Diabetes Mellitus Significantly Increases Trauma Associated Complications and Utilization of Resources

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M·TQIP

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Disclosures

- No Conflicts of Interest
- No Financial Disclosures

“To give anything less than your best is to sacrifice the gift.”

-Steve Prefontaine

Trauma Health Care Burden

Trauma accounts for 41 million ED visits and 2.3 million hospitalizations yearly

Life Years Lost[1] (2010, most recent available)

- Trauma injury accounts for 30% of all life years lost in the U.S.
- Cancer accounts for 16%
- Heart disease accounts for 12%

Economic Burden[2]

- $585 billion a year, including both health care costs and lost productivity

Deaths due to injury[3] (2010, most recent available) - 192,000

Ranking as cause of death[3]

- #1 for age group 1-46, or 47% of all deaths in this age range
- #3 as leading cause of death overall, across all age groups

Falls[4] (2009, most recent available)

- 8 million people were treated in the ED for nonfatal injuries related to falls
- 2.2 million were people aged over 65 years with substantial comorbidities
- In 2008 over 19,700 people died of fall-related injuries; over 17,700 > 65 years old

1 Life Years Lost: A measure to account for the age at which deaths occur, giving greater weight to deaths occurring at younger ages and lower weight to deaths occurring at older ages. The LYL (percentage of total) indicator measures the LYL due to a particular cause of death as a proportion of the total LYL lost due to premature mortality in the population. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web–based Injury Statistics Query and Reporting System (WISQARS) [online]. Accessed February 17, 2014.
2 Finkelstein, E.A., Corso, P.S., & Miller, T.R. The Incidence and Economic Burden of Injuries in the United States. USA: Oxford University Press. 2006
3 Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web–based Injury Statistics Query and Reporting System (WISQARS) [online]. Accessed February 17, 2014.
4 http://www.cdc.gov/HomeandRecreationalSafety/Falls/adultfalls.html

Obesity and Severe Injury

- Increased body weight and the risk for human disease is a major health concern
- The National Institutes of Health has classified individuals according to body mass index (BMI) to assess population-wide risks for comorbid diseases

NIH/WHO Body Mass Index Classifications

Class	Body Mass Index (kilogram/meter^2)
Underweight	<18.5
Normal Weight	18.5–24.9
Overweight	25–29.9
Obese	30–39.9
Morbidly Obese	≥ 40

Winfield, R., Delano, MJ., et. al. Crit Care Med. 2010 January ; 38(1): 51–58

Obesity and Severe Injury

- **Outcome differences between obese and nonobese patients following severe injury**

	Normal Weight (n = 173)	Overweight (n = 152)	Obese (n = 101)	Morbid (n = 29)	*p*
Any nosocomial infection	41.0	48.0	42.6	62.1	.150
Pneumonia	26.6	28.1	26.7	31.0	.958
Bloodstream infection	8.1	15.0	19.8	13.8	.043
Urinary tract infection	17.9	12.4	14.9	34.5	.028
Catheter-related bloodstream infection	2.9	3.9	5.0	10.3	.301
Ventilator-associated pneumonia	25.9	23.7	25.7	20.7	.915

Nosocomial Infections (%)

	Normal Weight (n = 173)	Overweight (n = 152)	Obese (n = 101)	Morbid (n = 29)	*p*
Any noninfectious complication	36.4	38.8	46.5	58.6	.078
Acute respiratory distress syndrome	20.2	21.1	27.7	41.4	.053
Cardiac arrest	2.3	2.6	2.0	17.2	<.001
Myocardial infarction	0.0	1.3	1.0	3.4	.253
Cerebral infarction	2.9	2.0	3.0	0.0	.765
Deep vein thrombosis	5.2	5.9	6.9	6.9	.941
Pulmonary embolism	2.3	3.9	3.0	3.4	.868
Rhabdomyolysis	1.2	5.2	4.0	10.3	.053
Acute renal failure	1.2	0.0	2.0	10.3	<.001
Multiple organ failure	43.9	46.7	58.4	72.4	.008

Noninfectious Complications (%)

Winfield, R., Delano, MJ., et. al. Crit Care Med. 2010 January ; 38(1): 51–58

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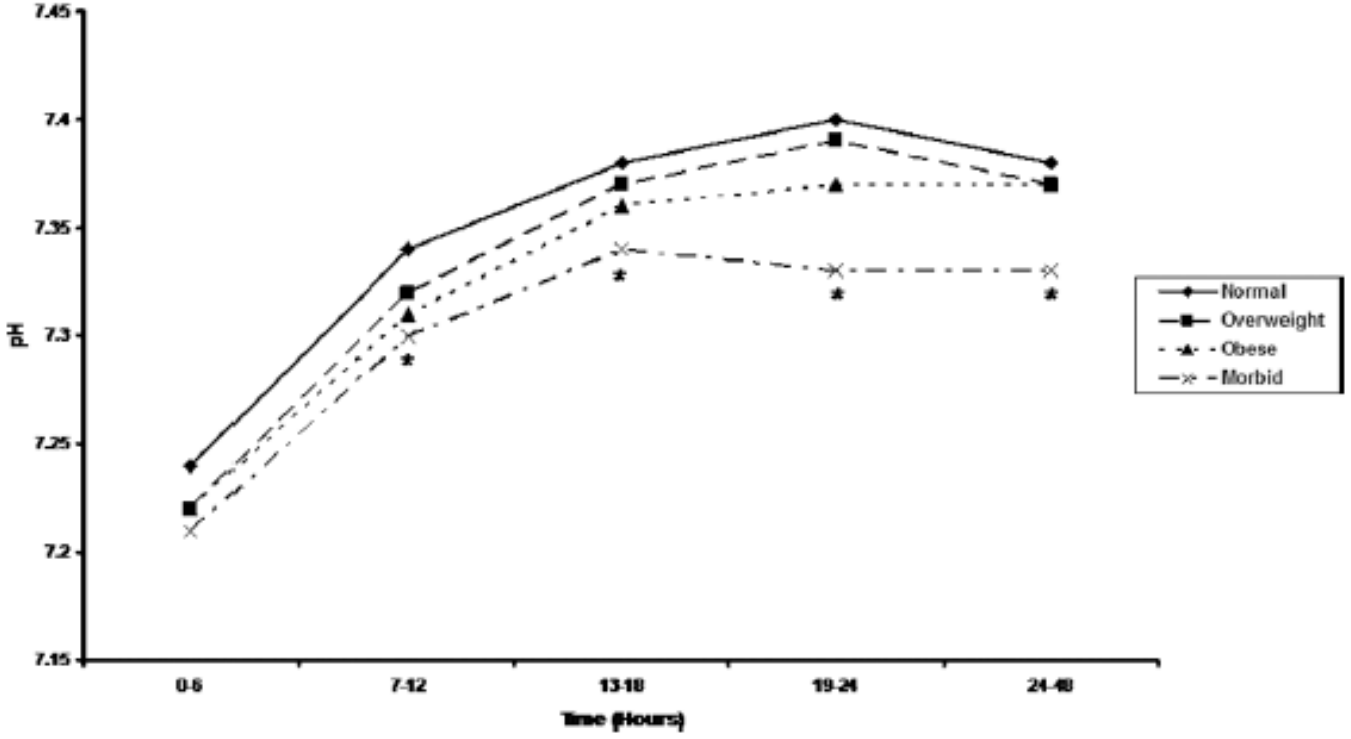
Obesity and Severe Injury

- **Study Conclusions:**
  - Complications increase with increasing BMI
  - Independent associations exist between BMI and morbidity
  - BMI-related increases in MOF including longer intensive care unit stays, greater number of ventilator days, cardiac arrests, and episodes of acute renal failure

Winfield, R., Delano, MJ., et. al. Crit Care Med. 2010 January ; 38(1): 51–58

Obesity and Severe Injury

- **What is/are the underlying mechanism(s) responsible for obesity related elevations in MOF and complicated outcomes?**



Winfield, R., Delano, MJ., et. al. Crit Care Med. 2010 January ; 38(1): 51–58

Obesity and Severe Injury

- Obese patients received greater resuscitation volumes per actual body mass, however this difference abated when volumes were adjusted for lean and ideal body mass

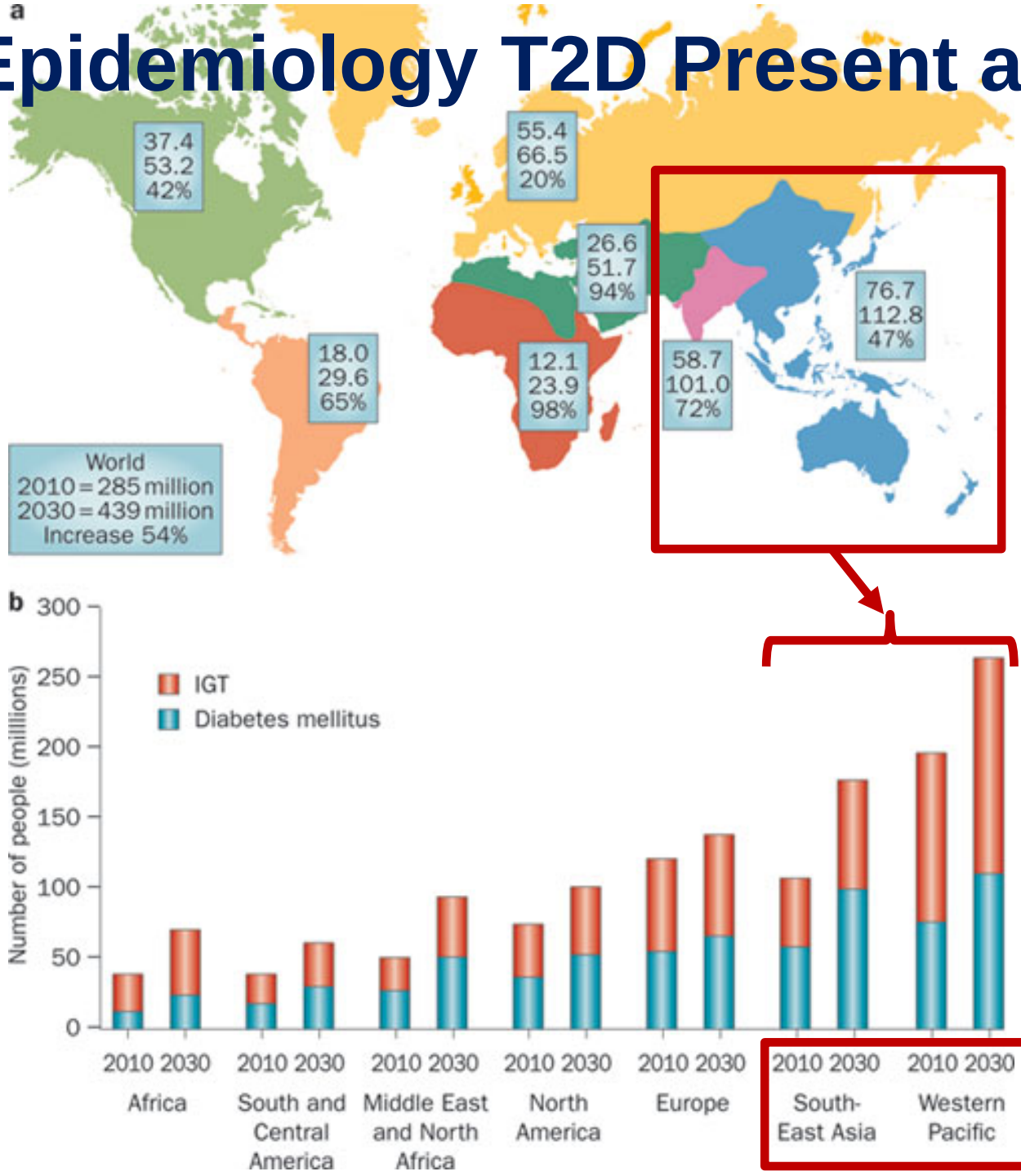
- **Study Conclusions Obese Patients:**
  - Morbidly obese patients show prolonged metabolic acidosis in severe blunt trauma
  - The prolonged metabolic acidosis is attributed to suboptimal resuscitation endpoints combined with underlying metabolic abnormalities

Type 2 Diabetes (T2D)

- 29 million people in the USA have diabetes of all types
- T2D comprises well over 90% of the total diabetic population (over **27 million now in the USA**)
- Over **50 million Indians** have T2D now (over 79 million by year 2030)
- **With increases in the prevalence of advanced age, obesity, poor diet, and inactivity the incidence of T2D is expected to rise dramatically**

Chen, L. *et al.* (2011) *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2011.183.
Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. *AMJ* 2014, 7, 1, 45-48.

Epidemiology T2D Present and Future



Chen, L. *et al.* (2011) *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2011.183

T2D and Trauma

- Hyperglycemia is associated with complications and worsened outcome among trauma victims
- Rapid expansion of the elderly and obese populations has increased the prevalence of T2D in trauma patients
- **<u>Hypothesis:</u> The presence of T2D is associated with poor outcomes among trauma patients**

Kao, LS, Todd, R, Moore, FA, The impact of diabetes on outcome in traumatically injured patients: an analysis of the National Trauma Data BankThe American Journal of Surgery 192 (2006) 710–714

McGwin G Jr, MacLennan PA, Fife JB, et al. Preexisting conditions and mortality in older trauma patients. J Trauma 2004;56:1291– 6.

Laird AM, Miller PR, Kilgo PD, et al. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma 2004;56:1058–62.

Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 2003;55:33– 8.

Bochicchio GV, Sung J, Joshi M, et al. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005;58:921– 4.

Materials & Methods

- Michigan Trauma Quality Collaborative data analyzed from 2012-2014 (~ 35,000 patients).
- Patients with no signs-of-life, Injury Severity Score < 5, age < 18 years, and hospitalization < 1 day were excluded.
- Multivariable logistic or linear regression was used to compare patients with and without T2D.
- Variables utilized in risk-adjustment include demographics, physiology, comorbidities, and injury scoring.
- Results were confirmed using propensity score matching.

Patient Characteristics

Table 1.

	No Diabetes (n=30,473)	Diabetes (n=4,238)	p-value	
Age	51.4 + 22.8	68.6 + 15.5	<0.001	
Male	64.7%	55.9%	<0.001	
ISS	12.8 + 8.7	12.1 + 7.3	<0.001	
Race (Non-White)	26.2%	17.2%	<0.001	
Congestive Heart Failure	2.3%	8.4%	<0.001	♦
PVD	0.3%	1.3%	<0.001	
Hypertension	28.6%	73.5%	<0.001	♦
Dialysis	0.5%	3.3%	<0.001	♦
Cirrhosis	0.5%	1.2%	<0.001	
Metastasis	0.3%	0.5%	0.0111	
Active chemotherapy	0.2%	0.4%	0.0024	
Acquired coagulopathy	6.9%	18.9%	<0.001	♦
Obesity	10.2%	23.8%	<0.001	♦
Ascites	0.1%	0.3%	0.0005	
Drug use	10.6%	4.1%	<0.001	
Smoker	27.1%	14.8%	<0.001	
Psych	10.0%	9.9%	0.8673	
Anticoagulated	8.7%	23.1%	<0.001	♦
Blunt Mechanism	90.7%	98.0%	<0.001	
Transfer	19.7%	21.0%	0.041	

Selected Outcomes Analyzed

Table 2.

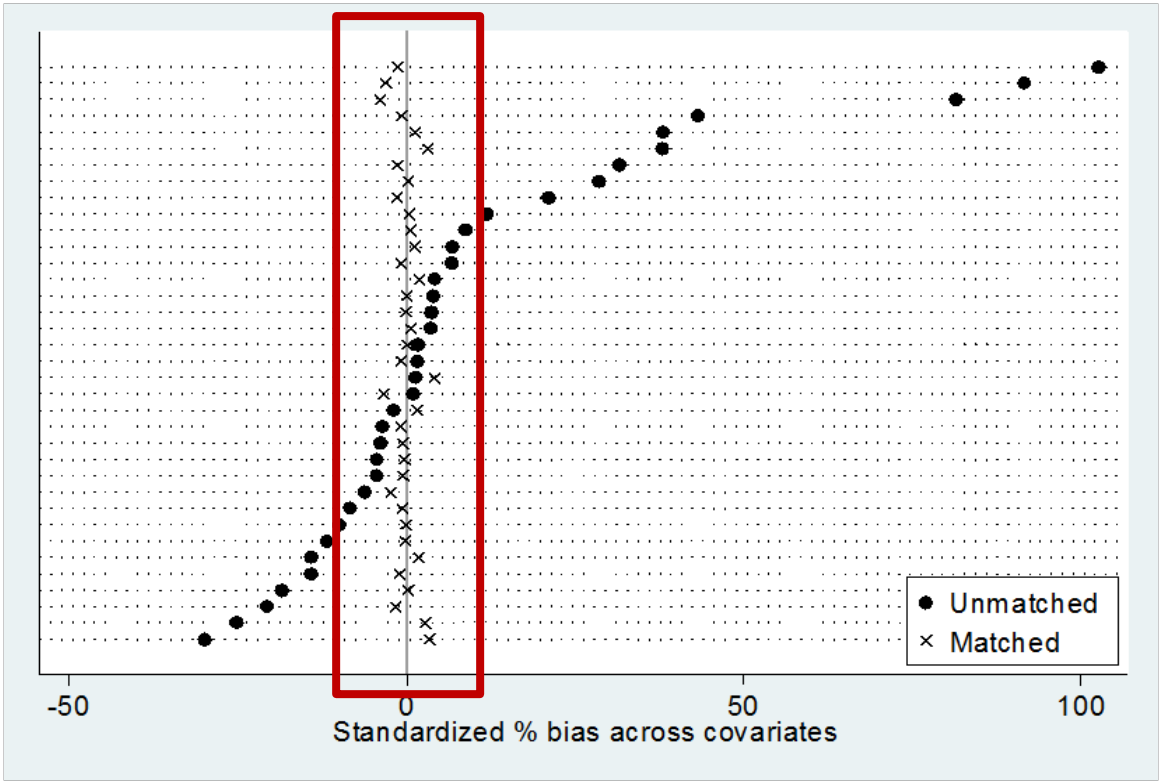
Complications:

Infection	Incisional SSI Organ Space SSI UTI Pneumonia C. Diff Systemic sepsis
Cardiac	Cardiac arrest requiring CPR MI
Renal	Acute renal failure
Venous Throm.	PE DVT - LE DVT - UE
Other	Wound Disruption Abdominal fascia left open ARDS Unplanned intubation Stroke/CVA Abdominal compartment syndrome Extremity compartment syndrome Decubitus ulcer Enterocutaneous fistula

Propensity Score Matching

Matching Variables

Age
Age²
Sex
ISS
ISS²
GCSM (categories)
Pulse (categories)
BP (categories)
Race
Mechanism of injury (Blunt)
Transfer
Congestive Heart Failure
PVD
Hypertension
Dialysis
Cirrhosis
Metastasis
Active chemotherapy
Acquired coagulopathy
Obesity
Ascites
Drug use
Smoker
Psych
Anticoagulated



Sample	Ps R2	LR chi2	p>chi2	MeanBias	MedBias	B	R	%Var
Unmatched	0.186	4795.03	0.000	19.5	9.9	125.4*	0.49*	100
Matched	0.002	21.51	0.973	1.2	1.1	10.1	1.10	40

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T2D Negatively Impacts Trauma Outcomes

- Univariate comparison of patients with and without T2D.

Table 3.

	No Diabetes (n=40,801)	Diabetes (n=5,598)	p-value
Complications (Any)	**7.4%**	9.5%	**<0.001**
Infection	**4.9%**	6.3%	**<0.001**
Cardiac	**1.0%**	1.7%	**<0.001**
Acute Renal Failure	**0.4%**	**0.6%**	0.008
VTE	**1.2%**	**1.1%**	0.849

T2D Negatively Impacts Trauma Outcomes

- Logistic regression analysis used to compare patients with and without T2D.

Table 4. **Logistic regression:**

	OR for Diabetes	[95% CI for OR]
Complications (Any)	1.26	[1.13, 1.41]
Complications (Severe)	1.29	[1.15, 1.44]
Infection	1.29	[1.13, 1.48]
SSI	0.89	[0.51, 1.57]
UTI	1.35	[1.10, 1.66]
Cdiff	0.83	[0.51, 1.35]
Systemic sepsis	1.54	[1.07, 2.23]
Pneumonia	1.33	[1.11, 1.59]
Cardiac	1.39	[1.08, 1.8]
Acute Renal Failure	1.3	[0.87, 1.96]
VTE	0.97	[0.73, 1.30]

T2D Associated With Increased Hospital and ICU Days

- Multivariable regression results

Table 4.

	No Diabetes	Diabetes	p-value
Vent Days	6.75	**8.02**	0.002
ICU Days	5.45	**6.40**	<0.001
Length of Stay	5.69	**6.35**	<0.001

T2D and Poor Outcome Not Associated with Advanced Age

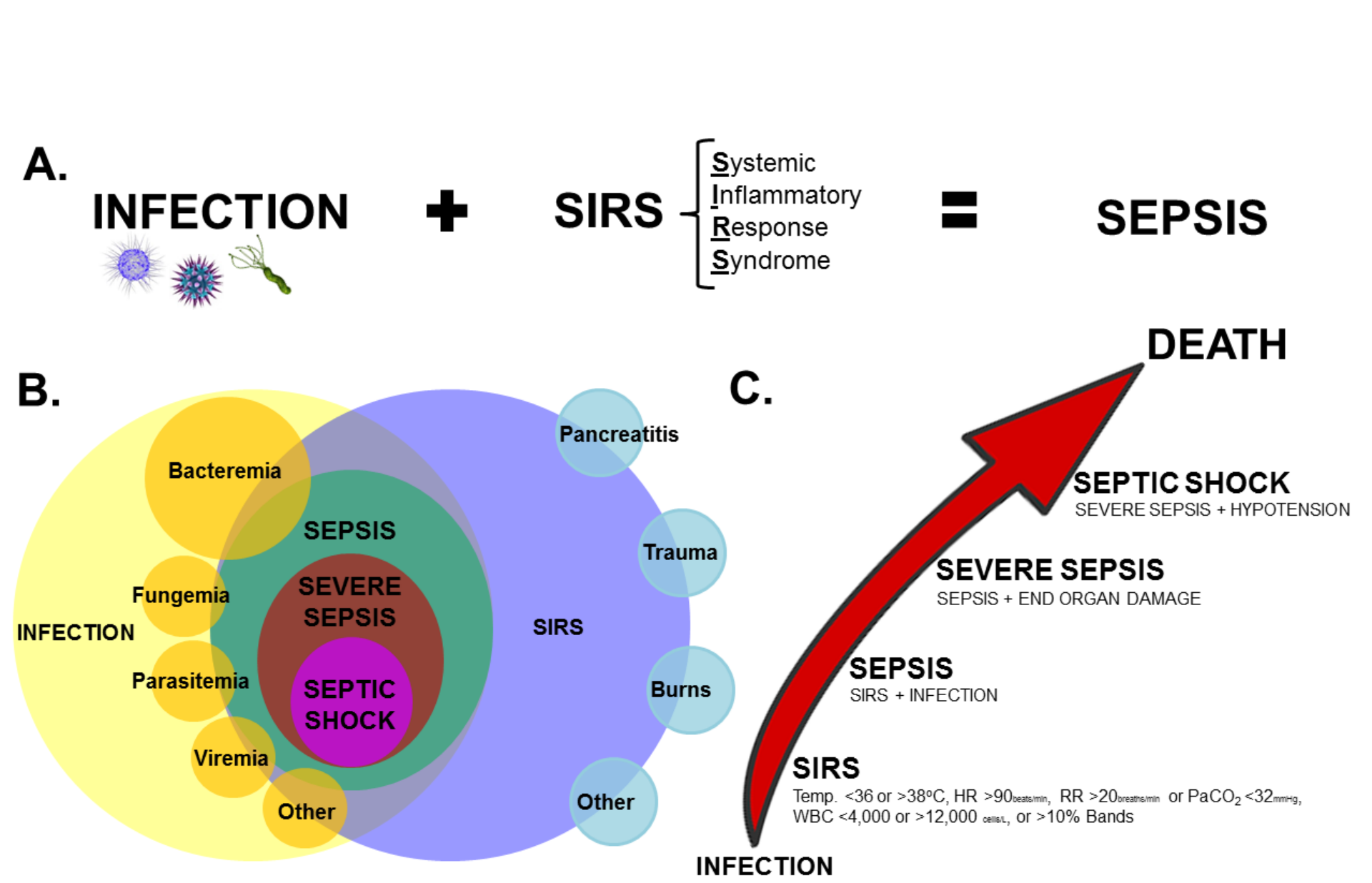
- Logistic regression results - Age >= 65

	OR for Diabetes	[95% CI LB for OR]	[95% CI UB for OR]	p-value
Complications (Any)	1.21	1.04	1.41	0.015
Complications (Severe)	1.18	1	1.4	0.057
Mortality	1	0.8	1.24	0.986
Infection	1.25	1.04	1.5	0.018
SSI	1.73	0.63	4.76	0.291
UTI	1.17	0.89	1.53	0.264
Cdiff	1.07	0.56	2.06	0.835
Systemic sepsis	1.85	1.08	3.17	0.025
Pneumonia	1.27	0.99	1.63	0.061
Cardiac	1.13	0.8	1.58	0.488
Acute Renal Failure	1.65	0.91	2.96	0.096
VTE	0.8	0.52	1.22	0.293

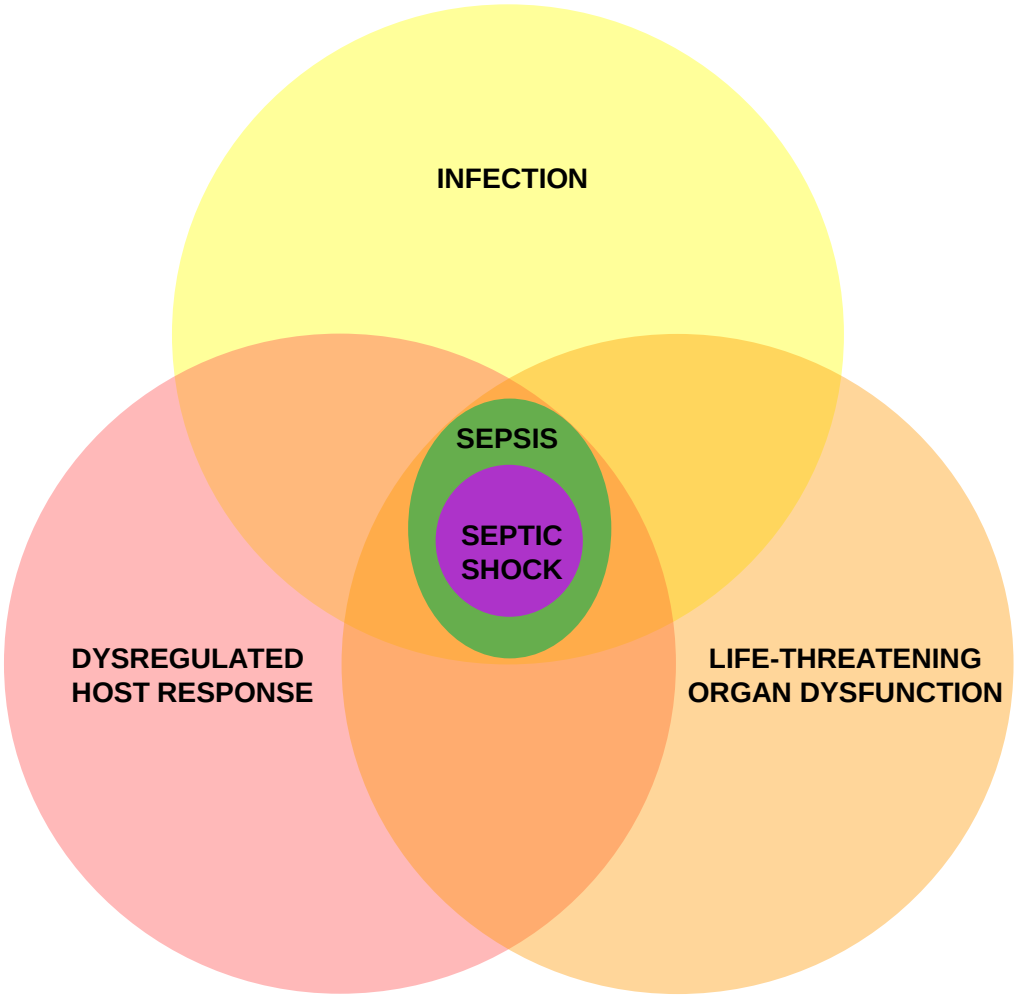
Sepsis:
A Significant HealthCare Challenge

- **Major cause of morbidity and mortality worldwide.**
  - Leading cause of death in non-coronary ICUs
  - 11th leading cause of death overall USA
- **More than 1 million cases annually in the USA.**
- **More than 500 patients die daily from sever sepsis in the USA.**
- **Number of cases of severe sepsis or septic shock among all ICU admissions increased every year**

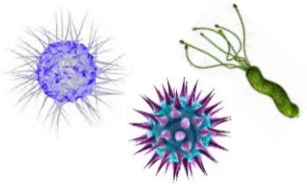
Sands, K.E. *et al. JAMA.* 1997 Jul 16;278(3):234-40.
Miniño AM. et al. Natl Vital Stat Rep. 2011 Dec 7;59(10):1-126
Iwashyna, T.J., Angus, D.C. *JAMA.* 2014;311(13):1295-1297.



Delano, MJ. Ward, PA., *Immunological Reviews* 2106



Delano, MJ. Ward, PA., *Immunological Reviews* 2106



INFECTION

Positive Blood Cultures
Urinary Tract Infection
Pneumonia, Etc…

+

Change in

Sepsis – Related
Organ
Failure
Assessment

≥ 2

Respiration
- ↓ PaO_2/FiO_2 Ratio

Coagulation
- ↓ Platelets

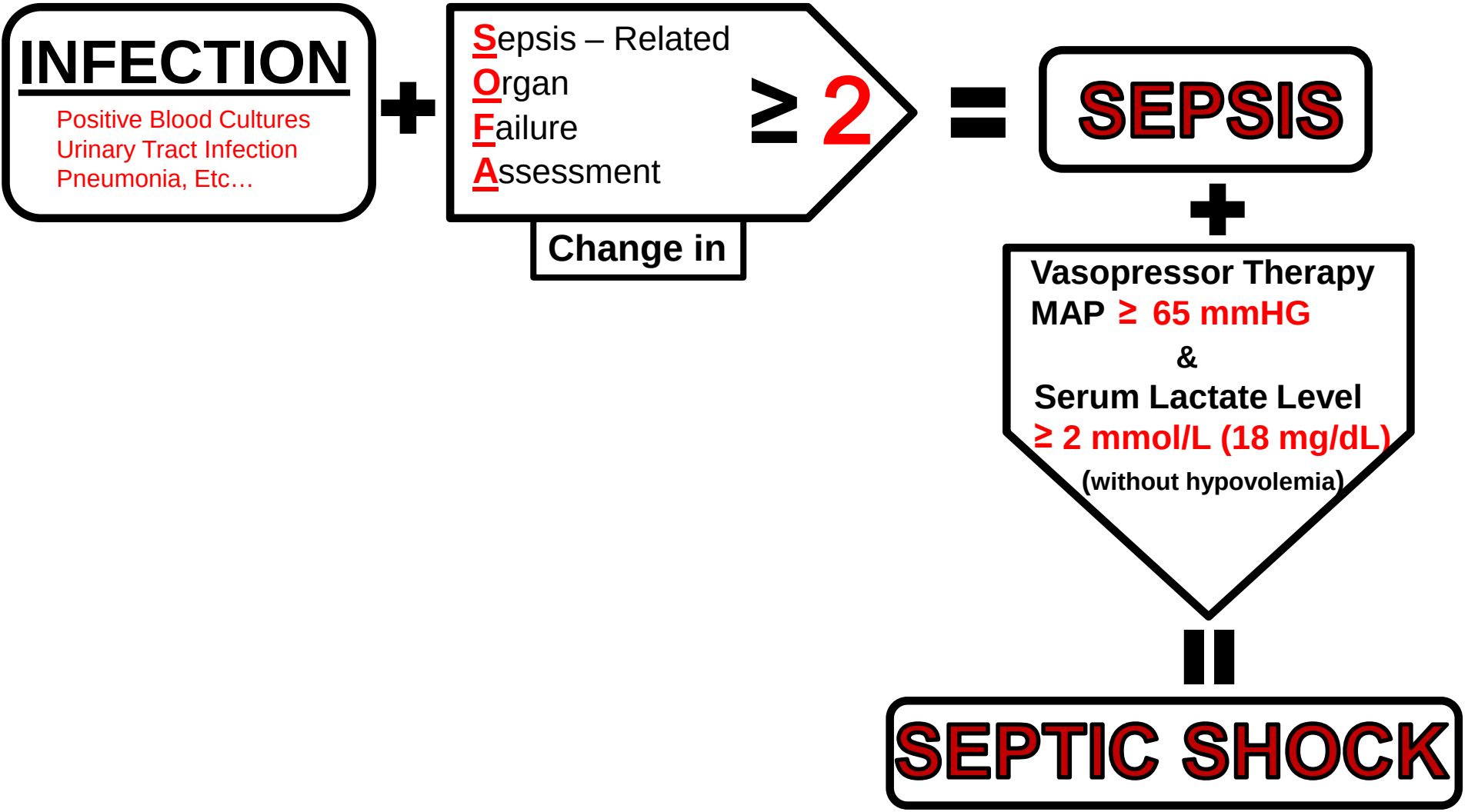
Central Nervous System
- ↓ Glasgow Coma Scale Score

Liver
- ↑ Bilirubin

Renal
- ↑ Creatinine
- ↓ Urine Output

Cardiovascular
- Hypotension or Vasopressors

Delano, MJ. Ward, PA., *Immunological Reviews* 2106



Delano, MJ. Ward, PA., *Immunological Reviews* 2106

Delayed Mortality in Severe Sepsis *circa* 2015

Early Recognition, Protocol Bundling, Benchmarking Outcomes, Goal Directed Therapy and Improved Education have just delayed severe sepsis mortality!!

	ProMISe	ProCESS	ARISE
Outcomes - all groups			
28 day mortality	24.5	--	14.8 - 15.9%
60 day mortality		18.2 - 21%	--
90 day mortality	**29.5%**	**30.8 - 33.7%**	**18.6 - 18.8%**
1 year mortality		~40%	--

The ProCESS/ARISE/ProMISe Methodology Writing Committee., *Intensive Care Med*. 2013 October; 39(10).

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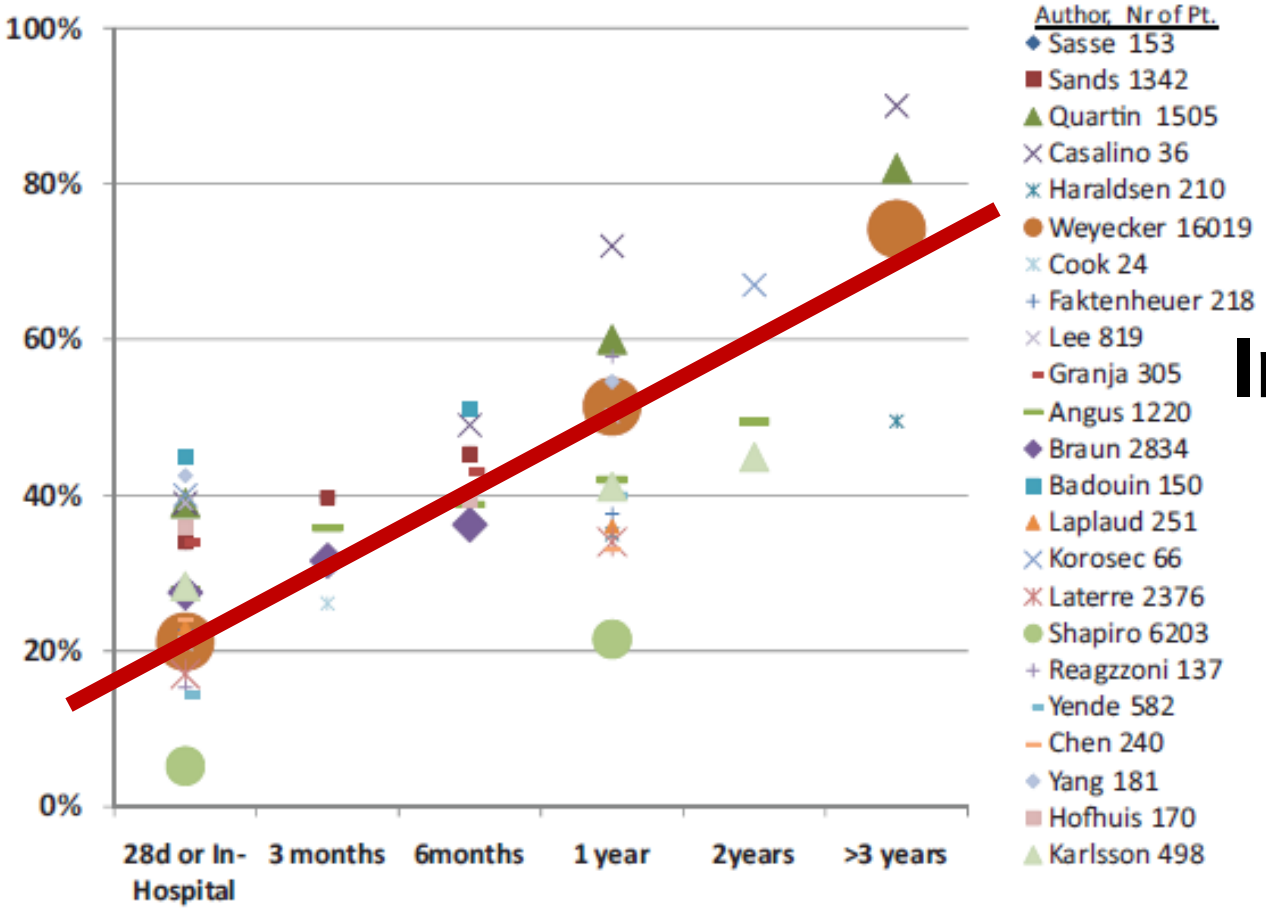
Substantial Severe Sepsis Mortality Occurs Long After Hospital Discharge

- Systematic review of studies reporting long-term mortality and quality-of-life data (>3 months) in patients with sepsis, severe sepsis, and septic shock using defined search criteria.



Mortality Increases With Time

WHY?

Winters, B.D. et. al. Crit Care Med 2010 Vol. 38, No. 5

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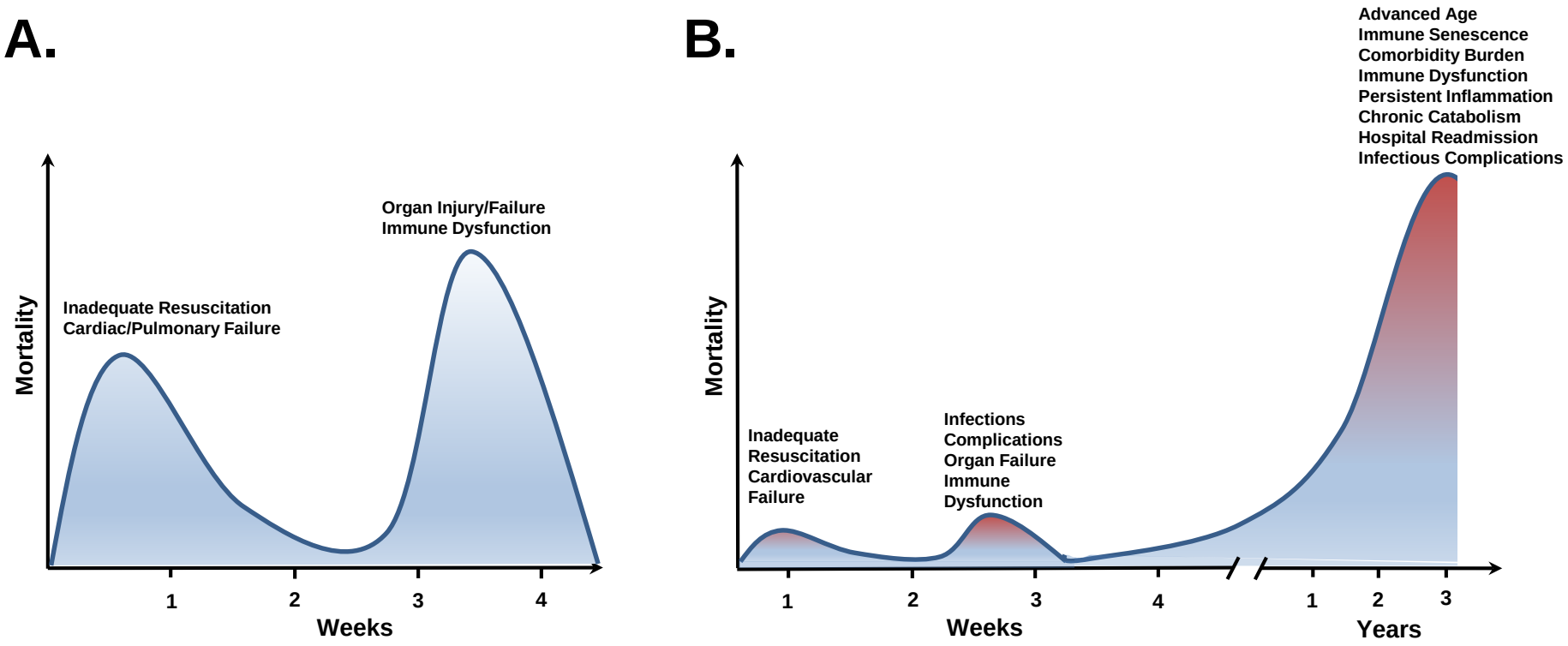

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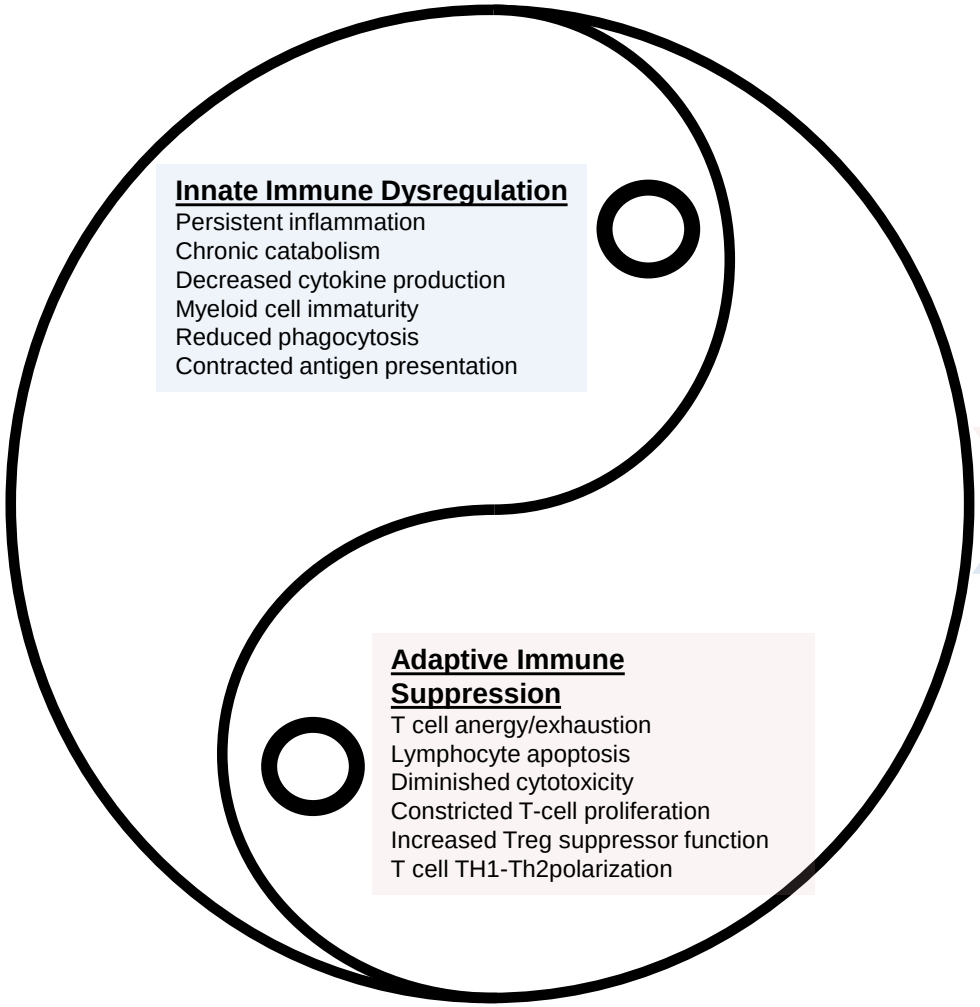

Ongoing Organ Injury
Poor Tissue Regeneration

Hospital Readmission

Recurrent, Persistent, Secondary and Nosocomial Infections

Long-Term Deaths

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T2D and Infection Susceptibility

Author	Year	Infection type	n	Study design	Main outcome measures	Main findings
Zhao (29)	2009	Skin infection	8,655	Longitudinal matched control	Incidence of skin infections	Higher risk for skin infections (adjusted OR 2.8)
Kornum (57)	2008	CAP	34,329	Population-based matched control	Pneumonia-related hospitalization	Increased risk for CAP-related hospitalization (RR 1.26 [95% CI 1.21–1.31])
Benfield (32)	2007	Infectious diseases	10,063	Prospective	Hospitalization, 28-day mortality	Higher risk for infection-related hospitalizations and UTI-related mortality (HR 3.9 [95% CI 1.2–12.7]); no difference in mortality because of sepsis, CAP, skin infection, and other infections
Boyko (30)	2005	UTI	1,017	Longitudinal matched control	Incidence of UTI	Higher risk of UTI (RR 1.8 [95% CI 1.2–2.7]) and antibiotic treatment (RR 2.3 [95% CI 1.3–3.9])
Thomsen (58)	2004	Pneumococcal bacteremia	598	Matched control	Bacteremia	Higher risk for pneumococcal pneumonia (OR 1.9 [95% CI 1.4 –2.6])
Shah (31)	2003	Infectious diseases	513,749	Matched control	Hospitalization, mortality	Higher risk for hospitalization (RR 2.17 [95% CI 2.10 –2.23]) and infection-related mortality (1.92 [1.79 –2.05]); no difference in in-hospital mortality (1.05 [0.89–1.01] and 0.84 [0.87–1.01])

↑ Infection = ↑ Sepsis

Schuetz, P. et.al. Diabetes Care, Volume 34, March 2011

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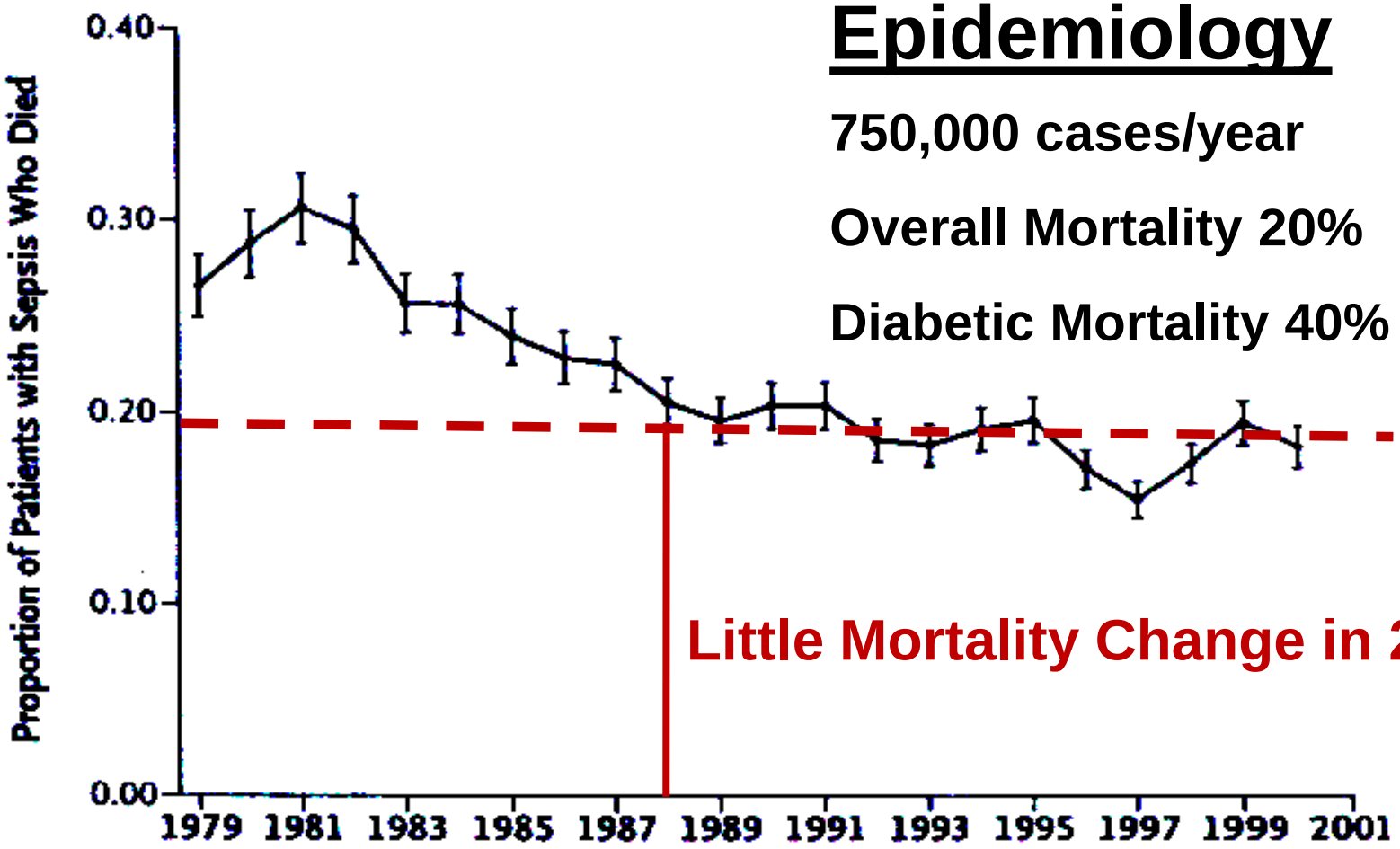
T2D and Sepsis

Author	Year	Infection type	n	Study design	Main outcome measures	Main findings
Kornum (37)	2007	CAP	29,900	Population-based cohort	Complications, bacteremia, mortality	Higher mortality rates (1.2 [95% CI 1.1–1.3]), but similar rates of complications and bacteremia; mortality within patients with diabetes increased when initial glucose levels >14 mmol/L in multivariate analysis (adjusted MMR 1.46 [95% CI 1.01–2.12] compared with patients with glucose <6.1 mmol)
Thomsen (36)	2005	*Enterobacteria* bacteremia	1,317	National registry	Bacteremia, 30-day mortality	Higher risk for bacteremia (OR 2.9 [95% CI 2.4–3.4]) and a trend toward higher 30-day mortality (1.4 [1.0–2.0])
Fine (35)	1996	CAP	33,148	Meta-analysis	30-day mortality	Higher risk for mortality (OR 1.3 [95% CI 1.1–1.5])

T2D ⟶ ↑Infection = ↑Sepsis ⟶ ↑Mortality

Schuetz, P. et.al. Diabetes Care, Volume 34, March 2011

Sepsis Mortality Rate



Epidemiology

750,000 cases/year

Overall Mortality 20%

Diabetic Mortality 40%

Little Mortality Change in 20 yrs!

Martin, GS, *et al*. 2003. *NEJM* 348:1546-54.

Hypothesis

Over-arching Hypothesis:

T2D acts as an immune deficiency associated with defects in neutrophil function that directly contribute to bacterial persistence and sepsis mortality.

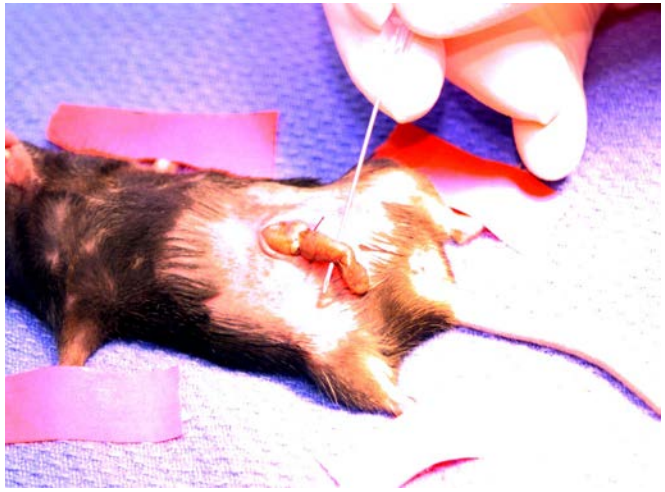
Diet Induced Obesity (DIO)

Key Points:

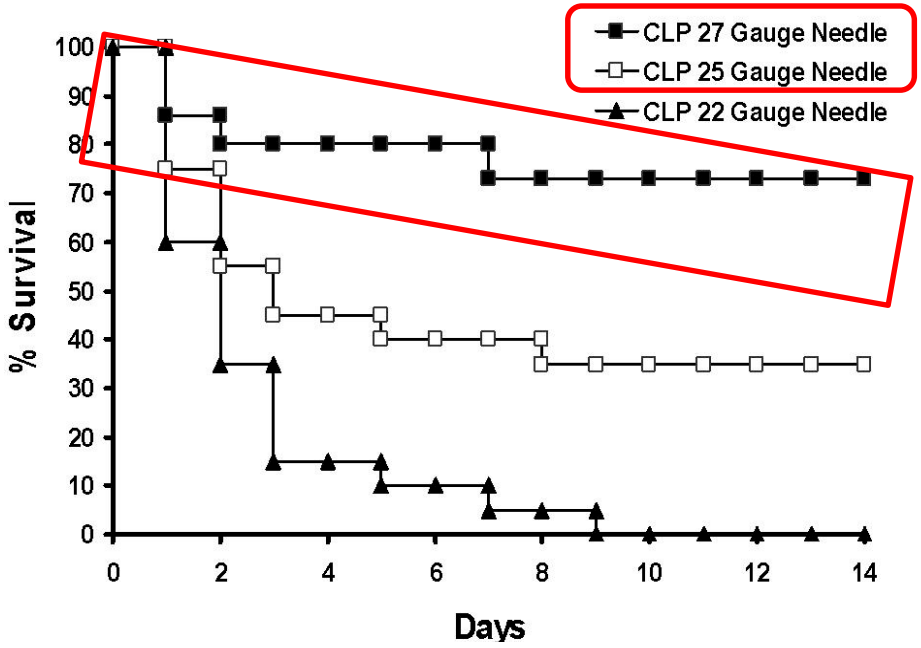
C57BL/6J males and controls at least 30 weeks of age to mimic middle aged and older humans

Model of pre-diabetic type 2 diabetes and obesity with elevated blood glucose and impaired glucose tolerance, hyperlipidemia

DIO and Cecal Ligation and Puncture (CLP)



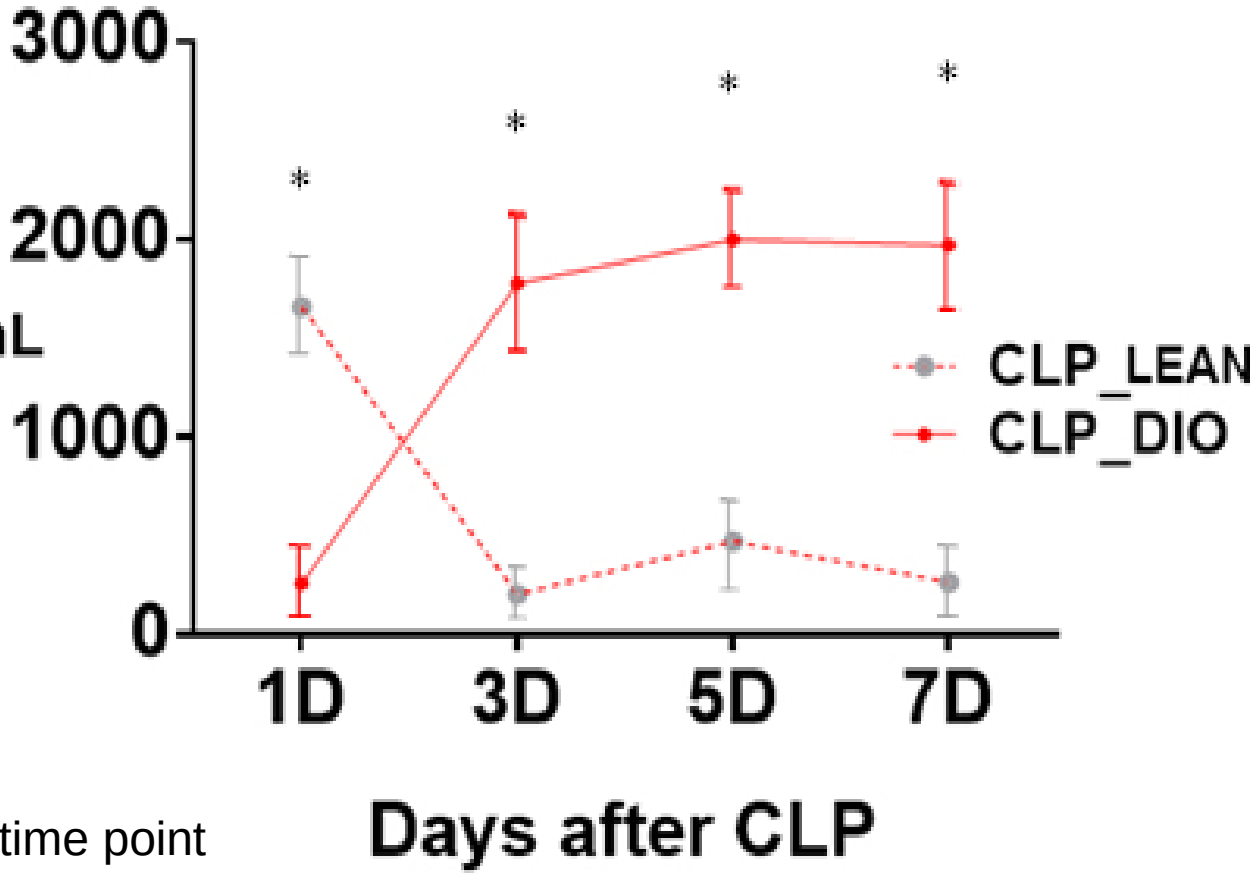
$LD_{10\text{-}20}$ in C57BL/6 mice at 7 days



Delano, M.J., et. al. *J Exp Med*. 2007. 204(6):1463-74.

Cuenca AG, Delano MJ, Kelly-Scumpia KM, Moldawer LL, Efron PA Curr Protoc Immunol. 2010 Nov;Chapter 19:Unit 19.13.

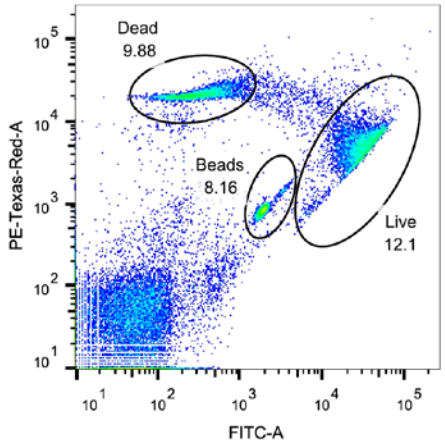
DIO vs WT : Bacteria Eradication

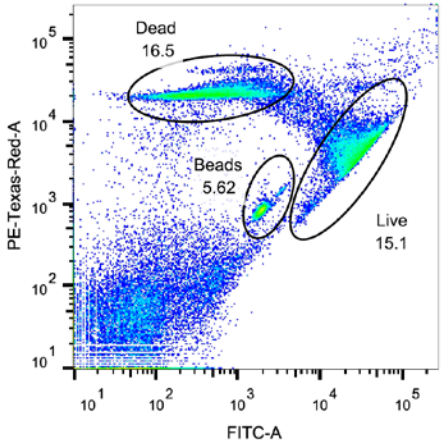


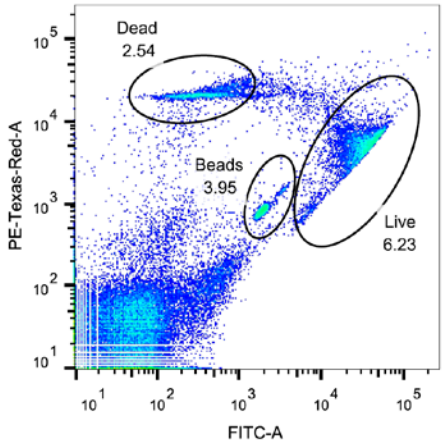
n=5 mice/group/time point
ANOVA

Detect Bacteria by Flow

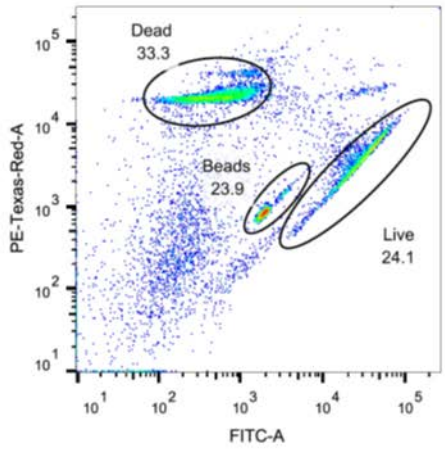
DIO

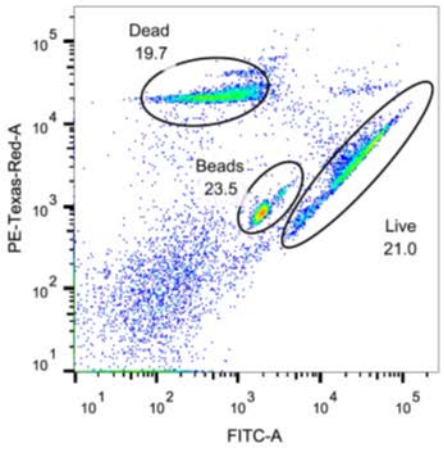


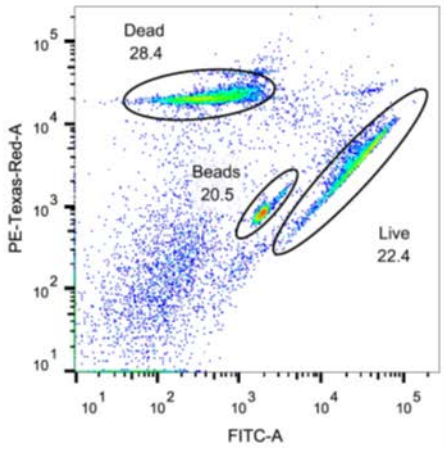




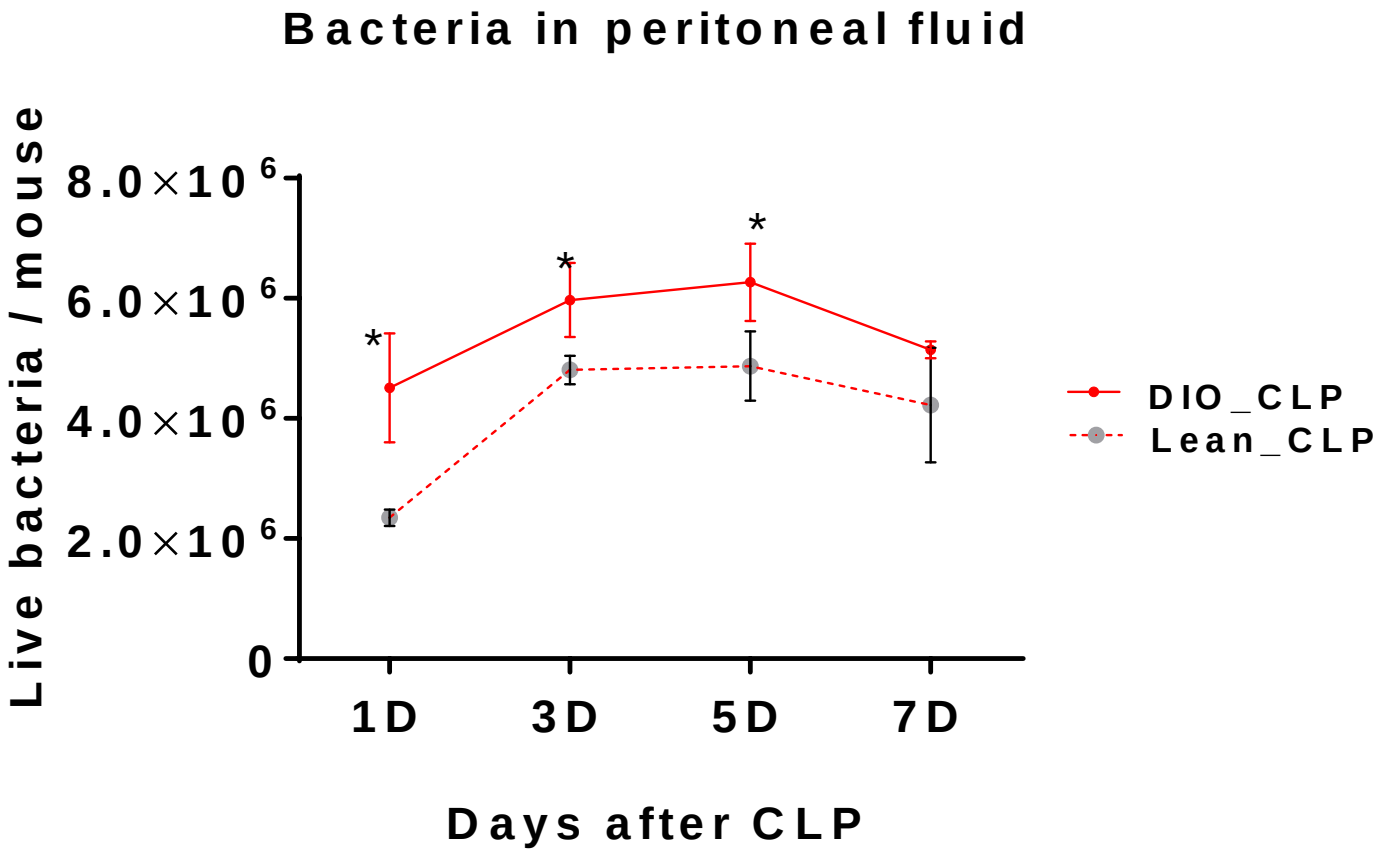
Lean







DIO *vs* Lean : Bacteria in peritoneal fluid



n=5 mice/group/time point, ANOVA

Conclusion

- DIO mice demonstrate overall bacterial persistence compared with Lean controls long after sepsis.
- What accounts for the bacterial persistence observed in the DIO mice?

Conclusions

- Trauma patients admitted with T2D experience much higher rates of all, serious, and infectious complications.
- A better understanding of the physiologic aberrations associated with T2D is necessary to reduce excess morbidity, resource consumption, and improve quality survival in trauma patients with T2D.

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Questions?