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Necrotizing Soft Tissue Infections: Delays in Treatment

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PS321: Necrotizing Soft Tissue Infections: Time Matters
Wednesday October 7, 2015

60 yo female with DM and HTN

Presents to ED ~36 hours after repair of contaminated LE laceration

- 10/10 pain
- LE swelling, erythema, ecchymosis
- Vitals: temp 98, HR 110, BP 107/76

1 hour after presentation

- Labs: WBC 13.8, HCT 50, Na 131, CO2 18, Glucose 348, Creat 2.05
- Plain X-ray: gas in tissue
- Broad spectrum IV antibiotics given

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60 yo female with DM and HTN

3 hrs after presentation - admit to OBSERVATION

- **Admission diagnosis: CELLULITIS**
- **Bullous lesions documented**

7.5 hrs after presentation – transferred to higher level of care

9.5 hrs after presentation – AKA

Died after several weeks in the hospital

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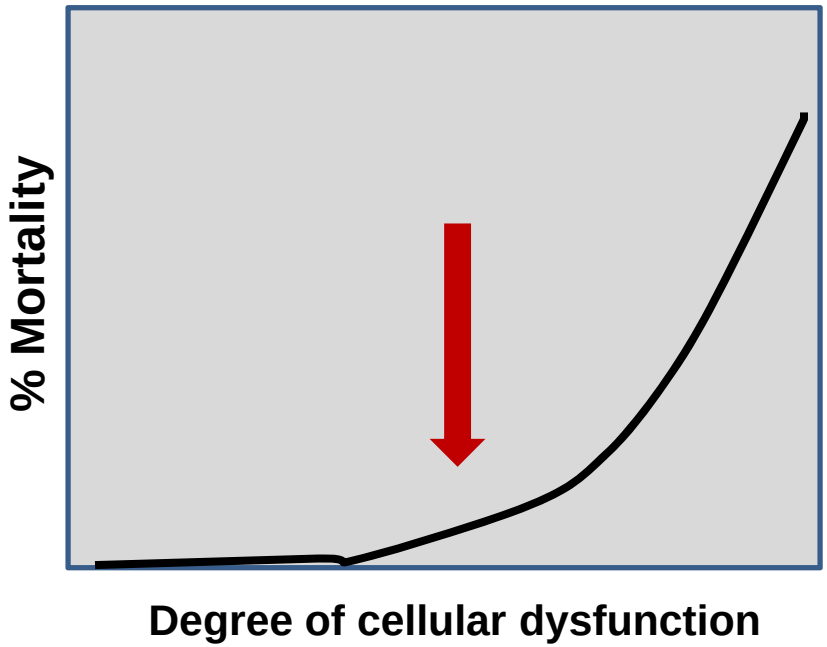
Disclosures:

- Receive research funding and consultant for AtoxBio
- Research funding from several pharmaceutical companies
- No significant conflicts to disclose for this presentation

Infectious and inflammatory stimuli develop in non-linear fashion

- The effects are not simply additive – geometric or exponential
- The greater the degree of cellular dysfunction, the more difficult to repair/correct injury
- Intervene before severe dysfunction develops



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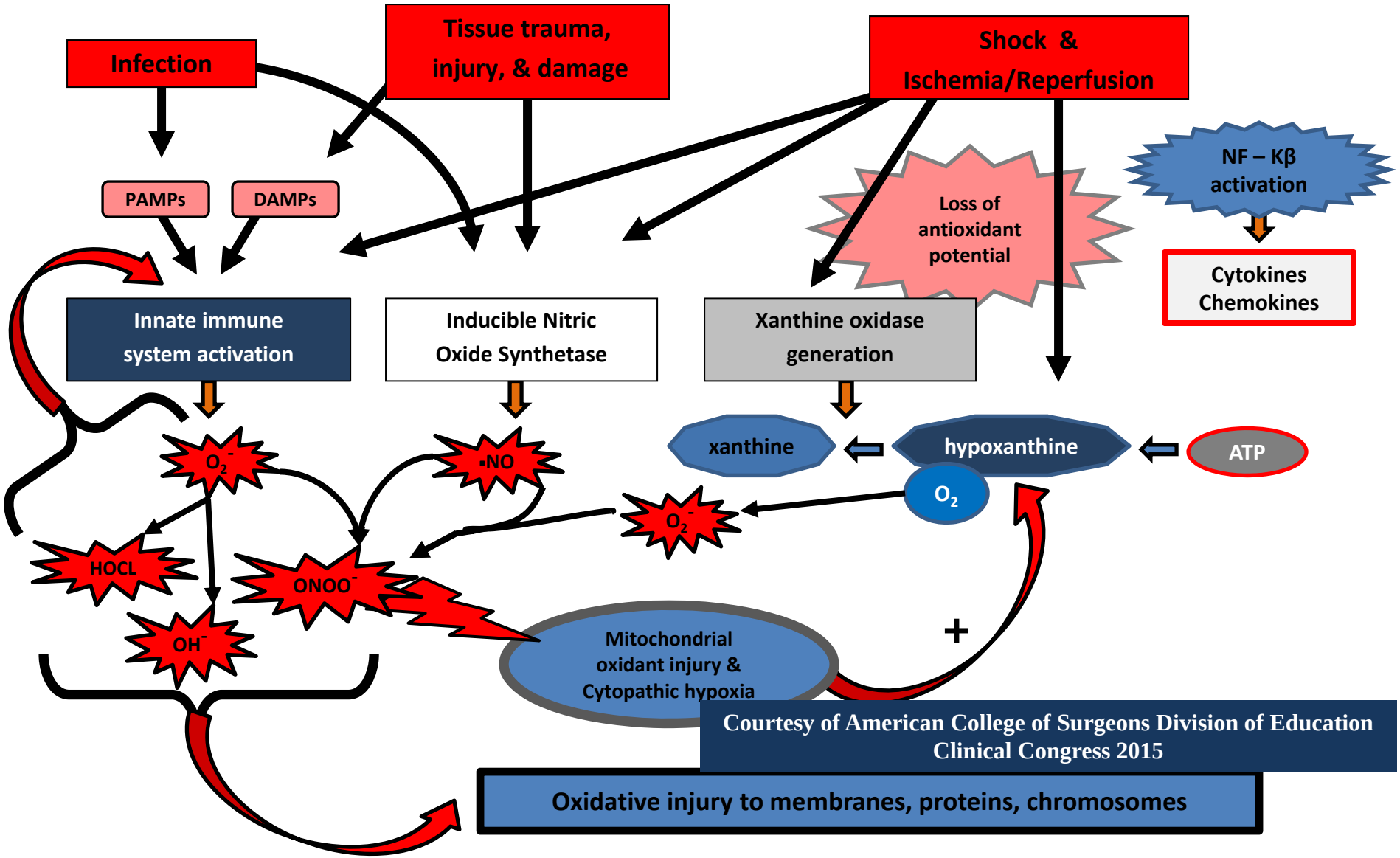
Simplified Model of Oxidant Stress in Sepsis , Shock, and Trauma



Mortality from NSTI is declining!

Mortality Tends in Published Series of Necrotizing Soft Tissue Infections				
Publication date:	Number of studies	Number of Cases	Number of deaths	Percent Mortality
1980 through 1990	17	375	119	31.7%
1991 through 2000	15	628	167	26.6%
2001 through 2010	37	2670	565	21.2%
2011 thought 2014	11	2508	394	15.7%
Total 1980 - 2014	**80**	**6181**	**1245**	**20.1%**

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Treatment of NSTI

1. **Resuscitation**
2. **Antibiotic therapy**
3. **Surgical debridement – source control**

Time to achieve each one matters!

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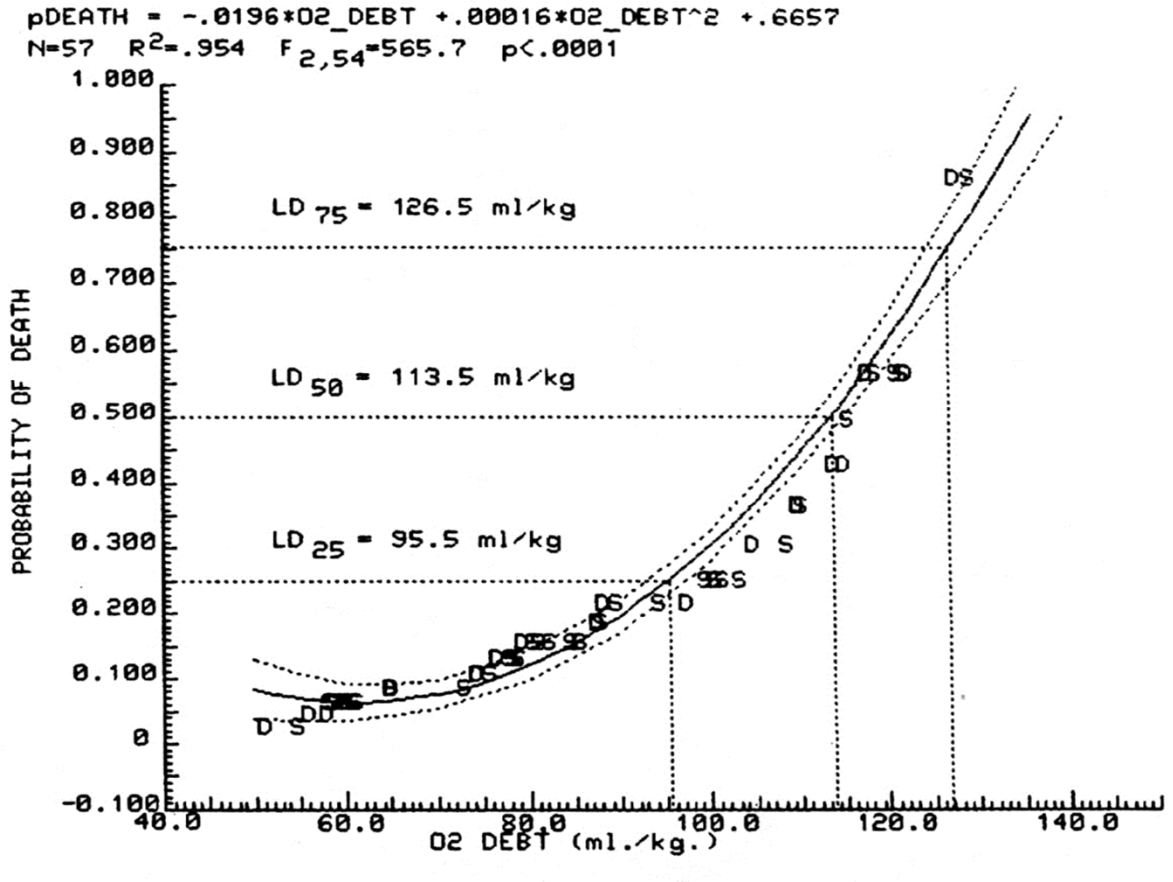
Time to Resuscitation Matters

- Goal of resuscitation is the restoration of tissue perfusion and elimination of cellular hypoxia



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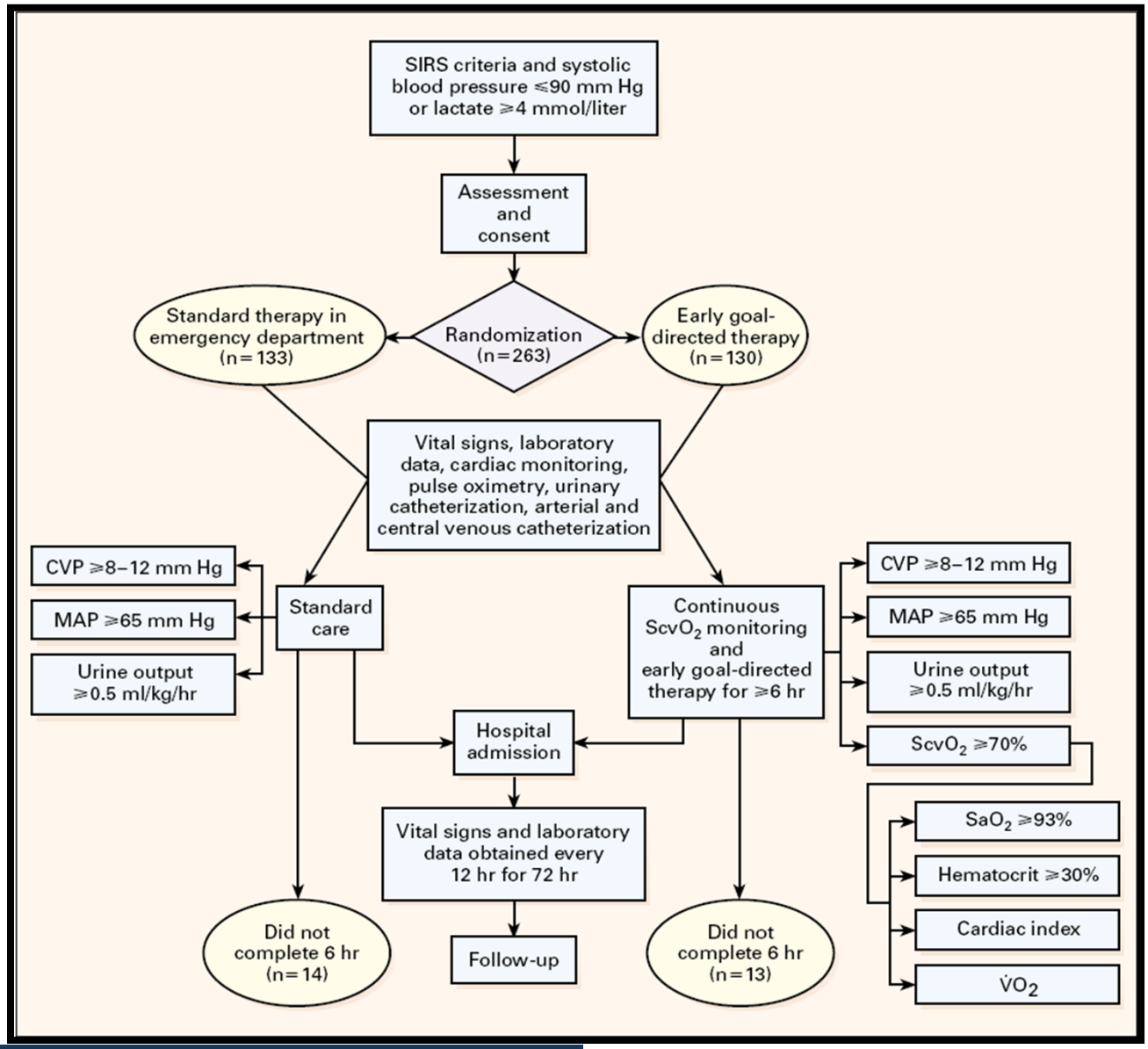
Use of Early Goal Targeted Resuscitation



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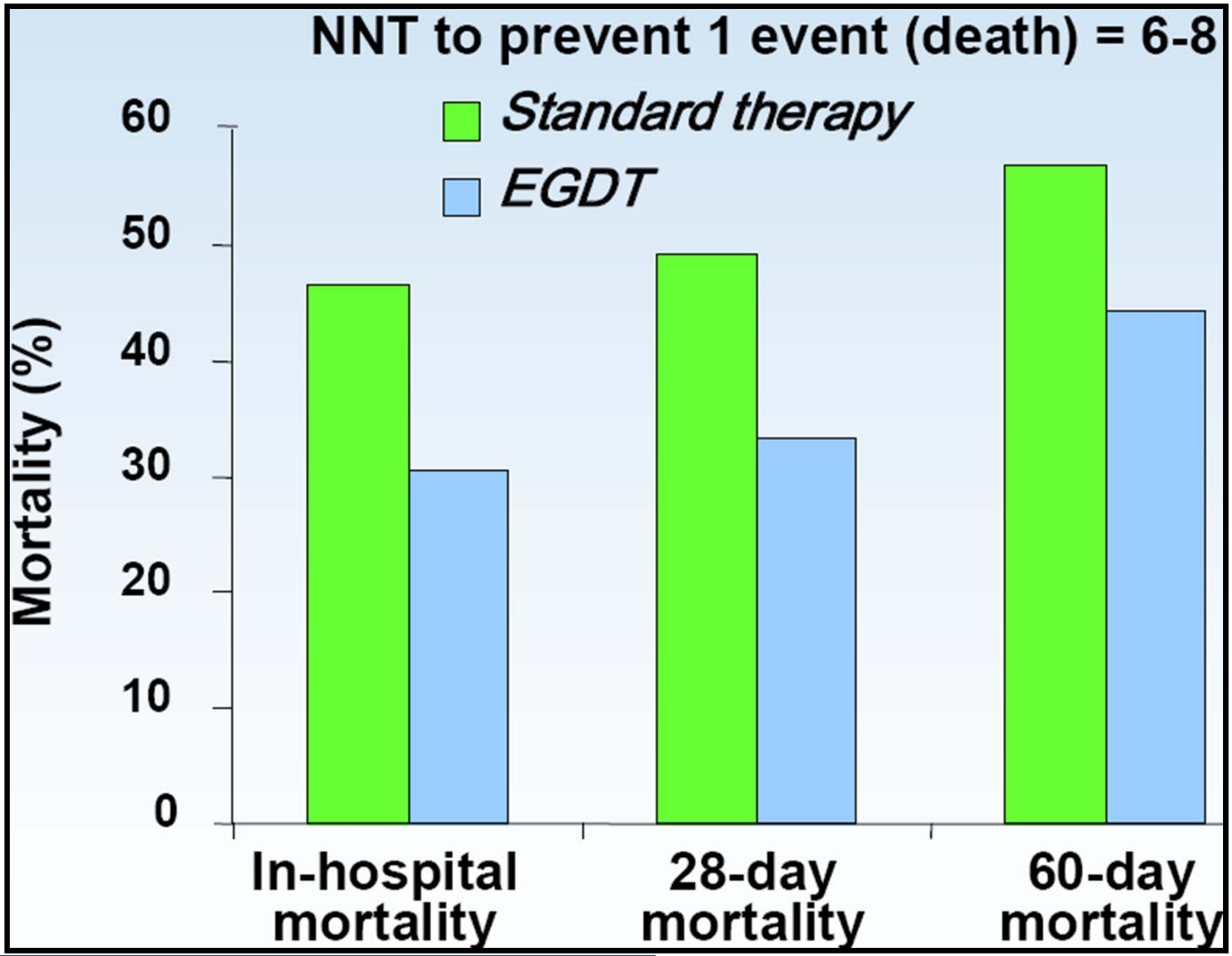
Rivers, E. *NEJM* 2001;345:1368-77

Use of Early Goal Targeted Resuscitation



Courtesy of American College of Surgeons Division of Education
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Rivers, E. *NEJM* 2001;345:1368-77

Time to Resuscitation Matters

Surviving Sepsis Campaign Resuscitation Bundle

Serum lactate measured.
Blood cultures obtained prior to antibiotic administration.
Broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions.
In the event of hypotension and/or lactate $\geq$4 mmol/L:
Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
Initiate vasopressor for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) $\geq$65 mmHg
Achieve central venous pressure (CVP) of $\geq$8 mmHg
Achieve central venous oxygen saturation $ScvO_2$ $\geq$70% or a mixed venous oxygen saturation (SvO2) $\geq$65%.

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Time to Resuscitation Matters

- Retrospective study before and after implementing SSC-RB

	Before	After
• Patients in septic shock:	96	384
• Mortality from sepsis:	57.3%	37.5%

- Regression model for risk of death: OR 0.5 (0.28-0.89)
- Compliance with six + components by 6 hrs: OR 0.3 (0.17-0.53)
- ScvO2 $\geq$70% by 6 hrs: OR 0.62 (0.38-0.99)

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Castellanos-Ortega, A. Crit Care Med 2010; 38:1036 –1043

Increased Fluid Administration in the First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality

A Retrospective Cohort Study

Sarah J. Lee, MD, MPH; Kannan Ramar, MBBS, MD; John G. Park, MD, FCCP; Ognjen Gajic, MD, FCCP; Guangxi Li, MD; and Rahul Kashyap, MBBS

- **Retrospective analysis – 594 pts with severe sepsis and septic shock**
- **Treatment directed by the SSC – RB**
- **Greater fluid administration in the 1st 3 hours in SURVIVORS**

	Survivors	Non-survivors	p value
1st 3 hrs:	2,085 ml	1,600 ml	0.007
2nd 3 hrs:	660 ml	800 ml	0.09

Multivariate analysis: age, weight, SOFA, APACHE III, total fluid in 6 hrs

- **higher fluid in 1st 3 hrs vs 2nd 3 hrs – OR 0.34 (0.15 – 0.75)**

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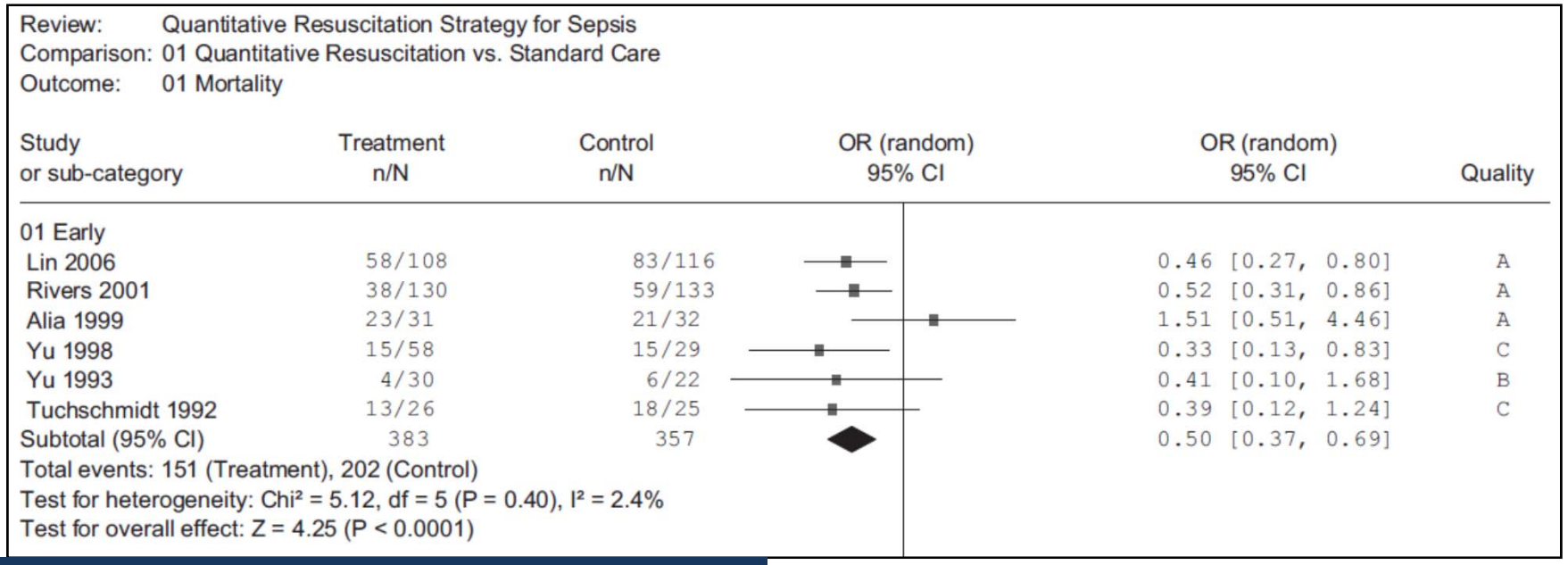
Lee SJ. *Chest*. 2014; 146:908-915

Metaanalysis of Quantitative Resuscitation in Sepsis

Study	Year	N[a]	Overall Mortality (%)	Mortality Timing	Study Location	Patient Selection	Concealment	Jadad Score	Intervention Timing	Quantitative Resuscitation Group End points[b]
Early										
Lin	2006	224	61	Hospital	ICU	A	A	2	Early	CVP, MAP, UO
Rivers	2001	263	37	Hospital	ED	A	A	4	Early	$ScvO_2$
Alia	1999	63	70	ICU	ICU	A	A	1	Early	DO_2I
Yu	1998	87	34	ICU	ICU	A	C	1	Early	DO_2
Yu	1993	52	19	30 day	ICU	A	B	1	Early	DO_2
Tuchschmidt	1992	51	61	14 day	ICU	A	C	2	Early	CI



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ones A.E. Crit Care Med 2008; 36: 2734–2739

Treatment of NSTI

1. Resuscitation

2. **Antibiotic therapy**

3. Surgical debridement – source control

Time to the RIGHT Antibiotic Matters

Influence of Inadequate Empiric Antibiotic Therapy

Author	Setting	Relative increase in mortality
Kollef	Mixed nosocomial ICU infections	133%
Luna	Ventilator associated pneumonia	139%
Alvarez-Lerma	Ventilator associated pneumonia	56%
Rello	Ventilator associated pneumonia	131%
Leibovici	Bloodstream infection	70%
Ibrahim	Bloodstream infection	121%
Mosdell	Intraabdominal infection	110%
Burke	Intraabdominal infection	192%
Montravers	Nosocomial intrabdominal infection	92%

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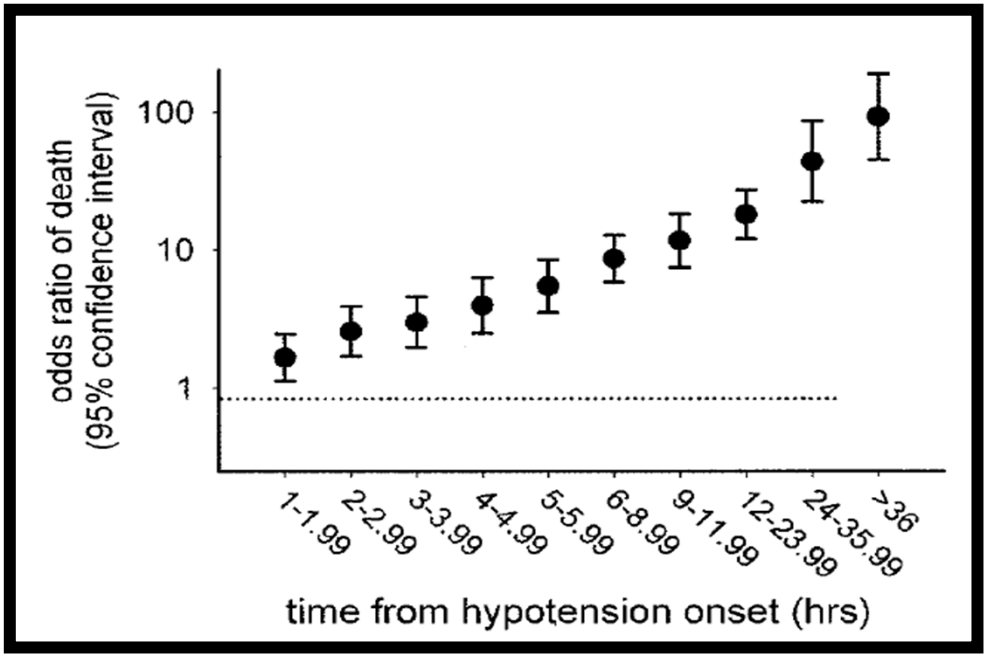
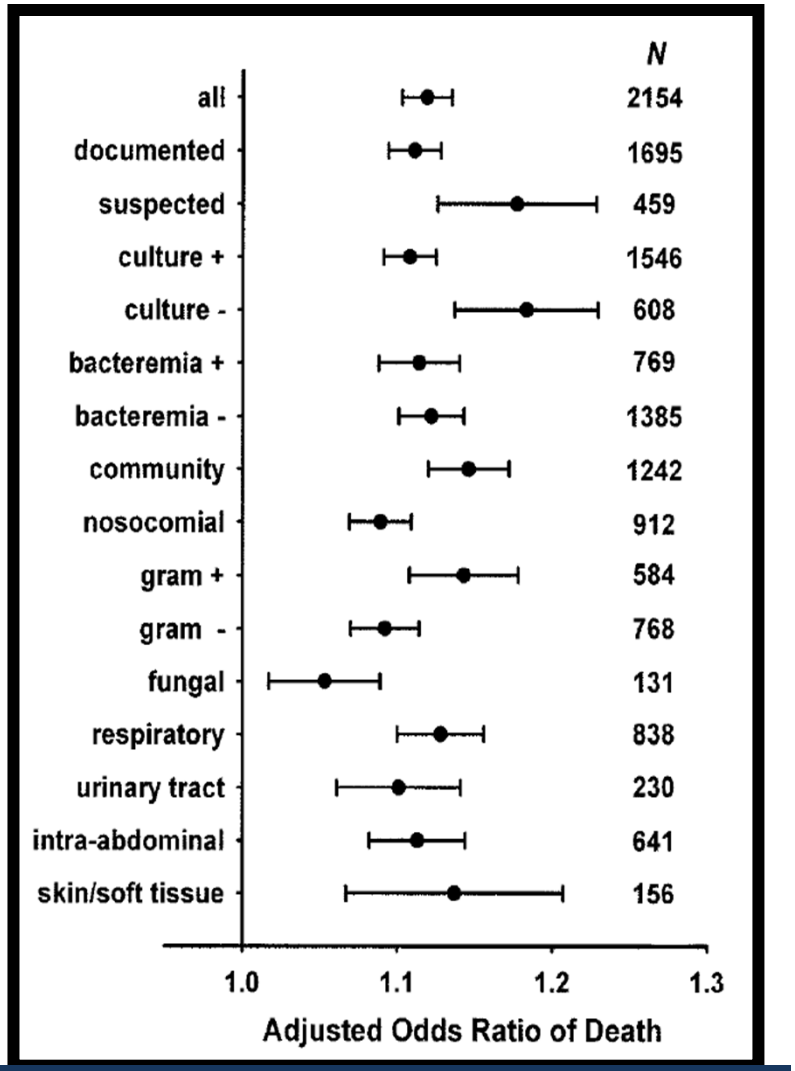
Time to Antibiotic Therapy Matters

- **2731 pts with septic shock (56% mortality)**
- **Time to AB Rx most strongly associated with outcome**
- **Each 1 hr delay → 12% increase in risk of death**

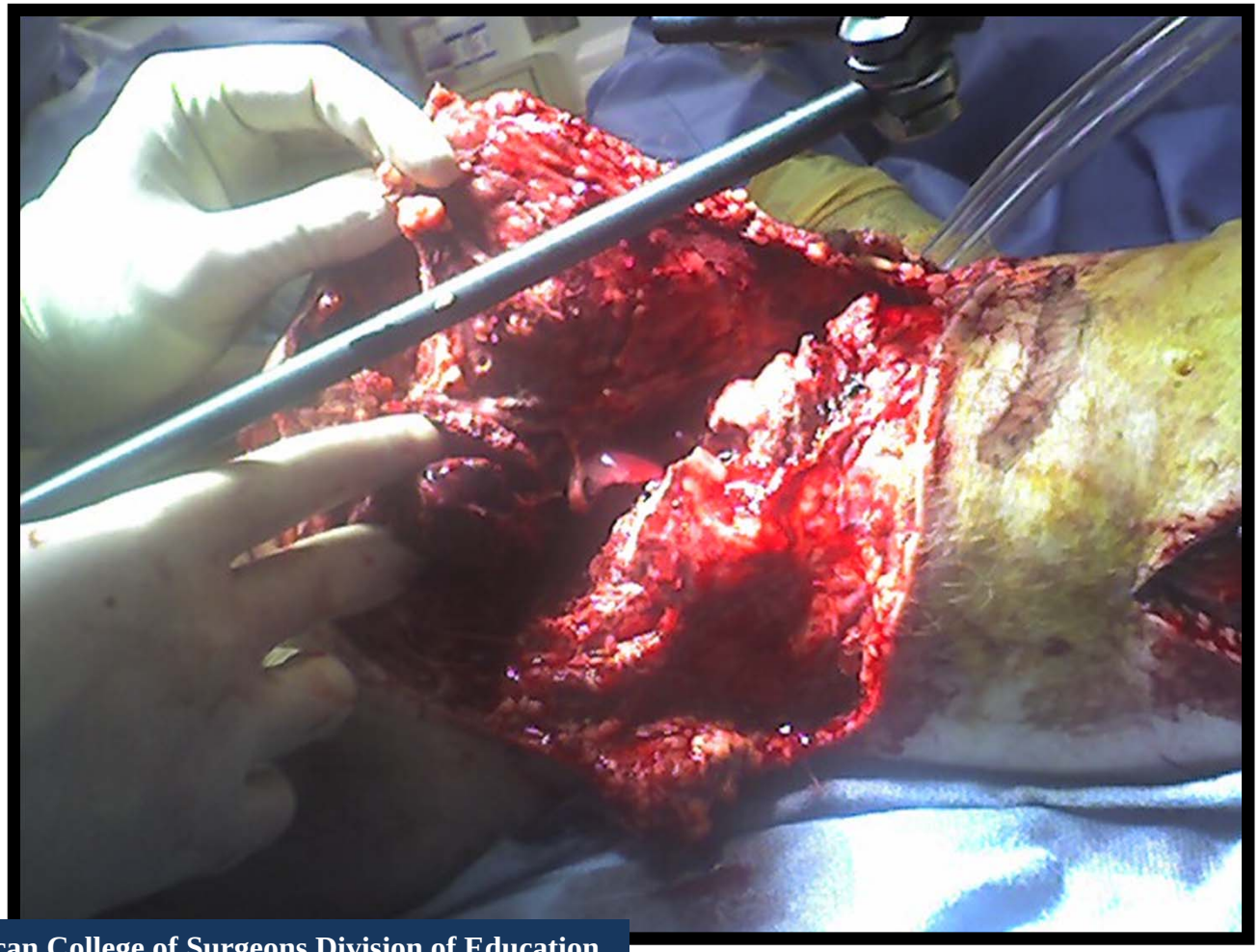




Kumar A. CCM. 2006; 34:1589-1595

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Resuscitation and Antibiotics Cannot Replace Surgical Source Control



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Time to surgical debridement matters!

Predictors of mortality by regression analysis in NSTI :

- **Time to first debridement**
- **Extent of tissue involvement**
- **# Failed organs on admission**
- **Inadequate first debridement**
- **Age > 60 years**
- **Bacteremia**
- **Elevated lactate**

McHenry CR. *Ann Surg.* 1995; 221:558-565
Bosshardt TL. *Arch Surg*. 1996;131:846-52
Elliott DC. *Ann Surg*. 1996; 224:672-83
Bilton BD. *Am Surg.* 1998; 64:397-400
Childers BJ. *Am Surg.* 2002; 68:109-116
Wong CH. *J Bone Joint Surg.* 2003; 85A:1454-1460

Time from admission to OR matters:

- Time from admission to OR independently associated with mortality

Author	Year	Finding:
– Lille	1996	> 24 hrs increased mortality
– Elliott	1996	OR 1.27 - days admit to debridement
– Wong	2003	RR 9.4 - > 24 hrs
– Liu	2005	> 24 hrs increased mortality
– Golper	2007	OR 5.32 - > 24 hrs
		OR 2.18 - < 12 hrs vs > 24 hrs (p=0.07)

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Does time always matter?

- Studies where time from admission to OR is <u>not associated</u> with mortality
  - Anaya 2005
  - Hsiao 2008
  - Gunter 2008

NSTIs: a heterogenous group of infections!

Type 1: polymicrobial

- typically arise from a chronic, indolent source
- spread along fascial planes
- most common ~ 50-75% of NSTIs

Type 2: monomicrobial virulent Gm +, aerobic cocci

- Streptococcus species
- CA-MRSA
- pathophysiology related to toxin production

Type 3: monomicrobial virulent Gm + or Gm – bacilli

- Clostridia species
- Bacillus species
- Vibrio species
- Aeromonas species
- Eikenella species
- pathophysiology related to toxin production and growth rate of pathogens

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Highly virulent pathogens associated with increased mortality:

- **Group A strep** ***(Childers-2002, Golper 2007)***
  - **Gram positive antiribosomal agent - Clindamycin**
- **Clostridia** ***(Anaya-2005)***
  - **Gram positive antiribosomal agent - Clindamycin**
- **Aeromonas and Vibrio** ***(Hsiao-2008)***
  - **Gram negative antiribosomal agent – tetracycline class**

Time to OR decreasing over time

Author	Year	# Cases	Mortality	Hours from admission to OR
McHenry	1995	65	29%	40 hours
Elliott	1996	198	25%	41 hours
Anaya	2005	166	17%	23 hours
Hsiao	2008	128	19%	60 hours
Gunter	2008	52	10%	9 hours

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Does time to re-debridement matter?

- 64 patients with NSTI at USC-LAC over 6 years
- Practice algorithms by 2 different services
  - Short duration (24-48 hrs) vs Extended duration (> 48 hrs) until second debridement
- Short duration associated with lower AKI and mortality

TABLE 4. *Comparison of Outcomes in Patients with Necrotizing Soft Tissue Infection Subjected to SIRD* vs *EIRD**

	All Patients (n = 64)	SIRD (n = 46)	EIRD (n = 18)	*P* Value	AOR (95% CI)	*P* Value
ICU admission	50/64 (78.1%)	38/46 (82.6%)	12/18 (66.7%)	0.190	0.6 (0.2–2.3)	0.433
Operative débridements; mean ± SEM	4.2 ± 2.8	4.5 ± 2.7	3.4 ± 3.1	0.197	–0.8 (–2.4 to 0.9)	0.356
ICU LOS (days); mean ± SEM	10.3 + 1.2	10.0 + 1.1	10.9 + 3.2	0.842	2.6 (–2.8 to 8.0)	0.344
HLOS (days); mean ± SEM	34.0 ± 3.7	36.5 ± 4.7	26.2 ± 5.2	0.237	–4.5 (–21.6 to 12.6)	0.601
Complications						
Septic shock	14/64 (22.2%)	8/45 (17.4%)	6/18 (33.3%)	0.197	3.1 (0.8–11.7)	0.093
Acute kidney injury	10/64 (15.9%)	4/46 (8.7%)	6/18 (33.3%)	0.026	4.7 (1.0–21.6)	0.046
Other†	7/64 (11.1%)	5/46 (10.9%)	2/18 (11.1%)	0.998	1.0 (0.1–6.2)	0.973
Mortality	9/64 (14.1%)	3/46 (6.5%)	6/18 (33.3%)	0.012	14.9 (2.4–94.1)	0.004

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Okoye O. *Amer Surg.* 2013; 79:1081-1085

Treatment of NSTI: TIME MATTERS

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Thank you for your attention

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