

Sepsis: A Medical Emergency

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Disclosures: 2010 – February 2017

- Non-industry grant monies:
 - NIH Clinical Research Loan Repayment Program (\$152,781, 10/03-6/05, 7/06-6/10)
 - NIA 1R01AG035117 (\$200,722, 3/11 – 6/12)
 - NHLBI 1U01HL102547 (\$250,182, 7/11 – 6/12)
 - NPSF (\$100,000, 7/11 – 6/12)
- Industry grant monies:
 - PI for calfactant (Pneuma, \$0, 9/08 – 6/12)
- Committee membership
 - **NQF Measures Committee – Pulmonary & Critical care (2016 – current)**
- Consultant/Speakers' Bureau:
 - **Board of Directors, Sepsis Alliance**
 - **Executive Board, Global Sepsis Alliance, World Sepsis Day**
- **Honoraria to Sepsis Alliance (Travel/accomodations may have been provided), various lectures, seminars, educational materials, advisory boards**
 - **GE, 2011; Siemens, 2011; Wolters-Kluwer, 2013; OrthoClinical Diagnostics, 2013; GE, 2014; Abbott, 2015; Webinar GE, 2016**
 - **Consultant, Tenax, 2015 - current**
 - **Consultant, GenEndeavor LLC, 2015 – current**
 - **Consultant, Quorum Therapeutics, 2016 - current**

Disclosures: 2010 – February 2017

I think sepsis is a medical emergency.

I think better sepsis care has a robust ROI.

I think the next challenge in sepsis care will be return to function.

I think we will eventually get our act together – it is just a question of how much we will spend and how many will die before then.

Pulmonary & Critical care (2016 –
current)

current

Objectives

- To understand the outcomes from sepsis when treated as a medical emergency
- To understand the core components of high-value sepsis care, including appropriate antibiotics and intravenous fluids
- To explore the unintended consequences of sepsis care, including antibiotic-resistance and fluid overload
- To explore methods for raising suspicion of sepsis in a variety of clinical settings

Framing the problem

What is Sepsis?

- Sepsis = SIRS + Infection
- Severe Sepsis = Sepsis + Organ Failure
- Septic Shock = Sepsis + Hypoperfusion (low blood pressure)
- Mortality increases with more organ failure

What is Sepsis?

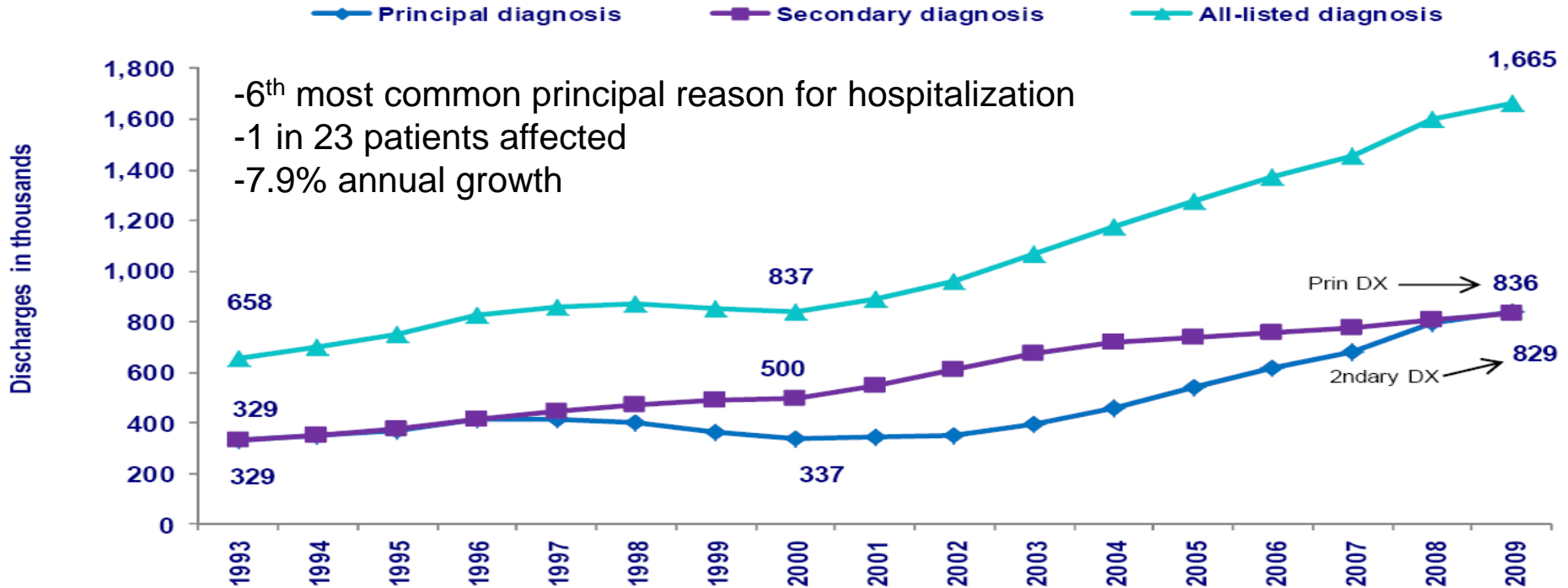
- Sepsis = ~~SIRS~~ + Infection
- ~~Severe Sepsis~~ = Sepsis + Organ Failure
- Sepsis = Sepsis + Organ Failure
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- Mortality increases with more organ failure

The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3)

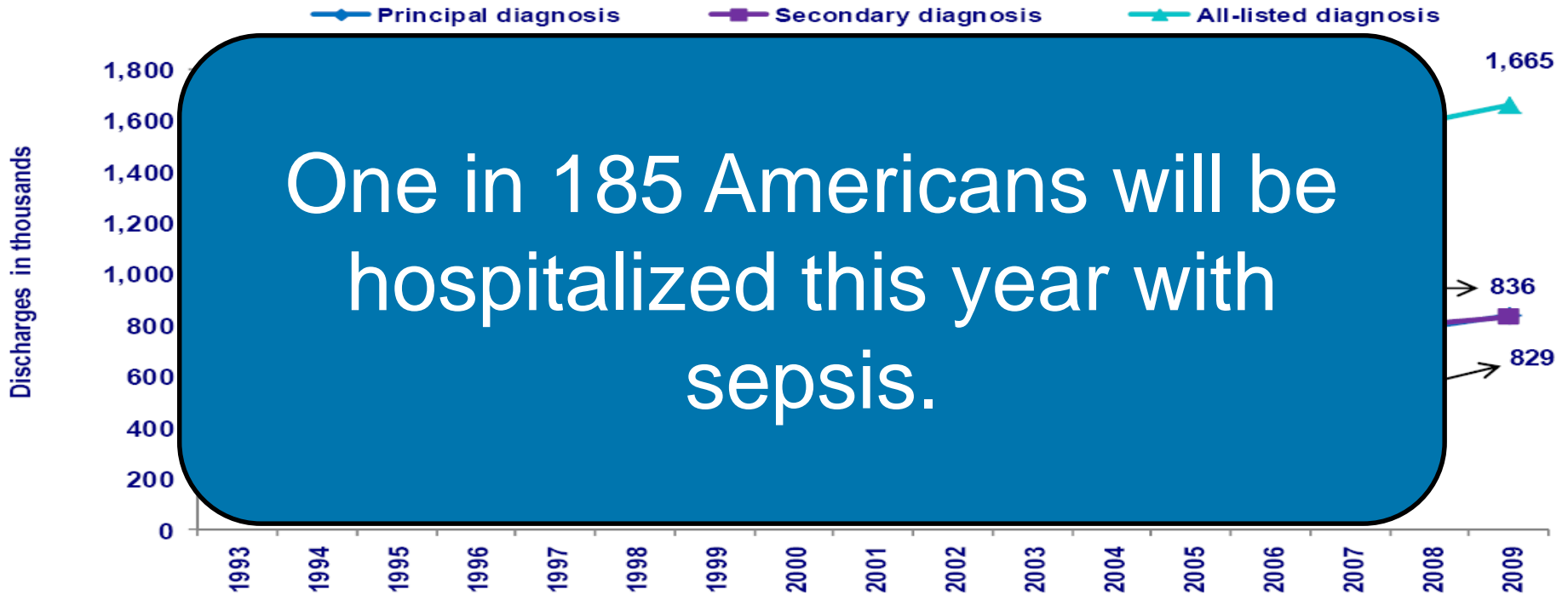
Singer *et al.* *JAMA* 2016; 315(8): 801-810

- Sepsis = a life-threatening organ dysfunction caused by a dysregulated host response to infection
 - *Used to be SEVERE SEPSIS
- Organ dysfunction can be identified by an acute change in SOFA score ≥ 2 (mortality risk $\sim 10\%$)
- Septic shock = a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
 - Blood pressure and Lactate

Sepsis Is Common And Becoming More Common



Sepsis Is Common And Becoming More Common



Patients hospitalized for septicemia or sepsis were more than eight times as likely to die during their hospitalization.

Table. Hospitalizations for septicemia or sepsis compared with hospitalizations for other diagnoses, by discharge disposition, 2008

Characteristic	Septicemia or sepsis	Other diagnoses
Disposition	Percent	
Routine¹	39	79
Transfer to other short-term care facility¹	6	3
Transfer to long-term care institution¹	30	10
Died during the hospitalization¹	17	2
Other or not stated	8	6
Total	100	100

¹Difference is statistically significant at the 0.05 level.

SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.

Patients hospitalized for septicemia or sepsis were more than eight times as likely to die during their hospitalization.

Table. Hospitalizations for septicemia or sepsis compared with hospitalizations for other diagnoses, by discharge disposition

Disposition	Septicemia or sepsis	Other diagnoses
Dispos		
Route		
Trans		
Trans		
Died		
Other		
Total		

Sepsis contributes to 1 in every 2 to 3 deaths in hospitals.
Majority had sepsis on presentation to the hospital.

Liu *et al.* JAMA May 18, 2014.

¹Difference is
SOURCE: CDC

258,000 deaths a year in the US



27 Deaths* every ~55 min
*2010-2014 US air traffic deaths



2974 Deaths
every ~4.2 days

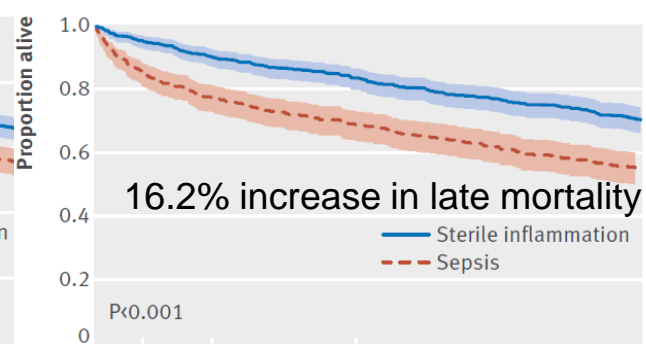
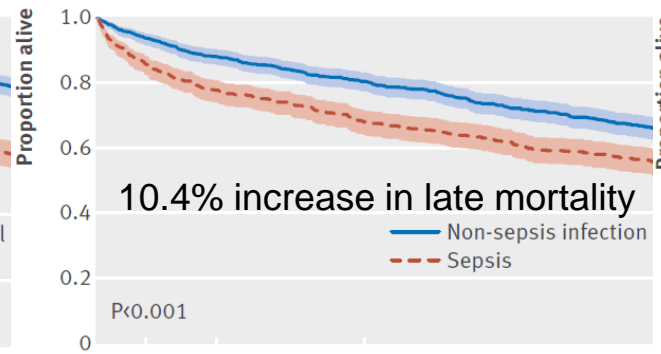
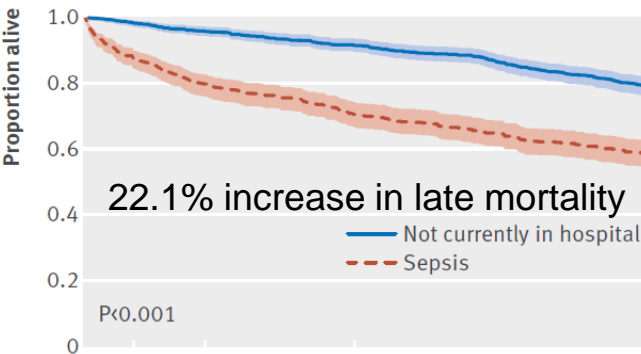
258,000 deaths a year in the US

Deaths from
Breast cancer
Lung Cancer
+Prostate Cancer

TOTAL < Deaths from Sepsis

Late mortality after sepsis: propensity matched cohort study

Prescott *et al. BMJ*. 2016;353: i2375



- Sepsis matched to:
 - Not currently in hospital
 - Admitted with non-sepsis infection – infection but no organ dysfunction
 - Admitted with sterile inflammation – trauma, fracture, burn, pancreatitis, etc
- Examined late mortality (31d to 2y)
- Infection was most common reason for terminal admission for ALL groups

Sepsis is the most costly in-patient hospital condition

Sepsis annual hospital costs (2013)*	\$23.6 Billion
Sepsis average cost per hospital stay** <i>Double the average cost per stay across all other conditions</i>	\$18,400
Sepsis average annual cost growth** <i>Annual growth 3x the growth rate of overall hospital costs</i>	11.5%
Annual costs of readmission after sepsis*** <i>Ranks in top 10 readmission for all payers</i>	\$4.0 Billion

*Torio *et al*, National Inpatient Hospital Costs *HCUP Statistical Brief #204*

**Pfundtner *et al*, Costs for Hospital Stays in the United States, 2013 *HCUP Statistical Brief #168*

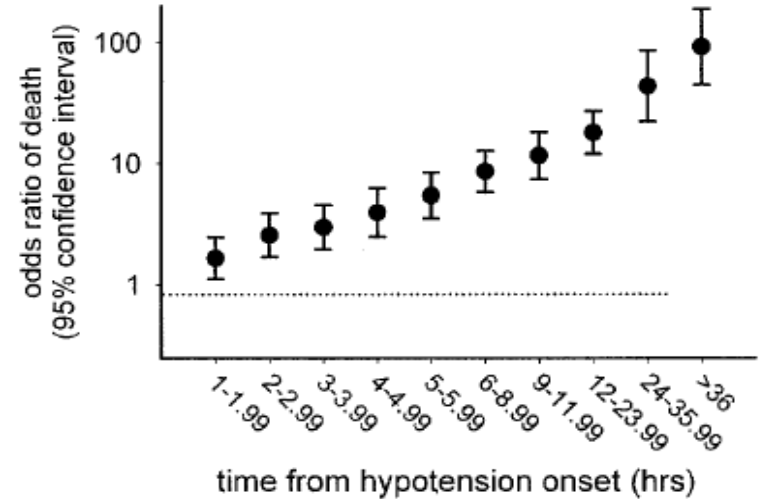
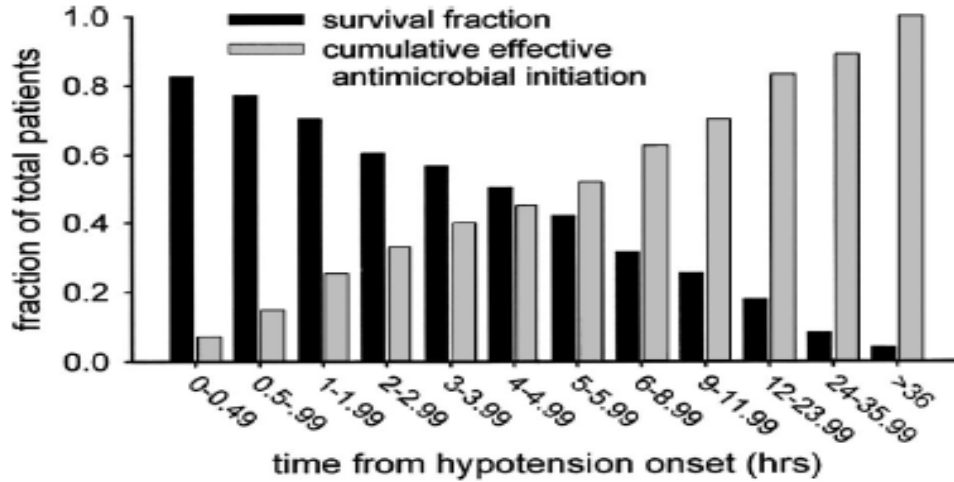
***Hines *et al*, *HCUP Statistical Brief #172*, April 2014

Survivorship Issues after Sepsis

- **20,000 new cases of cognitive dysfunction per year** among survivors of sepsis (Iwashyna *JAMA* 2010;304(16):1787-94)
- **74% with functional disabilities** after 3 years (Iwashyna *J Am Ger Soc* 2012; 60:1070-7)
- ~60% with symptoms of **depression and/or anxiety and/or PTSD** (Rosendahl *Crit Care Med* 2013; 41)
- **Brain atrophy and low-frequency on EEG** 6-24months after discharge (Semmier *J Neurol Neurosurg Psych* 2013; 84: 62-9)
- **Wives** of sepsis survivors four times more likely to experience **depressive symptoms** (Davydow *Crit Care Med* 2012; 40: 2335-41)
- One-quarter of **relatives** of survivors with **anxiety** and one-half with **PTSD symptoms at six months** post ICU (Jones *Intens Care Med* 2004; 30: 456-60)

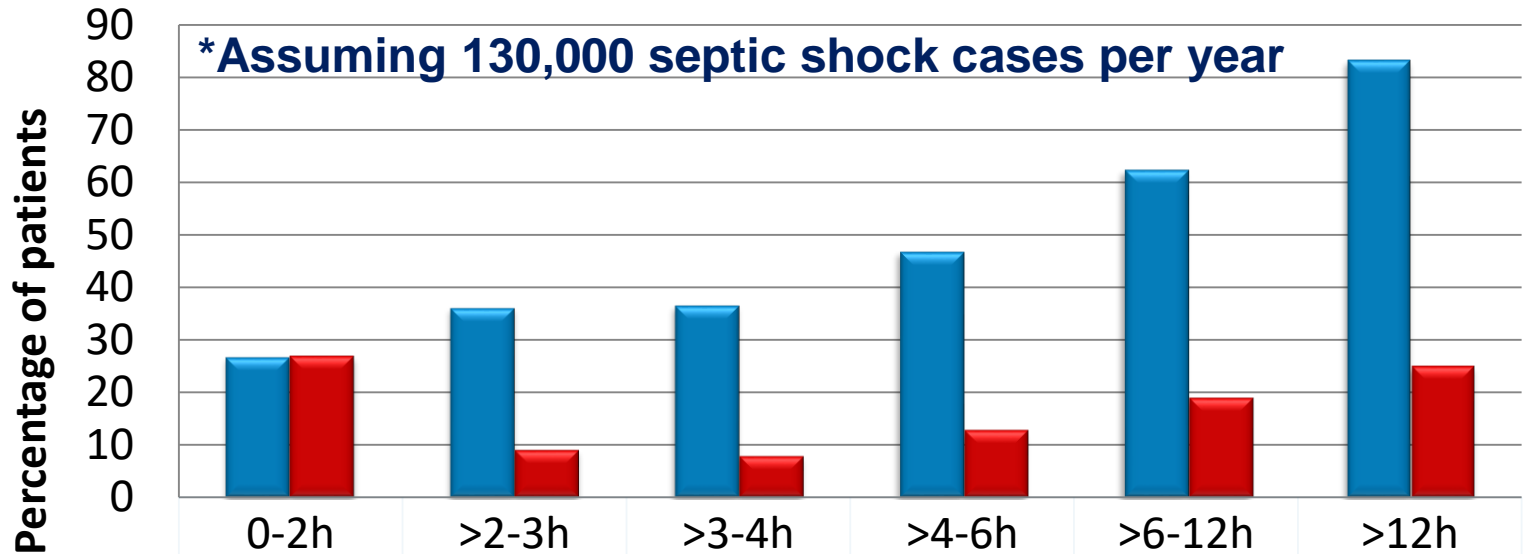
Sepsis as a medical emergency

Antibiotics – No time to waste



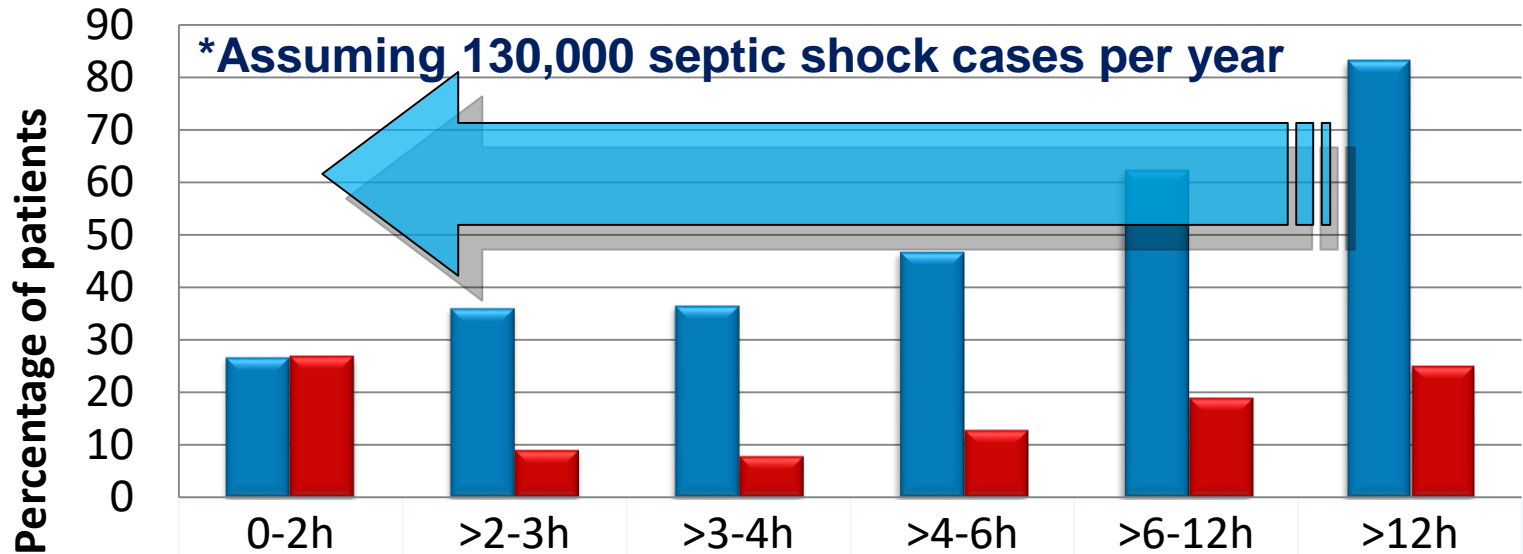
- Every hour in delay of appropriate atbx = 7.6% lower survival
- Median time to appropriate atbx = 6h

Shock to Effective Antibiotic Time and Mortality in Septic Shock*



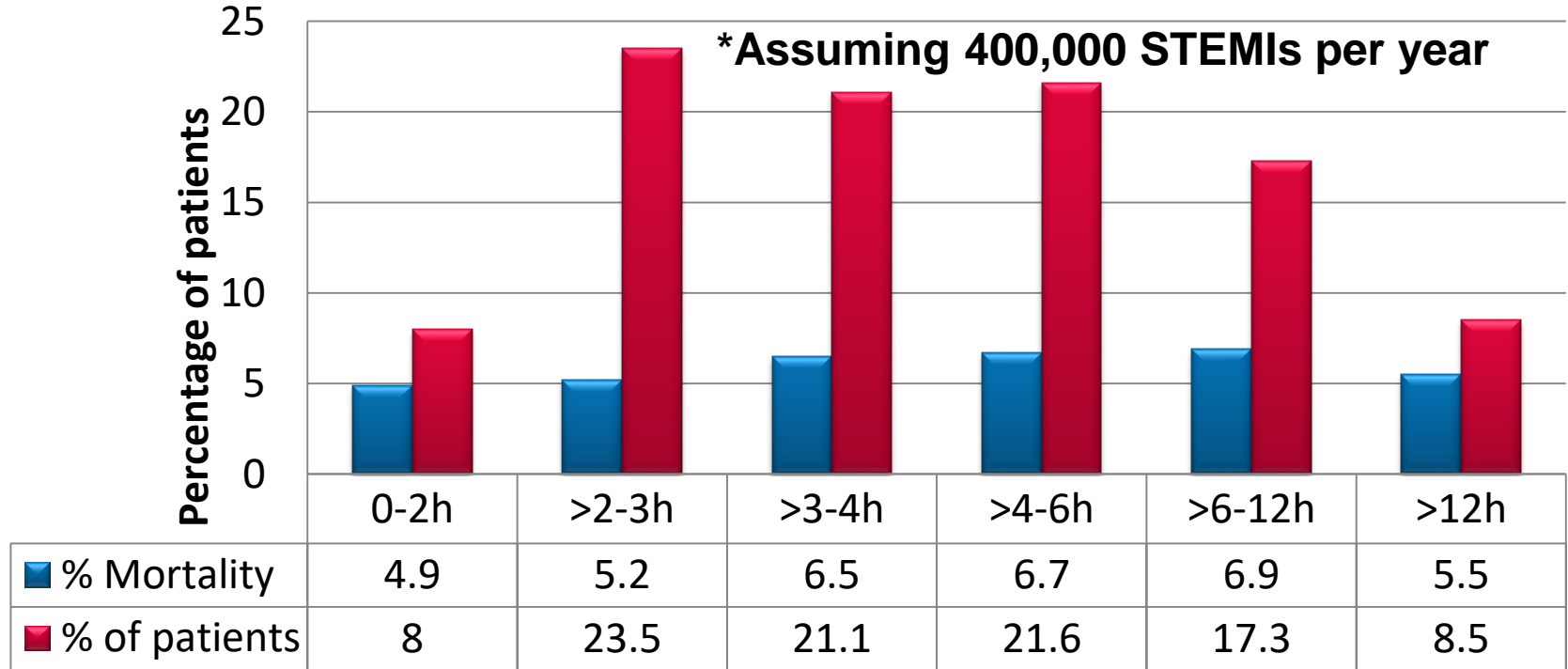
■ %Mortality	26.7	36.1	36.6	46.8	62.3	83.1
■ % of patients	26.8	9.0	7.8	12.8	18.8	24.9

Shock to Effective Antibiotic Time and Mortality in Septic Shock*

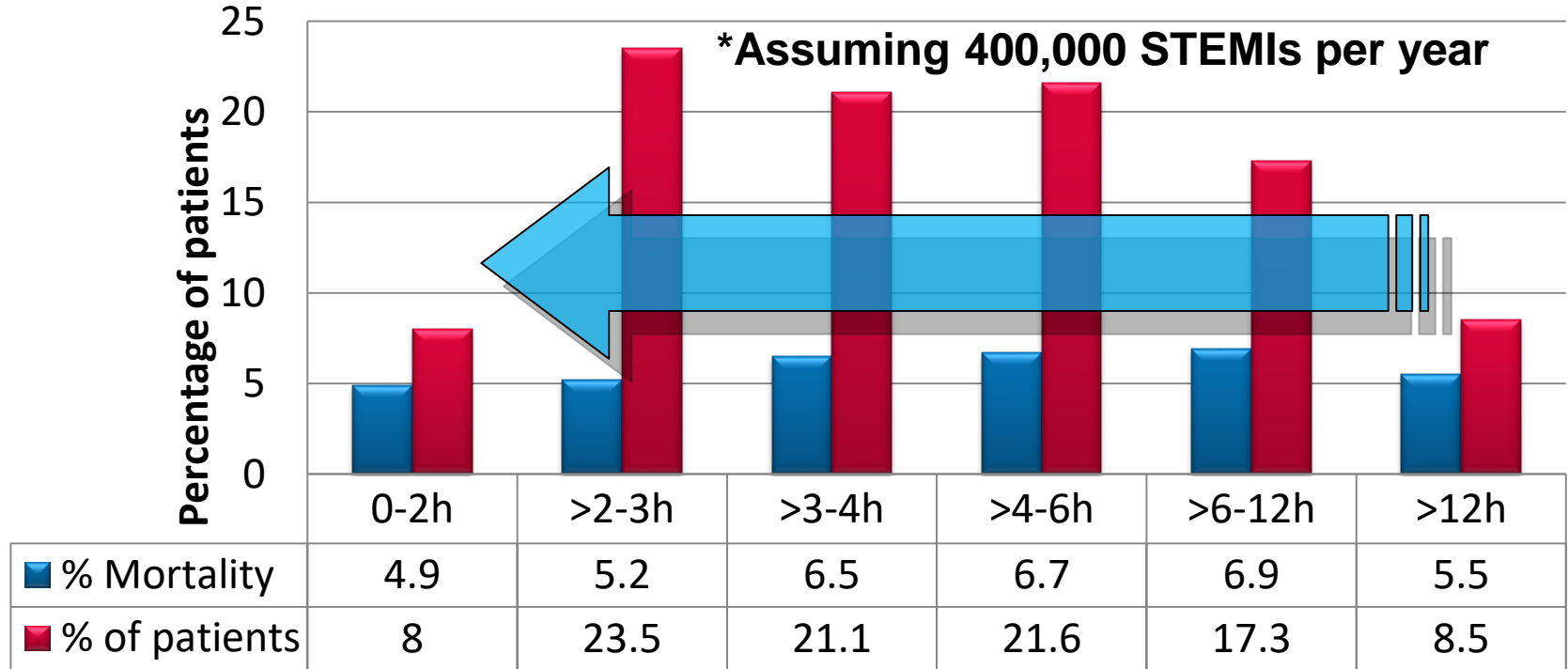


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Door to Balloon Time and Mortality in STEMI*



Door to Balloon Time and Mortality in STEMI*



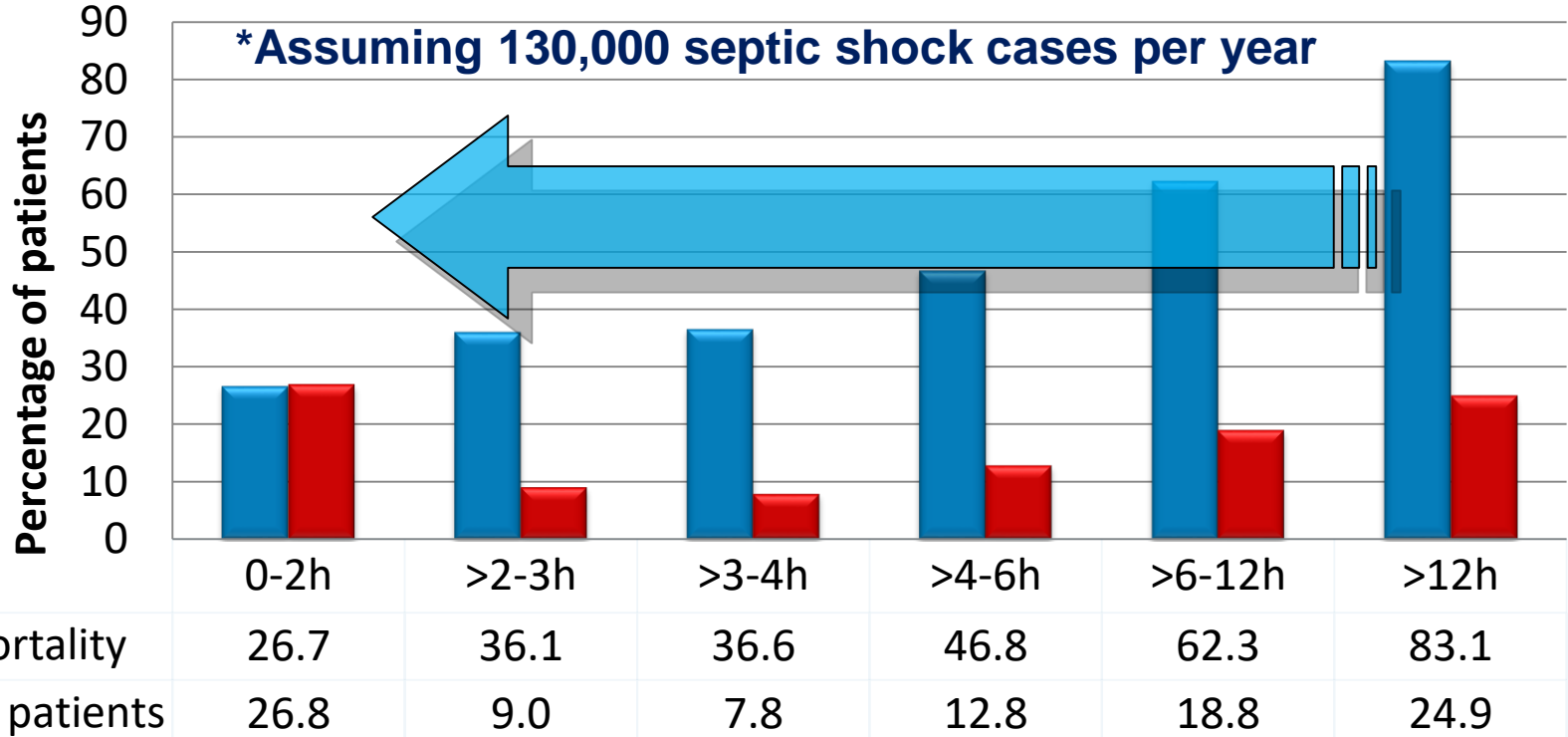
Door to Balloon Time and Mortality in STEMI*

25

By getting door-to-balloon times of <2h for ALL STEMI patients, we would save **4775 lives per year.** (13 people a day)

■ % Mortality	4.9	5.2	6.5	6.7	6.9	5.5
■ % of patients	8	23.5	21.1	21.6	17.3	8.5

Shock to Effective Antibiotic Time and Mortality in Septic Shock*



Shock to Effective Antibiotic Time and Mortality in Septic Shock

By getting shock-to-antibiotic times of <2h for ALL septic shock patients, we would save

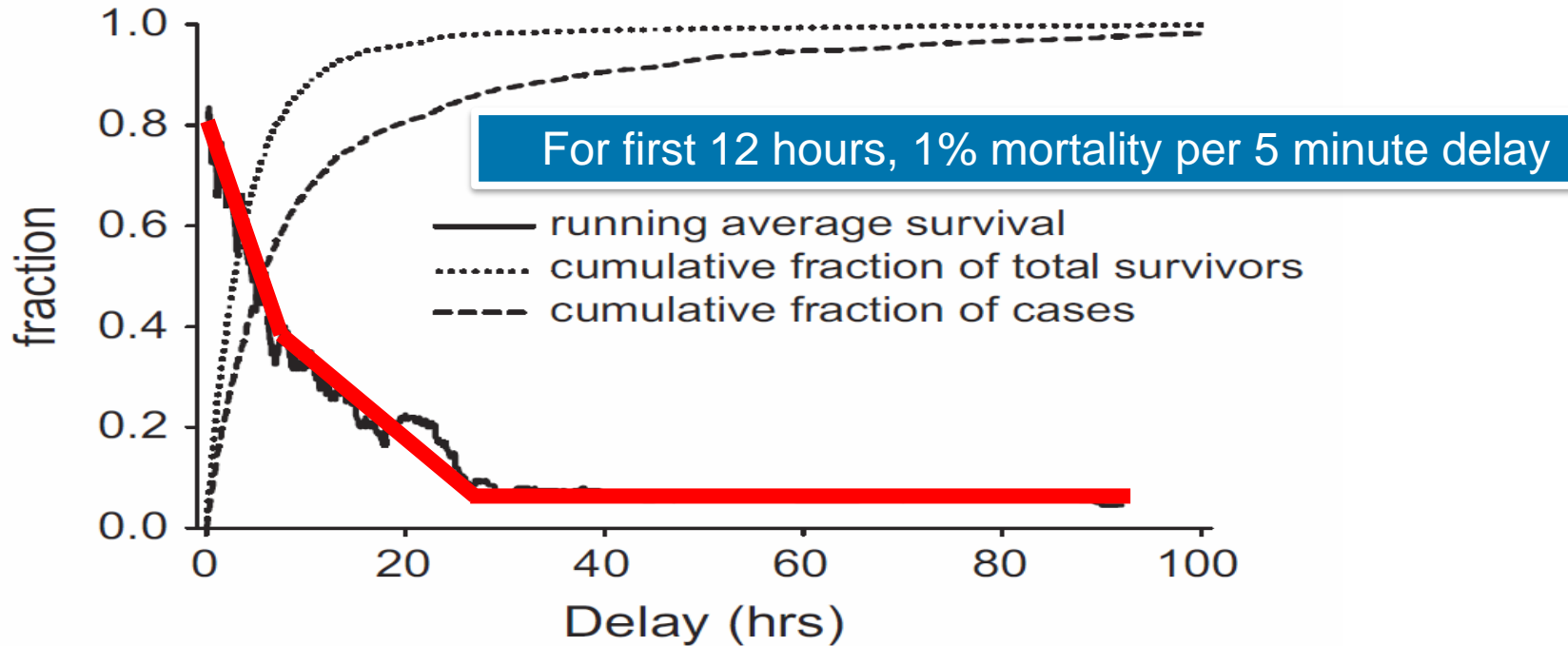
32,360 lives per year.

(89 people a day)

(3.7 people an hour)

(3.5 times the effect of STEMI intervention)

The First 12 Hours Matter Even More



Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle

- QI project in 11 hospitals in Utah and Idaho
- ED patients with severe sepsis or septic shock
- January 2004 – December 2010
- Screened 15,109 patients
- 4379 with severe sepsis or septic shock
 - 29.2% of patients screened
 - 2 of every 7 patients

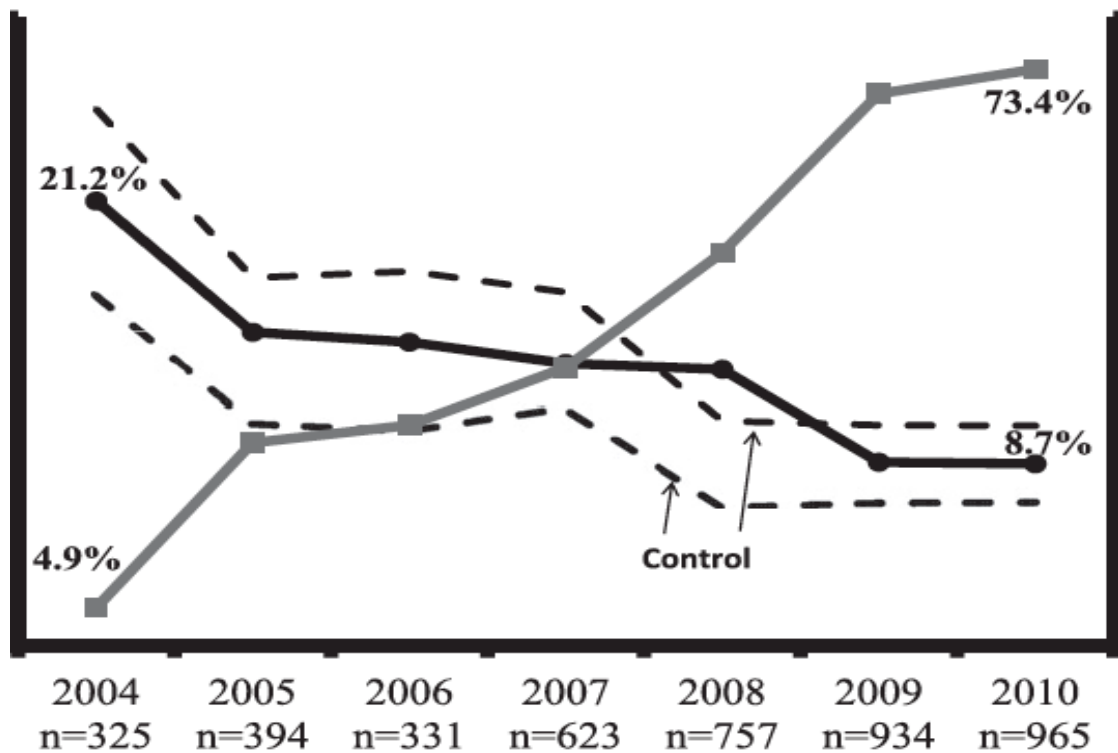
Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle

All patients get:

- Serum **lactate** within 3h of ED admission
- **Blood cx** prior to antibiotics within 3h of ED admission
- **Broad-spectrum atbx** within 3h of ED admission
- **Mean glucose ≤ 180** 12-24 h after ED admission

Eligible patients get:

- If sbp ≤ 90 , MAP ≤ 65 , or lactate ≥ 4 , at least 20 ml/kg PBW **crystalloid**
- If low bp continues after fluids, use **vasopressors**
- If low bp or high lactate. **CVP and ScvO₂ measured** regularly and goals of CVP ≥ 8 and ScvO₂ $\geq 70\%$
- If CVP ≥ 8 and ScvO₂ $\leq 70\%$, **inotropes or PRCs**
- If on higher dose vasopressors, give **steroids**
- If on vent, **tidal volume** 6ml/kg PBW



Absolute bundle compliance increase of 68.5%

Absolute mortality reduction of 12.5%

Control

Absolute bundle compliance

If care remained as provided in 2004
(vs 2008-10), these hospitals would:

- consume 1416 more hospital days a year
- consume 266 more ICU days a year
- kill 99 patients a year



ion of

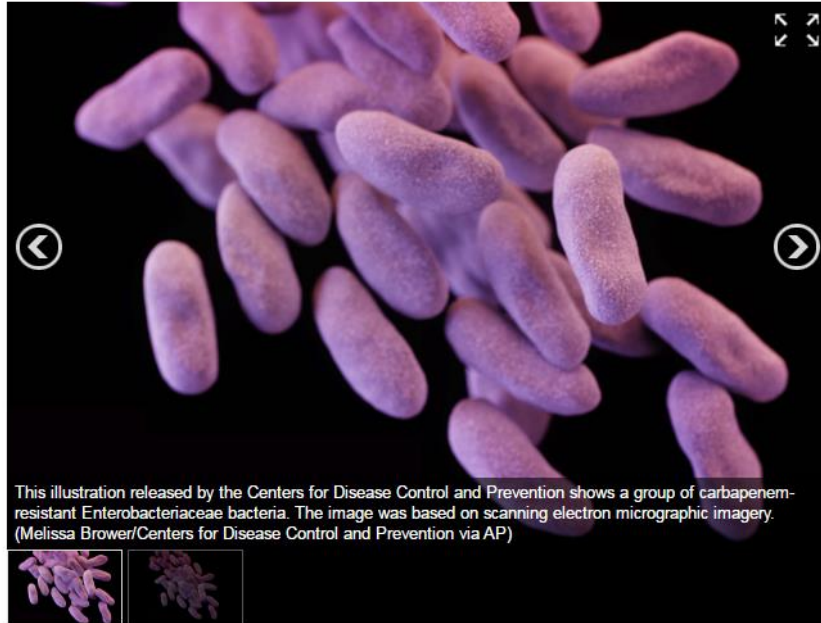
	2004	2008-10	“Relative waste reduction”
<i>Eligible for later bundle elements*</i>			
Fluid resuscitation	75%	71%	5%
Vasopressors	63%	35%	44%
CVP and ScvO2 monitoring	64%	29%	55%
Inotropes and RBC transfusions	59%	13%	78%
Glucocorticoids	63%	21%	67%
Lung protective ventilation	43%	14%	67%

*By diagnosing severe sepsis and providing atbx, blood cultures and lactate measurement at very high rates

Unintended consequences

Posted January 12, 2017 - 7:23pm | Updated January 12, 2017 - 9:55pm

'Superbug' resistant to all available antibiotics killed elderly northern Nevada woman



This illustration released by the Centers for Disease Control and Prevention shows a group of carbapenem-resistant Enterobacteriaceae bacteria. The image was based on scanning electron micrographic imagery. (Melissa Brower/Centers for Disease Control and Prevention via AP)

By PASHTANA USUFZY
LAS VEGAS REVIEW-JOURNAL

A Northern Nevada woman died last year from a bacterial infection resistant to all 26 antibiotics available in the U.S., highlighting the growing public health threat posed by so-called "superbugs."

The woman, an unidentified Washoe County resident in her 70s who had traveled to India,

Where to start

- 70% of total medically important antibiotic sales by volumes are in food animal production
 - FDA policy implemented in Jan 2017 – addition of antibiotics to feed or water requires oversight of a veterinarian
- Antibiotic stewardship programs - <40% of US hospitals have full program
- 13% of outpt visits result in an antibiotic prescription
 - 30% (47million) are unnecessary

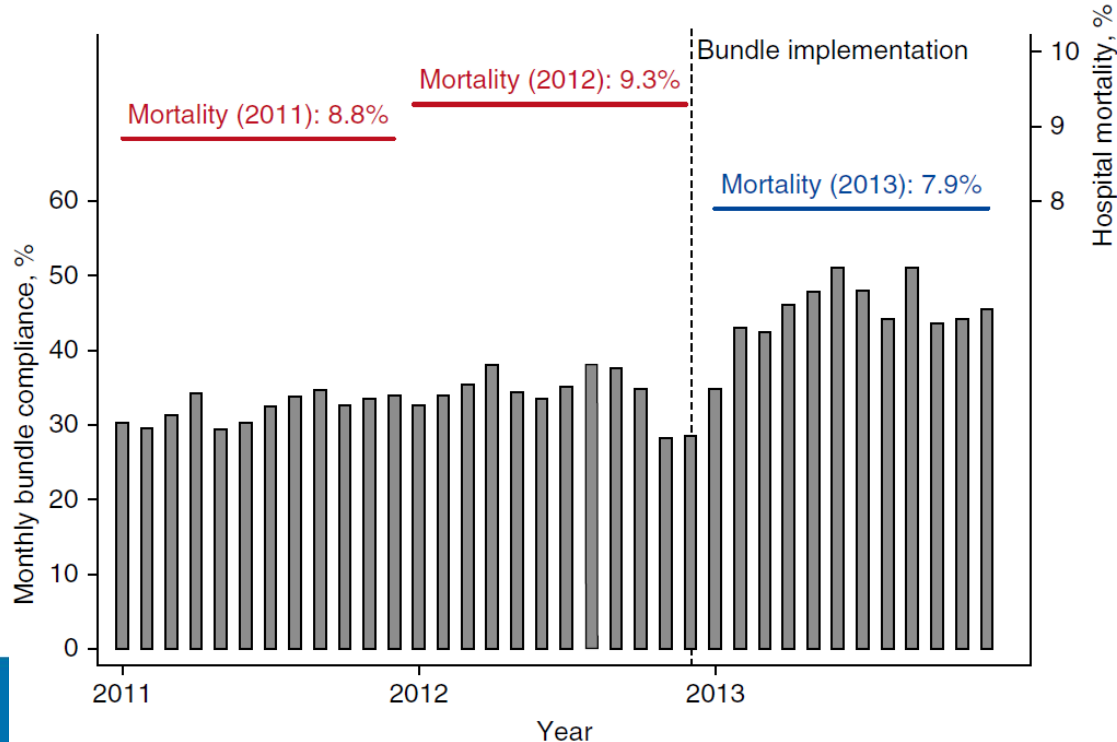
Multicenter Implementation of a Treatment Bundle for Patients with Sepsis and Intermediate Lactate Levels

Liu *et al.* *AJRCCM* 2016; 193(11): 1264-70.

- QI project in 21 community hospitals, Mar 11- Feb 14, n=18,122
- Sepsis POA with lactate 2-4, without shock
- Antibiotics, intravenous fluids (30ml/kg OR 2L), repeat lactate
- Already robust process for checking lactate (974% increase in # annual tests) and antibiotic administration (>95% within 3h of arrival)
- Evaluated interaction with pre-existing diagnosis of heart failure and/or chronic kidney disease

Multicenter Implementation of a Treatment Bundle for Patients with Sepsis and Intermediate Lactate Levels

Liu *et al.* *AJRCCM* 2016; 193(11): 1264-70.



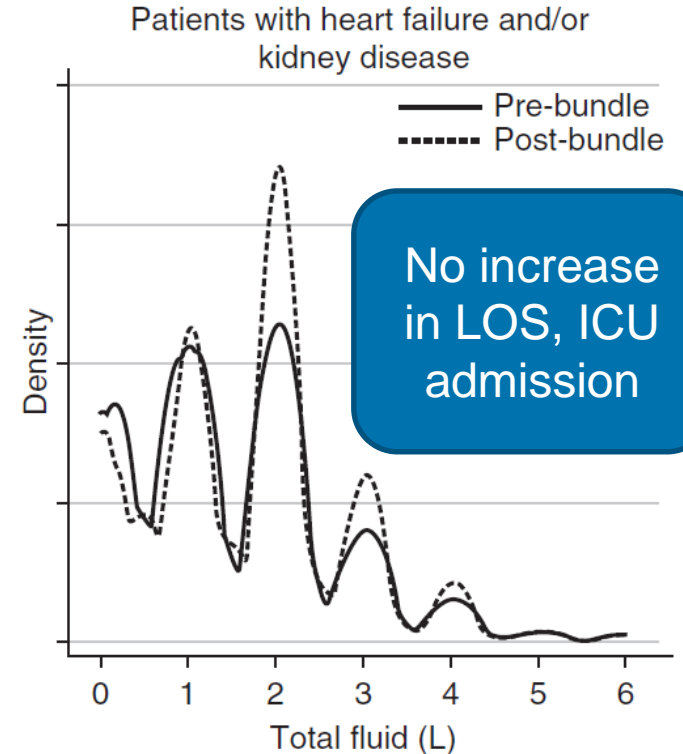
- Bundle compliance increased from 32.2% to 44.9%
- Driven by increases in lactate goal (10% reduction) and fluid goal
- Risk adjusted 30d mortality 16% lower

Multicenter Implementation of a Treatment Bundle for Patients with Sepsis and Intermediate Lactate Levels

Liu *et al.* *AJRCCM* 2016; 193(11): 1264-70.

Table 4. Hospital Mortality in Heart Failure and Chronic Kidney Disease Subgroups

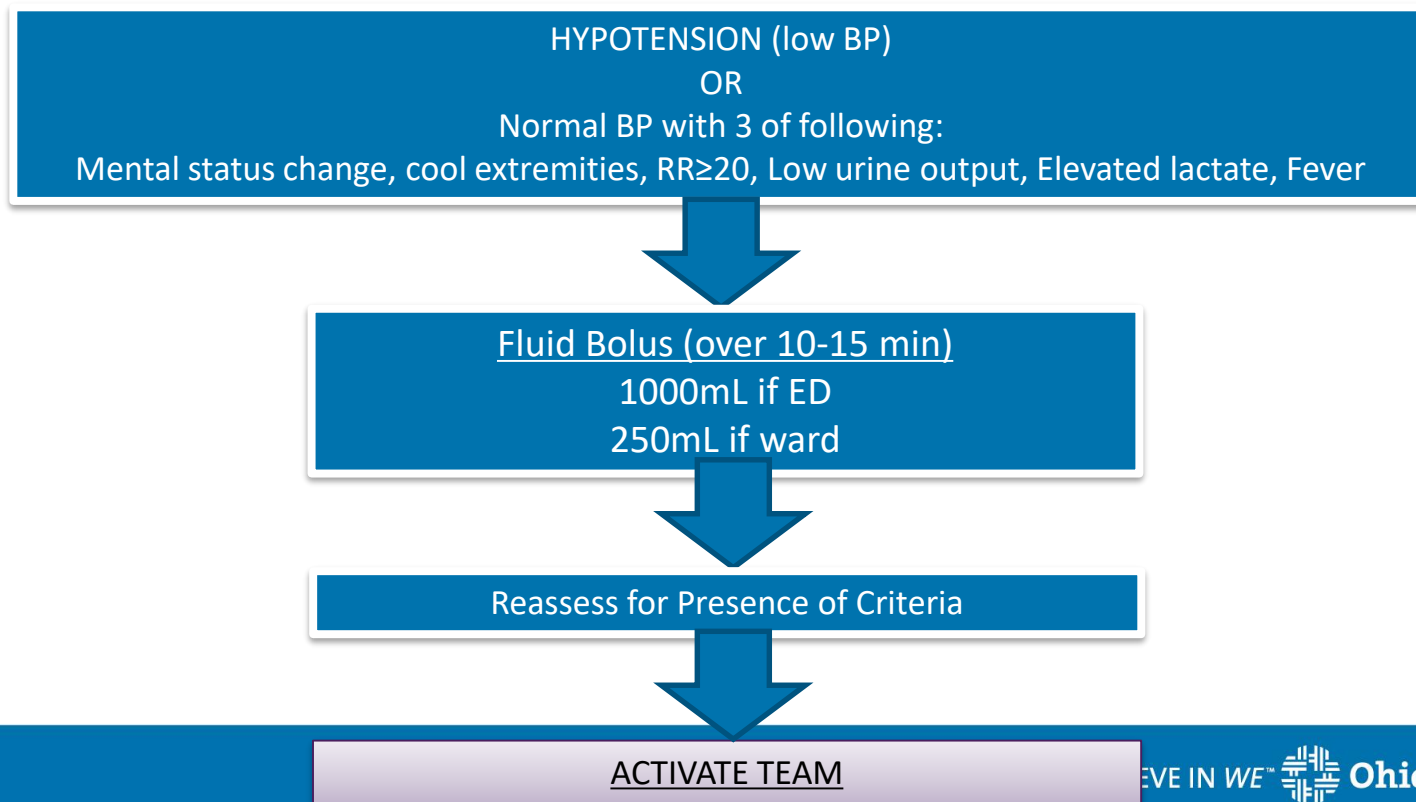
	n	Mortality (%)			P Value
		Prior (2011)	Prebundle (2012)	Postbundle (2013)	
All patients	18,122				
Hospital		8.8	9.3	7.9	0.02
30 d		13.7	14.1	12.6	0.03
History of heart failure	4,144				
Hospital		13.0	14.8	11.6	0.03
30 d		18.8	20.7	17.8	0.13
History of kidney disease	6,285				
Hospital		9.7	11.5	7.5	<0.01
30 d		15.9	17.7	13.3	<0.01
Heart failure or kidney disease	8,322				
Hospital		10.7	12.5	8.7	<0.01
30 d		16.8	18.3	14.5	<0.01
No heart failure or kidney disease	9,800				
Hospital		7.4	6.5	7.2	0.40
30 d		11.3	10.5	10.8	0.60



Finding needles in piles of needles

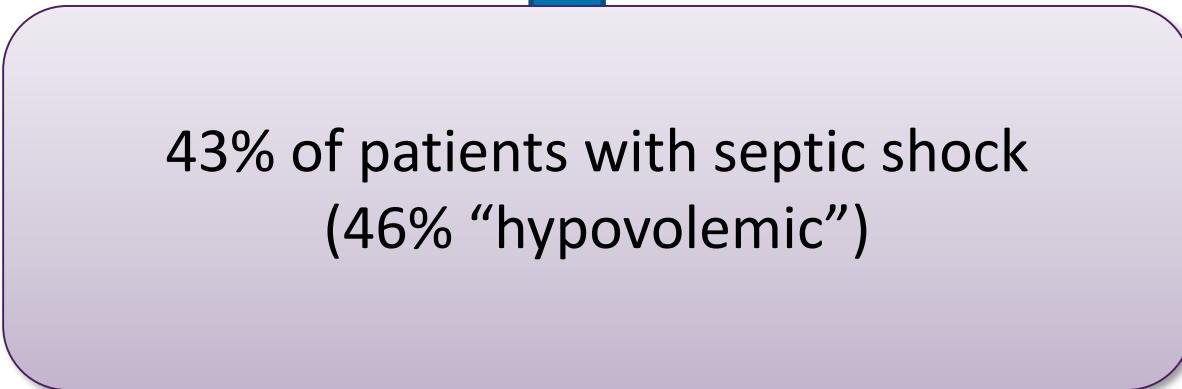
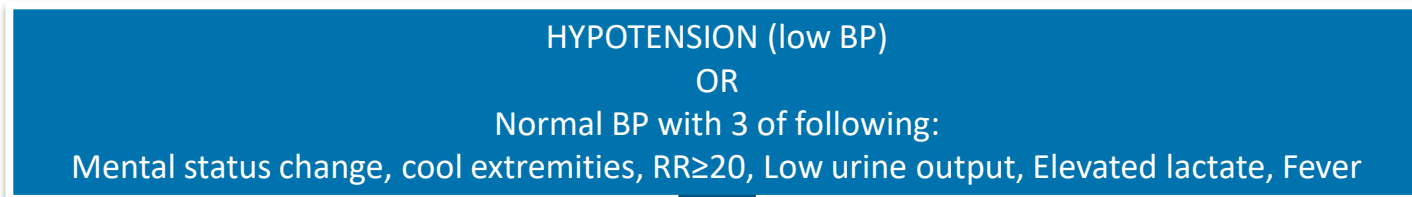
Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years

Sebat *et al* *CHEST* 2007; 35: 2568-2575



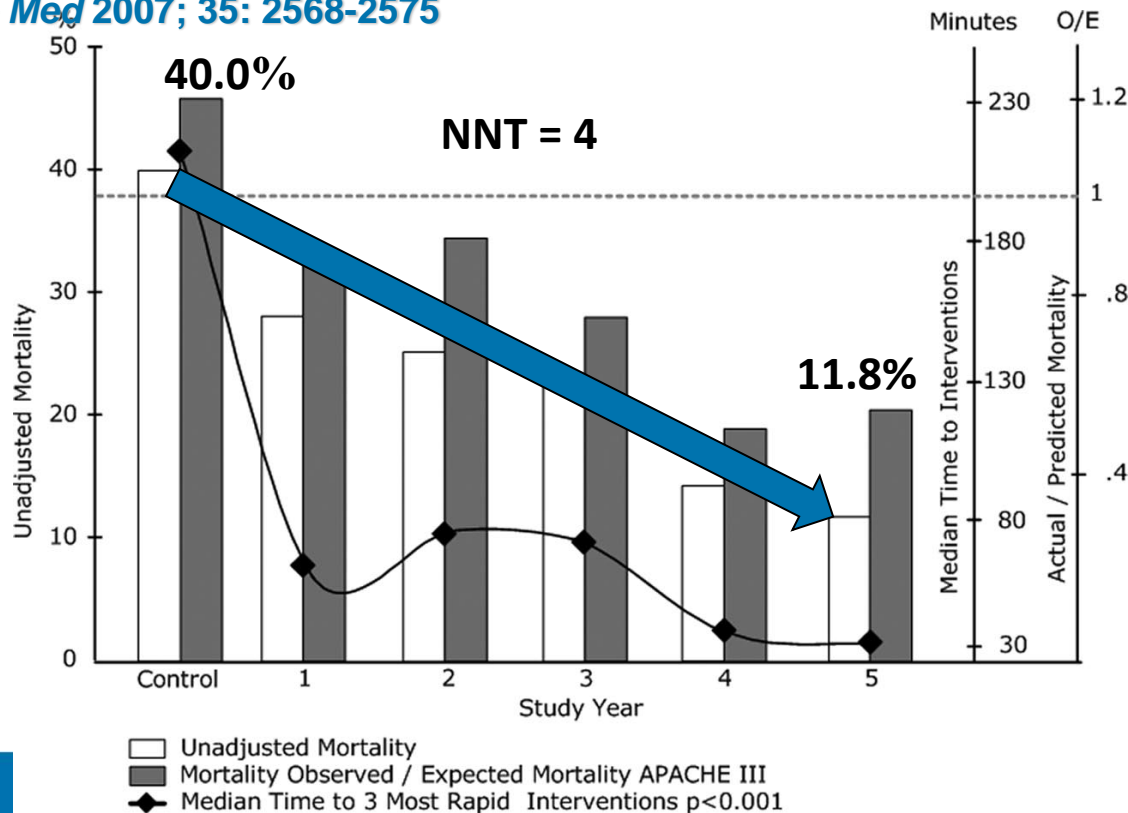
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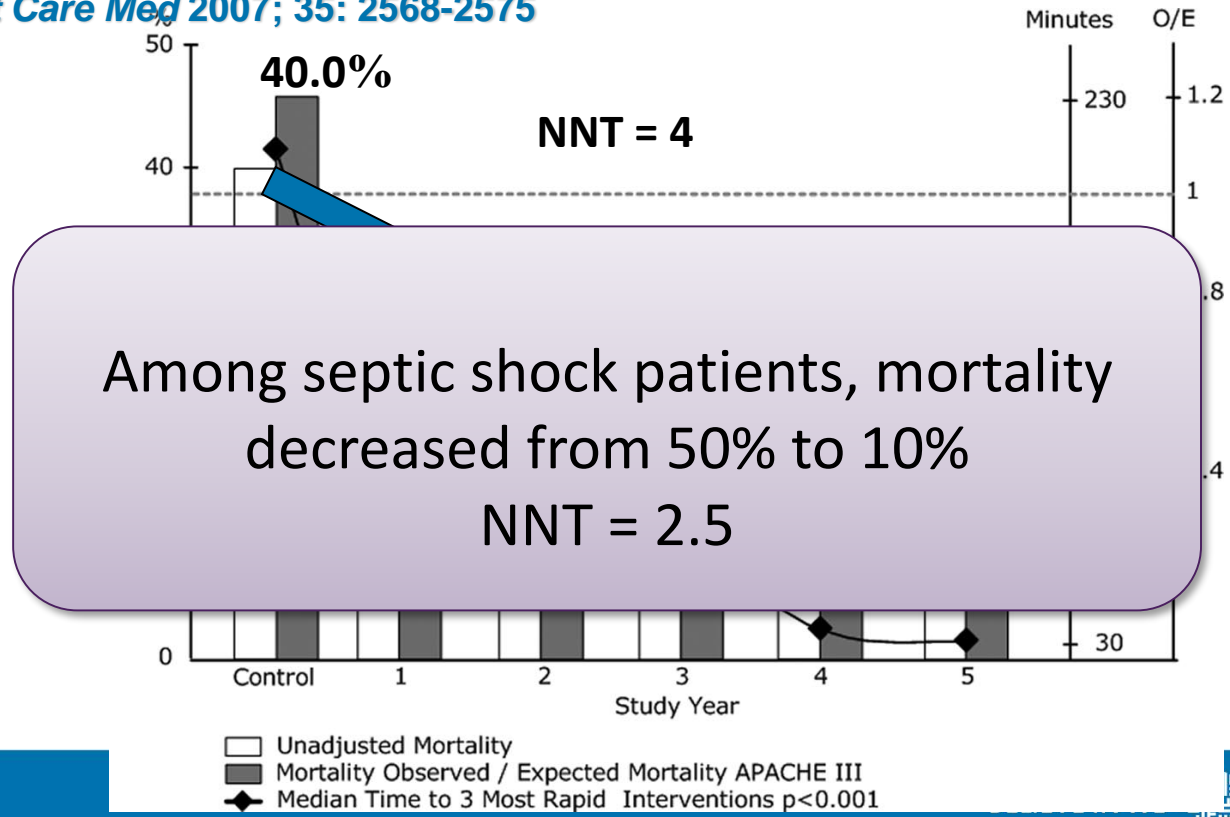
Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years

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Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years

Sebat et al *Crit Care Med* 2007; 35: 2568-2575



Unadjusted Mortality
 Mortality Observed / Expected Mortality APACHE III
 Median Time to 3 Most Rapid Interventions p<0.001

Evaluating the impact of a computerized surveillance algorithm and decision support system on sepsis mortality

Manaktala and Claypool *J Am Med Inform Assoc* 2016

Figure 2: Overview of Clinical Decision Support Surveillance.

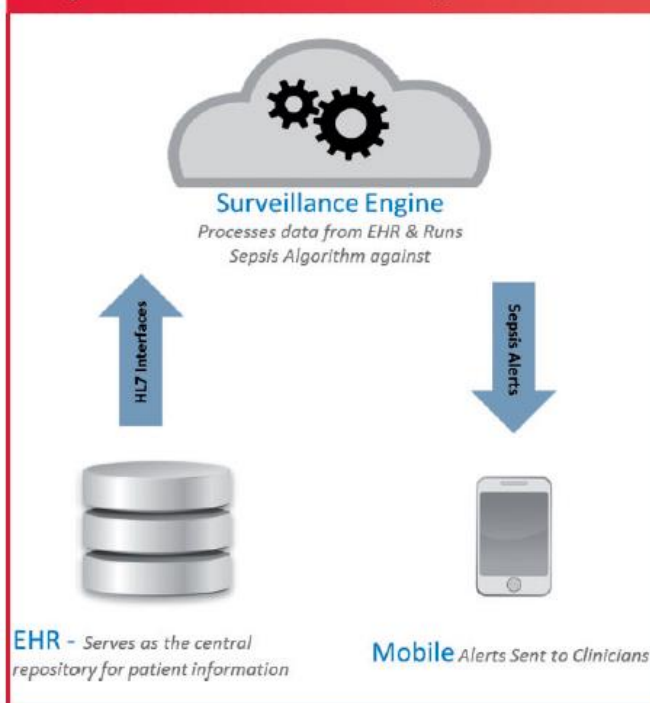
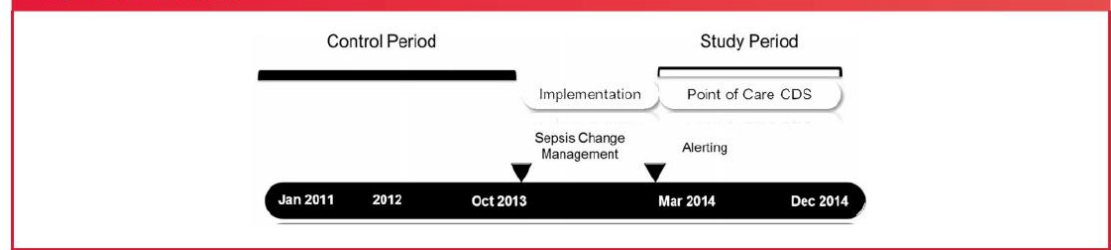


Figure 1: Study Timeline.



- Real-time electronic sepsis surveillance performed in 2 medical units
- Nurses received alerts on mobile and desktop computers on a secured network
- Alerts included: informational prompts, diagnostic alerts, advice alerts, reminder alerts

Evaluating the impact of a computerized surveillance algorithm and decision support system on sepsis mortality

Manaktala and Claypool *J Am Med Inform Assoc* 2016

Table 4: Test Characteristics for the Electronic Diagnosis of Sepsis vs. Gold-Standard Comprehensive Chart Review

Statistic	Result (95% CIs)
True positives	118
False negatives	6
False positives	117
True negatives	530
Sensitivity	95.16 (89.77-98.20)
Specificity	81.92 (78.73-84.8)
Positive likelihood ratio	5.26 (4.45-6.23)
Negative likelihood ratio	0.06 (0.03-0.13)
Sepsis prevalence ^a	16.08 (13.56, 18.87)
Positive predictive value ^a	50.21 (43.64, 56.78)
Negative predictive value ^a	98.88 (97.58, 99.59)

- Sepsis-related mortality dropped from 90 to 42 deaths per 1000 sepsis cases
- Patients screened using the sepsis CDS system had 2.1 times lower risk of death compared to pre-implementation period
- Readmissions after sepsis dropped from 19.1% to 13.2%

In summary

- Sepsis is a time-sensitive disease = medical emergency
- Getting the basics right as soon as possible improves outcomes AND simplifies care
- We still have much to learn about sepsis and its care – but there is much we can offer patients today
- There may be unintended consequences to ideal sepsis care – but some of these consequences are also due to less than ideal care
- There are more and more tools available to identify sepsis patients – but none is the standard



"I believe that this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the Moon and returning him safely to the Earth."

–President John F. Kennedy, 5/25/1961

“We choose to go to the moon in this decade and do the other things, *not because they are easy, but because they are hard*, because that goal will serve to organize and measure the best of our energies and skills, because the challenge is one we are willing to accept, one we are unwilling to postpone, and one which we intend to win.”

—*President John F. Kennedy,*
9/12/1962



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