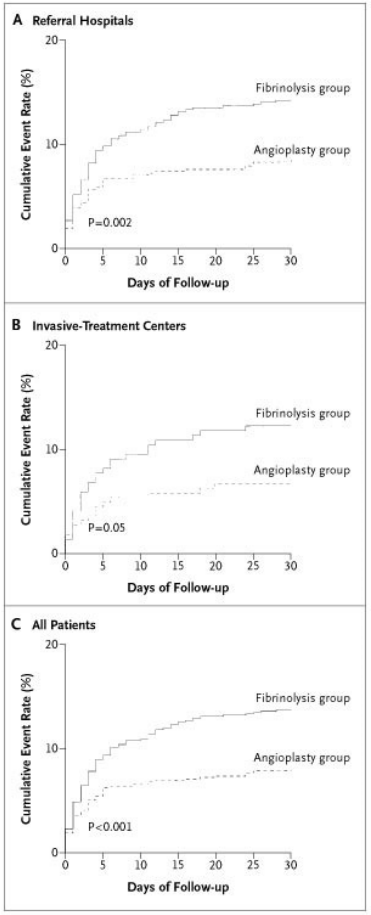
- 4278 patients were screened for inclusion
  - Enrollment stopped early due to superiority of angioplasty.
  - 1129 underwent randomization to referral hospitals and 443 to primary intervention hospitals.
  - Baseline characteristics of patients were similar.
- 27% underwent angioplasty within 1 hour, 31% between 1-2 hours, 24% between 2-4 hours and 18% > 4 hours.
- Angioplasty was superior in both clinical settings and found to be safe (4% were too unstable for transfer).

PCI vs. Thrombolytics in STEMI

Table 3. Clinical Outcome at 30 Days.

Outcome	Referral Hospitals			Invasive-Treatment Centers			All Hospitals		
	Fibrinolysis Group (N=562)	Angioplasty Group (N=567)	P Value	Fibrinolysis Group (N=220)	Angioplasty Group (N=223)	P Value	Fibrinolysis Group (N=782)	Angioplasty Group (N=790)	P Value
	no. (%)			*no. (%)*			*no. (%)*		
Death	48 (8.5)	37 (6.5)	0.20	13 (5.9)	15 (6.7)	0.72	61 (7.8)	52 (6.6)	0.35
Reinfarction	35 (6.2)	11 (1.9)	<0.001	14 (6.4)	2 (0.9)	0.002	49 (6.3)	13 (1.6)	<0.001
Disabling stroke	11 (2.0)	9 (1.6)	0.64	5 (2.3)	0	0.02	16 (2.0)	9 (1.1)	0.15
Composite end point	80 (14.2)	48 (8.5)	0.002	27 (12.3)	15 (6.7)	0.05	107 (13.7)	63 (8.0)	<0.001

PCI vs. Thrombolytics in STEMI

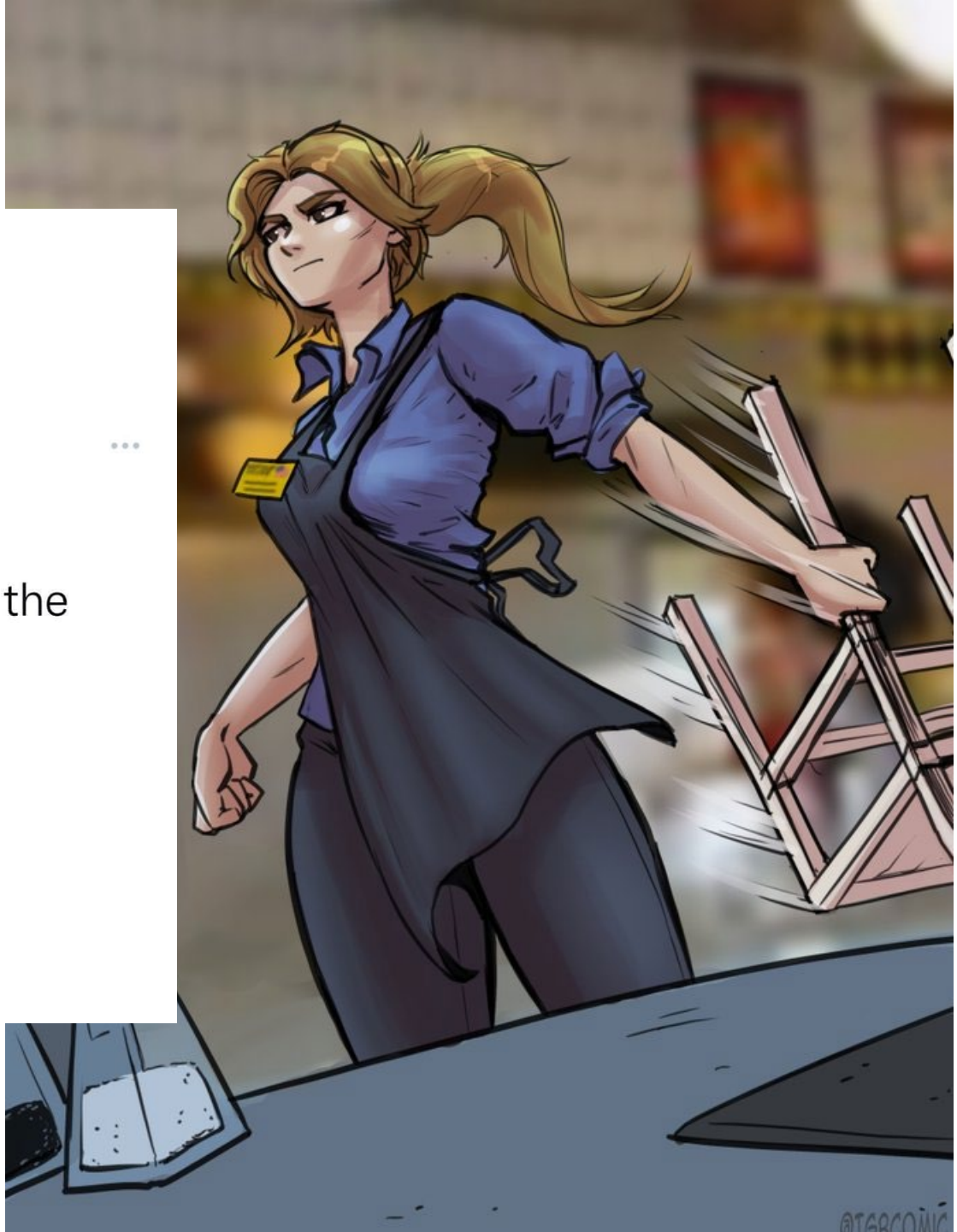


PCI vs. Thrombolytics in STEMI

- Primary angioplasty for STEMI, even when requiring transfer to an intervention center, is superior to fibrinolysis, and was a touchstone for modern STEMI care:
  - In 50 years, randomized trials have demonstrated a decline in early mortality of >70% STEMI in patients.
  - Genesis of the concept of “door-to-balloon time” become one of the most ubiquitous process measures in cardiology.
    - In 2004, a door-to-balloon time within 90 minutes was included for the first time in the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for STEMI management.
    - Shortly thereafter became a publicly reported metric tied to financial reimbursement by Medicare.

Code Blue Memes
@codebluememes

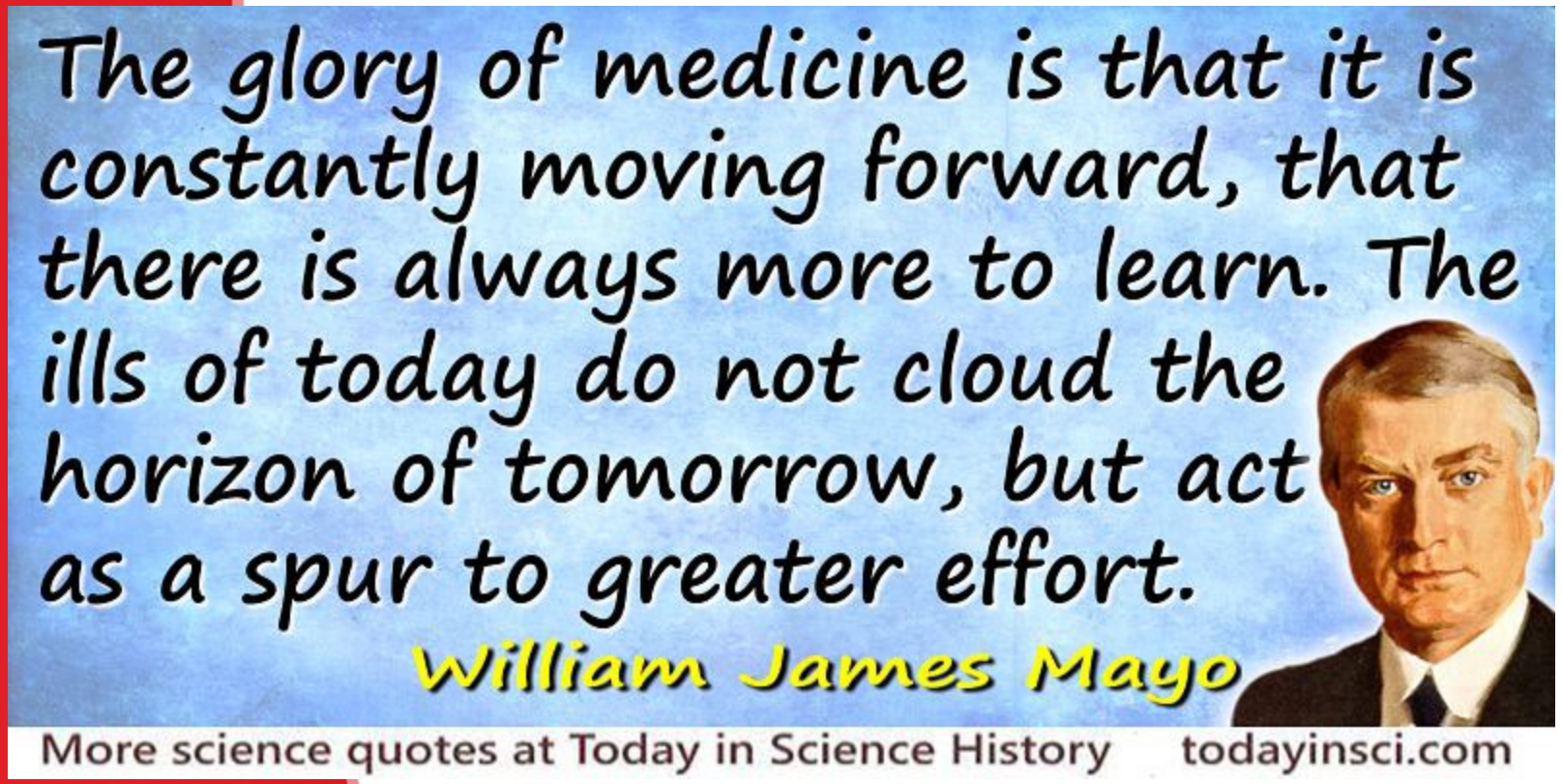
the ER is the Waffle House of the hospital



Summary Fab 5

- ✓ NINDs changed the emergent treatment of ischemic stroke forever – now widely used but at times still controversial.
- ✓ Rapid and aggressive treatment of core areas in sepsis leads to improved outcomes.
- ✓ Regional trauma centers have saved countless lives.
- ✓ The “chain of survival” is a bedrock concept in OHCA.
- ✓ Transfer to regional angioplasty centers has better STEMI outcomes.

Questions??


The glory of medicine is that it is constantly moving forward, that there is always more to learn. The ills of today do not cloud the horizon of tomorrow, but act as a spur to greater effort.
William James Mayo
More science quotes at Today in Science History
todayinsci.com