سبع آيات

بسم الله الرحمن الرحيم

الحمد لله رب العلمين الرحمن

الرحيم ملك يوم الدين

اياك نعبد واياك نستعين

اهدنا الصراط المستقيم صراط

الذين انعمت عليهم غير

المغضوب عليهم ولا الضالين

سورة البقرة مدنية وهي مائتان وست وثمانون آية

بسم الله الرحمن الرحيم

الم ذلك الكتب لا ريب فيه

هدى للمتقين الذين يؤمنون

بالغيب ويقيمون الصلوة ومما

رزقنهم ينفقون والذين

يؤمنون بما انزل اليك وما

انزل من قبلك وبالاخرة هم

Challenging the dogma

Amr Abdalla

Ass Prof of Critical Care Medicine
Faculty of Medicine – Alexandria University

'A lie told often enough becomes the truth'

Mission statements

- to challenge existing concepts on sepsis and infection
- to highlight new mechanistic insights
- to highlight new therapeutic developments

Questions, questions ..

1. Which one of the following statements is FALSE

Outcomes from sepsis have improved because of:

1. earlier identification & intervention of the septic patient?
2. reductions in harmful iatrogenic therapy?
3. the introduction of specific care bundles?
4. better surgical intervention?
5. less use of antibiotics?

Questions, questions ..

2. Which one of the following statements is FALSE

Factors increasing susceptibility to sepsis include:

1. genetic polymorphisms?
2. age?
3. gender?
4. immunosuppressive therapy?
5. inflammatory bowel disease?

Questions, questions ..

3. How many organisms per ml are usually present in blood to cause a bacteraemia?

    1. 1–10 ?
    2. 10^2 – 10^3 ?
    3. 10^4– 10^5 ?
    4. 10^5– 10^6 ?
    5. 10^6– 10^8 ?

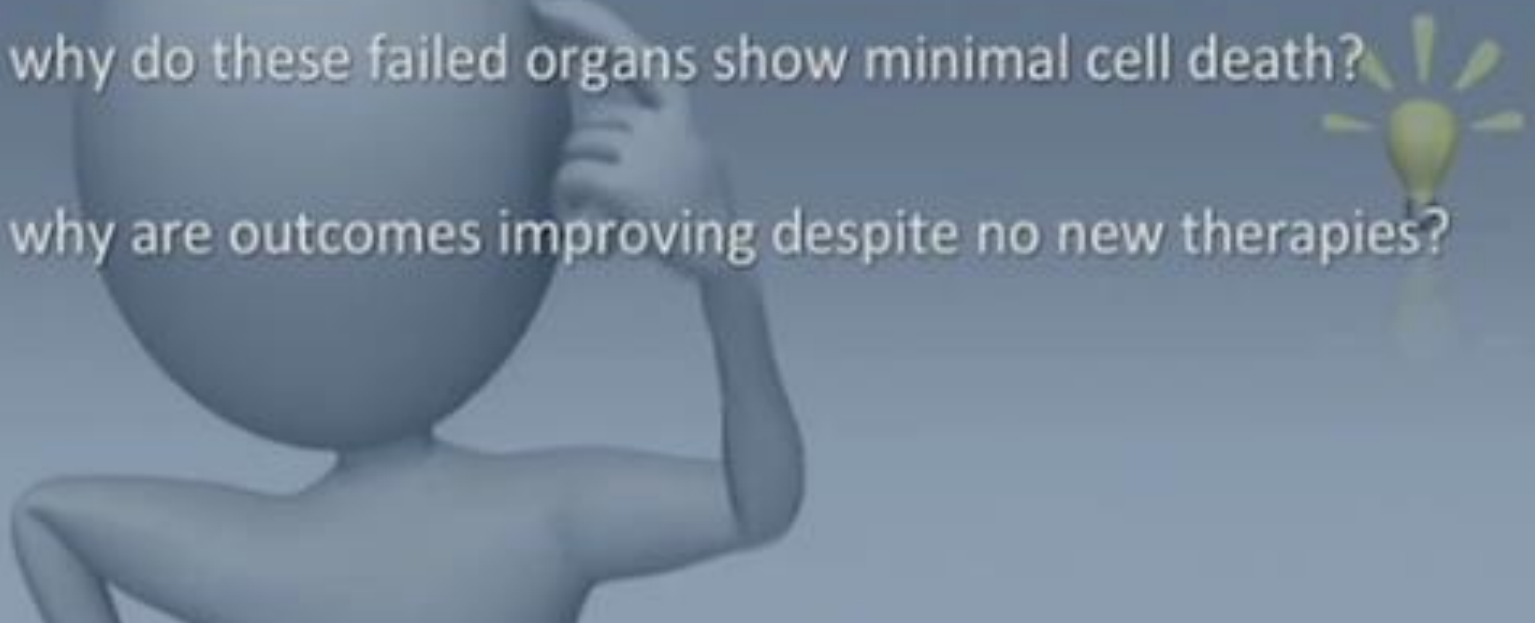
Questions, questions ..

4. Which one of the following statements is TRUE

1. delay in antibiotic treatment increases mortality?
2. corticosteroids should be used to treat specific infections?
3. the inflammatory response is driven predominantly by the infecting organism?
4. the infecting organism usually requires seven days of antibiotic therapy?
5. MOF is due to significant amounts of cell death?

The very basic questions need answering ..

- how many doses of antibiotic does it take to kill bugs?
- how does systemic inflammation cause organs to fail ...?
- ... yet in a variable manner?
- why do these failed organs show minimal cell death?
- why are outcomes improving despite no new therapies?



The infecting organism is merely the touchpaper

- organism:
  - variable virulence (e.g. all MRSA are not created equal - - mortality ranges from 0-42% depending on strain)
  - bacterial load
  - site of infection (e.g. E coli UTI vs E coli peritonitis)
- host:
  - genetic factors influence susceptibility and survival
  - many susceptibility factors, e.g.
    - age
    - gender
    - co-morbidities
    - medications e.g. immunosuppressives, sedation ..
- resistance - 'preconditioning'

  e.g. ?? from inflammatory bowel disease

Danger is everywhere!

PAMP
= pathogen-associated molecular pattern

DAMP
= damage-associated molecular pattern
('alarmin')

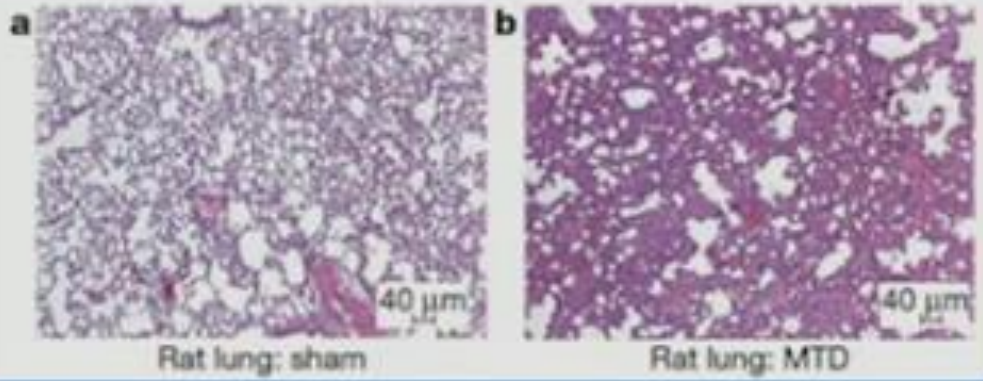
Damage-Associated Molecular Patterns

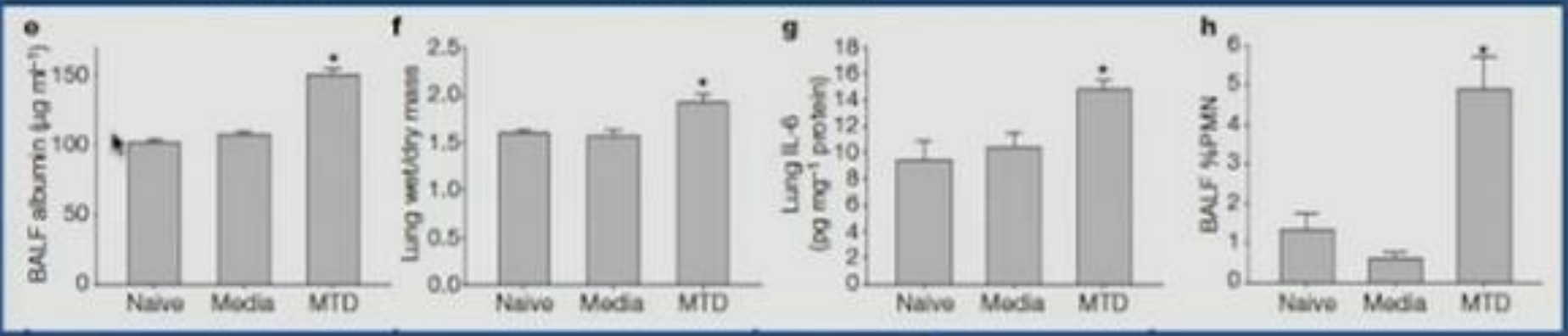
- protein DAMPs
  - intracellular proteins, e.g. heat-shock proteins, HMG-B1 (high-mobility group box 1), histones
  - S100 proteins
  - extracellular matrix proteins generated post-tissue injury, e.g. hyaluronan fragments
- purine metabolites (ATP, adenosine, uric acid)
- DNA
- mitochondria

Circulating mitochondrial DAMPs cause inflammatory responses to injury

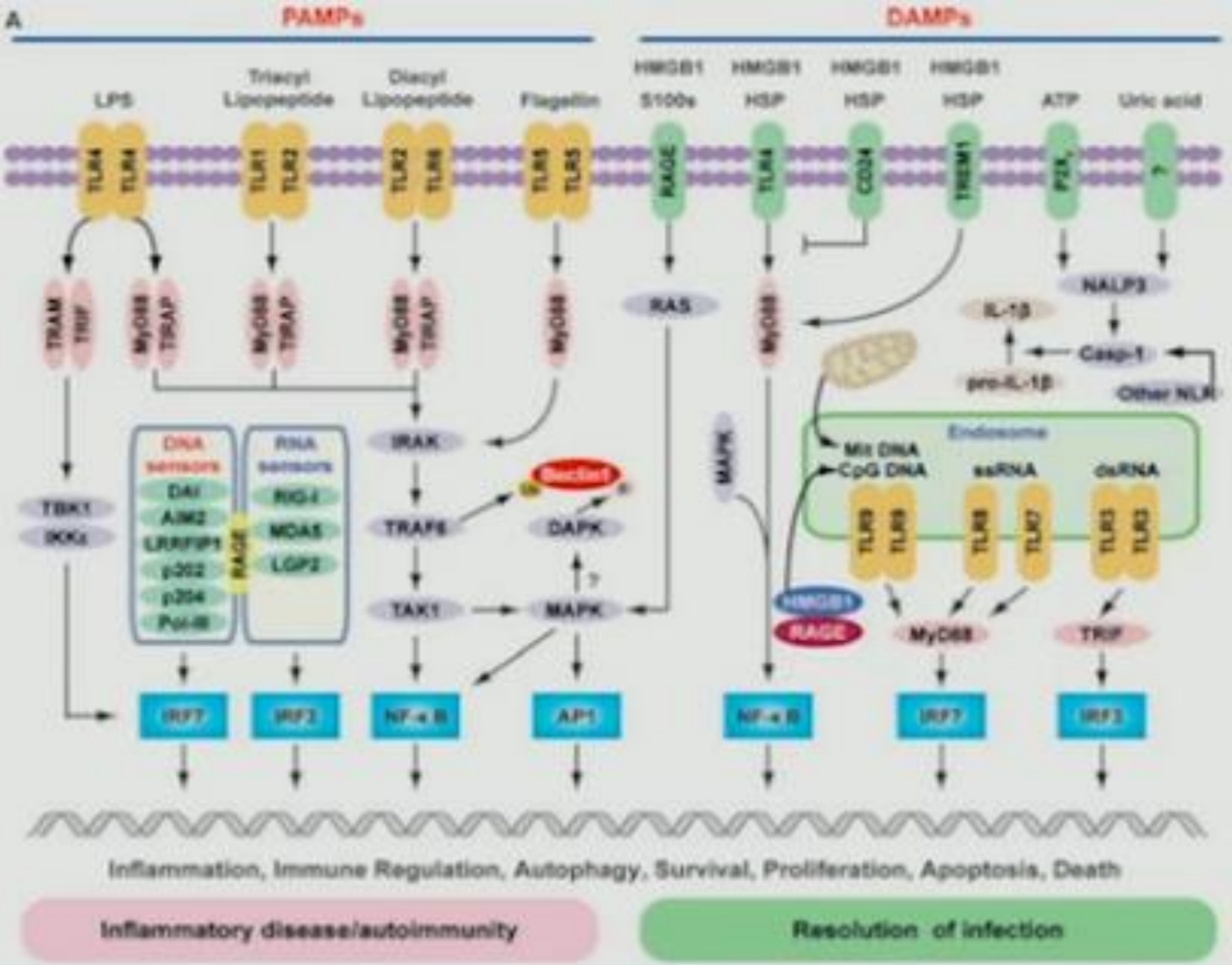
Qin Zhang[1], Mustafa Raoof[1], Yu Chen[1], Yuka Sumi[1], Tolga Sursal[1], Wolfgang Junger[1], Karim Brohi[2], Kiyoshi Itagaki[1] & Carl J. Hauser[1]

NATURE | Vol 464 | 4 March 2010





MTDs cause systemic inflammation and organ injury *in vivo*.

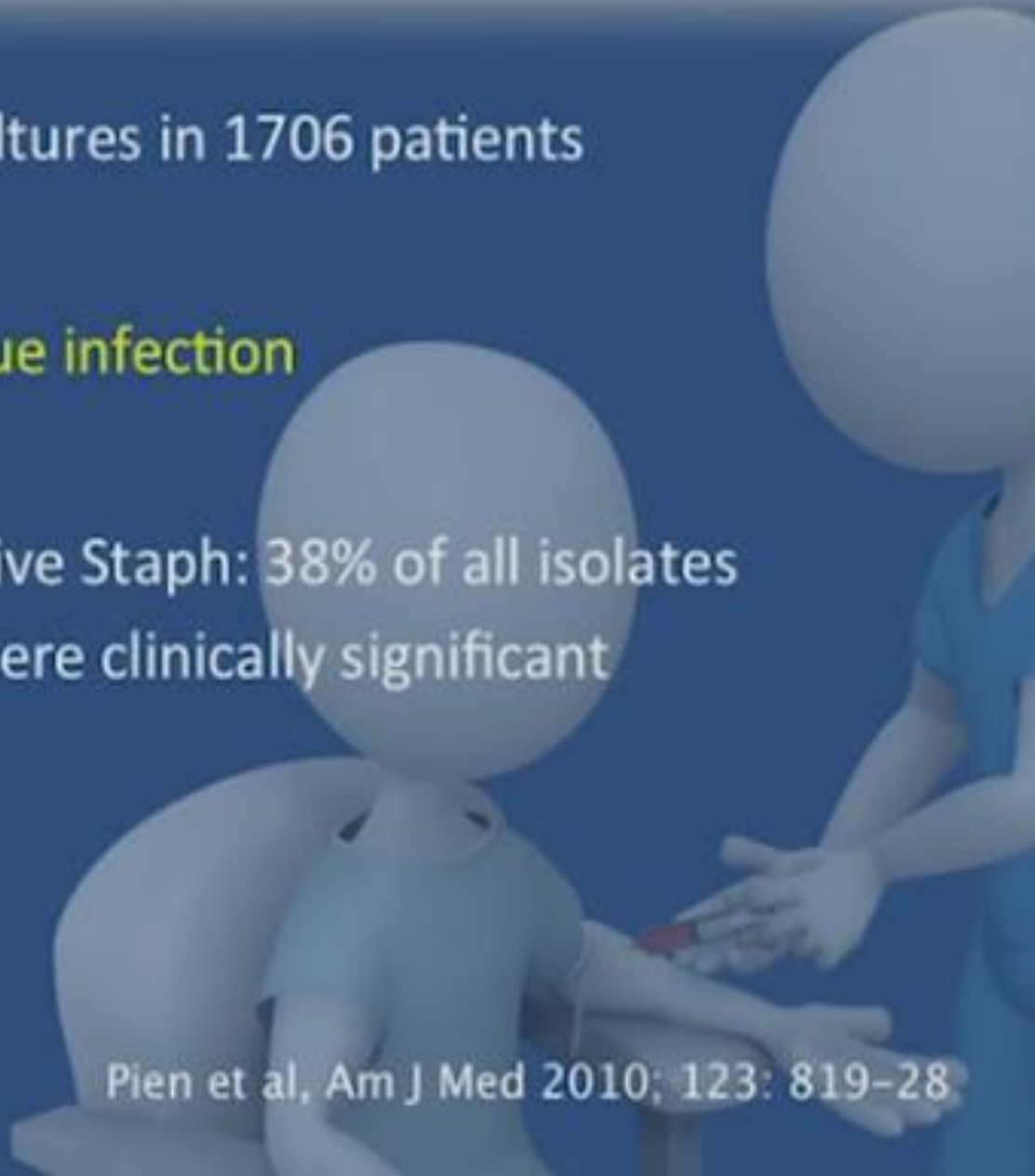

A
PAMPs
DAMPs
LPS
Triacyl Lipopeptide
Diacyl Lipopeptide
Flagellin
HMGB1 S100s
HMGB1 HSP
HMGB1 HSP
HMGB1 HSP
ATP
Uric acid
TLR4
TLR4
TLR1
TLR2
TLR2
TLR6
TLR5
TLR5
RAGE
TLR4
CD24
TREM1
P2X7
?
TRAM
TRIF
MyD88
TIRAP
MyD88
TIRAP
MyD88
TIRAP
MyD88
RAS
MyD88
NALP3
IL-1β
Casp-1
pro-IL-1β
Other NLR
DNA sensors
DAI
AIM2
LRRFIP1
p202
p204
Pol-III
RAGE
RNA sensors
RIG-I
MDA5
LGP2
IRAK
TRAF6
Beclin1
DAPK
?
TAK1
MAPK
TBK1
IKKε
MAPK
Endosome
Mit DNA
CpG DNA
ssRNA
dsRNA
TLR9
TLR9
TLR8
TLR7
TLR3
TLR3
HMGB1
RAGE
MyD88
TRIF
IRF7
IRF3
NF-κB
AP1
NF-κB
IRF7
IRF3
Inflammation, Immune Regulation, Autophagy, Survival, Proliferation, Apoptosis, Death
Inflammatory disease/autoimmunity
Resolution of infection

Septic or non-septic SIRS

- tissue damage -> DAMP release -> SIRS
- an infecting organism may not even be present
- does this explain (in part) our frequent inability to find a causative bug in 'septic' patients?
- .. and when we do grow something, is it a commensal or causative of infection???

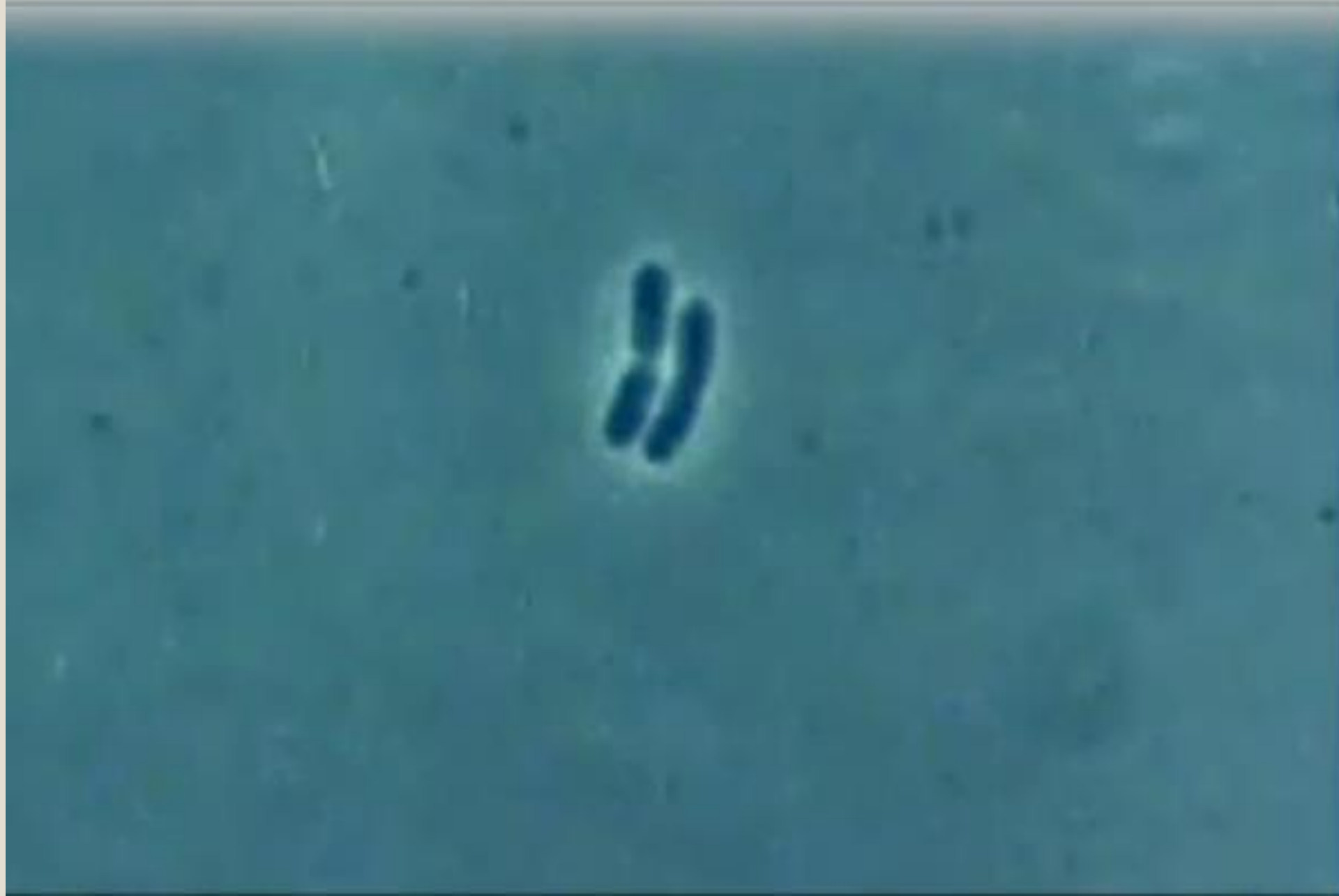
Contamination

- ★ 2270 positive blood cultures in 1706 patients
- ★ relevance?
  - ★ 51% adjudged as true infection
  - ★ 41% contamination
    - ★ coagulase-negative Staph: 38% of all isolates
      - but only 10% were clinically significant
  - ★ 8% uncertain



Pien et al, Am J Med 2010; 123: 819–28

Bugs and bacteraemia



Bugs and bacteraemia

- ★ very few organisms are present in blood during a bacteraemia (<1 to 10 CFU/ml)
- ★ bacteria replicate every 20 minutes
- ★ 1 bacterium can produce 5,000 billion billion bacteria in a day!
- ★ yield from blood cultures increase markedly with amount taken

Hall et al, J Clin Microbiol 1976; 3:643-5
Tenney et al, J Clin Microbiol 1982; 15: 558-61
Cockerill et al, Clin Infect Dis 2004; 38: 1724-30

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blood volume comparison	increase in yield (%)
15 ml vs 5 ml	25%
20 ml vs 10 ml	29.8%
30 ml vs 20 ml	13.4%
40 ml vs 30 ml	7.2%

Hall et al, J Clin Microbiol 1976; 3:643-5
Tenney et al, J Clin Microbiol 1982; 15: 558-61
Cockerill et al, Clin Infect Dis 2004; 38: 1724-30

Antibiotic management

- ★ choosing the right antibiotic makes sense (though at a cost)
- ★ avoiding unnecessary (or wrong) antibiotics also makes sense
  - ★ will not kill the bacterium
  - ★ only causes complications/side-effects without any benefit
    - ★ encourages antibiotic resistance
    - ★ overgrowth of fungi, pathogenic hospital bacteria, C difficile
    - ★ gut/liver/kidney/skin complications
    - ★ immunosuppressive
    - ★ bioenergetic (inhibit mitochondrial activity/regeneration)

Jarisch-Herxheimer reaction (1902)

- fever, rigors, myalgia, tachycardia, vasodilation, hypotension seen after first dose of mercury for syphilis (....'sepsis')
- lasts from 12-24h with variable severity
- seen after 1st antimicrobial dose in wide range of parasites, brucellosis ...
- .. for Gram -ve bacteria, 1st seen in typhoid fever -> lethal vasomotor collapse
- basis for steroids before/with first antibiotic dose for meningitis, miliary TB ...

Antibiotics and toxin release in meningitis

Bacterial products released into CSF during antibiotic-induced bacterial lysis in treatment of meningitis

-> release of proinflammatory cytokines

-> increased meningeal inflammation

-> increased brain oedema

Bottcher T et al. J Infect Dis 181: 2095-8
Mustafa MM et al. J Infect Dis 1999; 160: 891-5
Burroughs M et al. J Clin Invest 1993; 92, 297-302

The New England
Journal of Medicine

VOLUME 347 NOVEMBER 14, 2002 NUMBER 20

DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

JAN DE GANS, PH.D., AND DIEDERIK VAN DE BEEK, M.D., FOR THE EUROPEAN DEXAMETHASONE IN ADULTHOOD BACTERIAL MENINGITIS STUDY INVESTIGATORS*

The New England
Journal of Medicine

VOLUME 347 NOVEMBER 14, 2002 NUMBER 20

TABLE 2. OUTCOMES EIGHT WEEKS AFTER ADMISSION, ACCORDING TO CULTURE RESULTS.*

OUTCOME AND CULTURE RESULTS	DEXAMETHASONE GROUP	PLACEBO GROUP	RELATIVE RISK (95% CI)†	P VALUE
	no./total no. (%)			
Unfavorable outcome				
All patients	23/157 (15)	36/144 (25)	0.59 (0.37–0.94)	0.03
Streptococcus pneumoniae	15/58 (26)	26/50 (52)	0.50 (0.30–0.83)	0.006
Neisseria meningitidis	4/50 (8)	5/47 (11)	0.75 (0.21–2.63)	0.74
Other bacteria	2/12 (17)	1/17 (6)	2.83 (0.29–27.8)	0.55
Negative bacterial culture‡	2/37 (5)	4/30 (13)	0.41 (0.08–2.06)	0.40
Death				
All patients	11/157 (7)	21/144 (15)	0.48 (0.24–0.96)	0.04
S. pneumoniae	8/58 (14)	17/50 (34)	0.41 (0.19–0.86)	0.02
N. meningitidis	2/50 (4)	1/47 (2)	1.88 (0.76–20.1)	1.00
Other bacteria	1/12 (8)	1/17 (6)	1.42 (0.10–20.5)	1.00
Negative bacterial culture	0/37	2/30 (7)	—	0.20

Infections in which steroids work (RCT data)

Review

Clinical review: A systematic review of corticosteroid use in infections

Jody Aberdein[1] and Mervyn Singer[2]

- bacterial meningitis
- ?community acquired pneumonia
- typhoid fever
- miliary tuberculosis
- Pneumocystis jirovecii
- septic arthritis
- croup
- onchocerciasis
- infectious mononucleosis ..

Critical Care 2006, **10**:203

Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study

Daniel H Kett, Ennie Cano, Andrew A Quartin, Julie E Mangino, Marcus J Zervos, Paula Peyrani, Cynthia M Cely, Kimbal D Ford, Ernesto G Scerpella, Julio A Ramirez, and the Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators*

Lancet Infect Dis 2011; 11: 181–89

Summary

Background The American Thoracic Society and Infectious Diseases Society of America provide guidelines for management of hospital-acquired, ventilator-associated, and health-care-associated pneumonias, consisting of empirical antibiotic regimens for patients at risk for multidrug-resistant pathogens. We aimed to improve compliance with these guidelines and assess outcomes.

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For patients at risk of infection with a multidrug-resistant pathogen, the guidelines[13] recommend empirical treatment with the following drugs: an antipseudomonal cephalosporin, carbapenem, or β-lactam and β-lactamase inhibitor; an aminoglycoside or antipseudomonal fluoroquinolone; and linezolid or vancomycin.

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Lancet Infect Dis 2011; 11: 181–89

- 303 pts at risk of multi-drug resistant CAP/HAP/VAP in 4 ICUs
- followed IDSA & ATS antibiotic guidelines
  (i.e. dual Rx for Gram -ve plus MRSA cover)
- empiric cover active in 81% (compliant) v. 85% (non-compliant)
- reasons for non-compliance (n=174):
  - not using 2nd anti-Gram-ve (154)
  - not using primary anti-Gram-ve (24) or anti-MRSA drug (24)

	Compliant treatment (n=129)	Non-compliant treatment (n=174)	p value
Survival through day 28 (total population)	65% (3)	79% (4)	0·004
Baseline CPIS <7	68% (6)	80% (4)	0·063
Baseline CPIS ≥7	63% (6)	78% (5)	0·037

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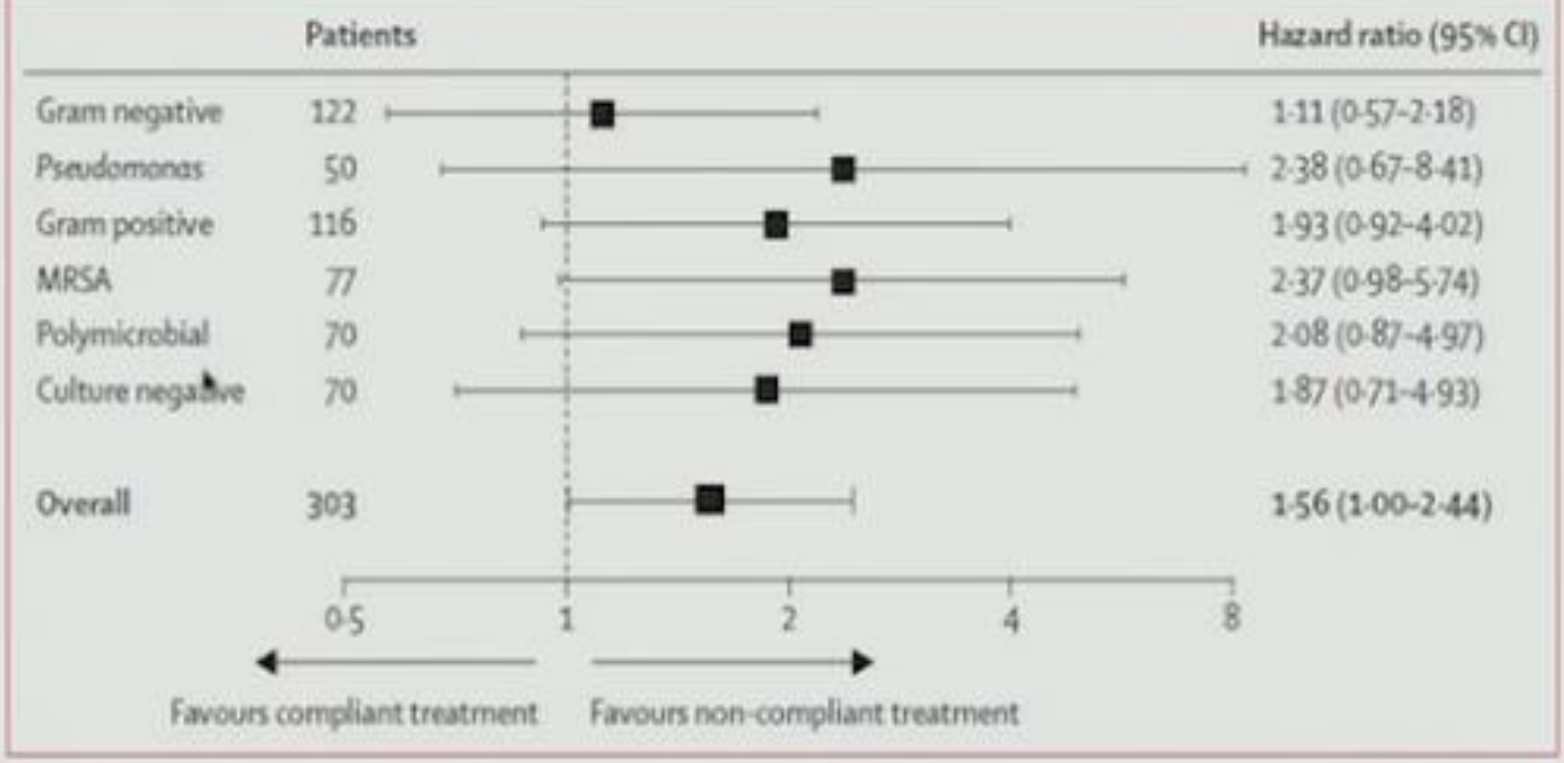
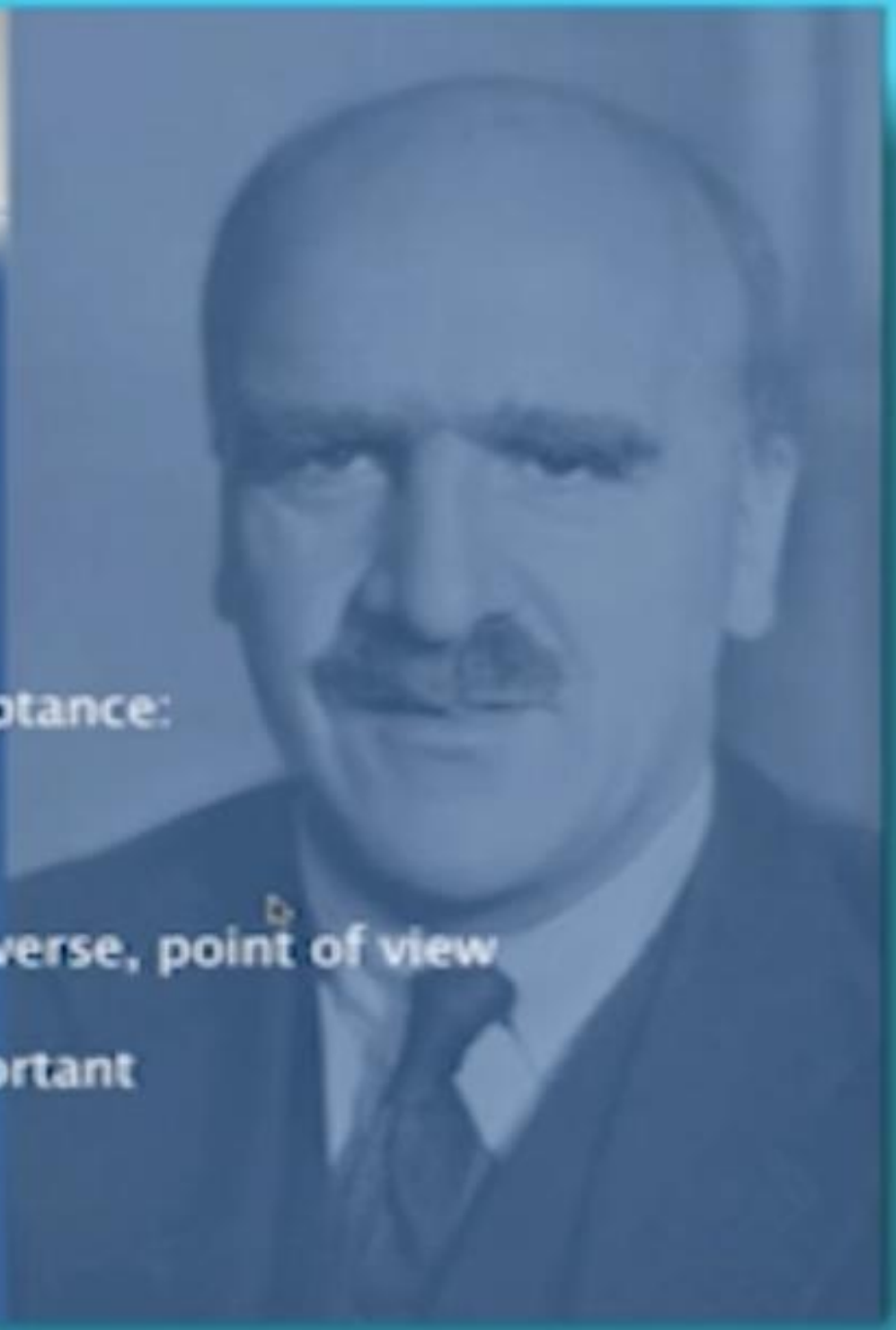


Figure 3: Guideline-compliant empirical treatment outcomes for 28-day mortality, grouped by pathogen and adjusted for treatment-independent risk

JBS ("Jack") Haldane
(1892–1964)



Theories have four stages of acceptance:

(i) this is worthless nonsense

(ii) this is an interesting, but perverse, point of view

(iii) this is true, but quite unimportant

(iv) I always said so

Antibiotic management

How many doses of antibiotic would you use to treat meningococcal meningitis?

MAJOR ARTICLE

Three Days of Intravenous Benzyl Penicillin Treatment of Meningococcal Disease in Adults

Rod Ellis-Pegler,[1] Lesley Galler,[2] Sally Roberts,[1] Mark Thomas,[1] and Andrew Woodhouse[3]
Departments of [1]Infectious Diseases, [2]Critical Care Medicine, and [3]Microbiology, Auckland Hospital, Auckland, New Zealand

n = 58 adults (>15y.o.)

21% septic shock, 10% severe sepsis

Rx: 12 MU benzylpenicillin/day for 3 days

> In summary, no patients relapsed after receiving 3 days of treatment with intravenous benzyl penicillin for meningococcal disease, no patient required joint aspiration, and 4 of the 5 deaths occurred during the 3 days of benzyl penicillin treatment.

Clinical Infectious Diseases 2003; 37:658–62

Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study

N Nathan, T Borel, A Djibo, D Evans, S Djibo, J P [illegible] M Guillerm, K P Alberti, L Pinoges, P J Guerin, D Legros

one dose given in peripheral clinics in Niger

	Overall		Chloramphenicol		Ceftriaxone		Difference % (90% CI)
	n (%)	Total	n (%)	Total	n (%)	Total	
Intention-to-treat analysis							
Treatment failure at 72 h	44 (9%)	503	22 (9%)	256	22 (9%)	247	0·3% (-3·8 to 4·5)
Death at 72 h	26 (5%)	503	12 (5%)	256	14 (6%)	247	1·0% (-2·3 to 3·8)
Second injection between 24 h and 48 h	35 (7%)	481	19 (8%)	247	16 (7%)	234	-0·9% (-4·7 to 3·0)
Neurological sequelae at 72 h	29 (6%)	477	13 (5%)	244	16 (7%)	233	1·6% (-2·1 to 5·1)

Lancet 2005; 366: 308–313

Antibiotic management

How aggressively should you treat sepsis with antibiotics?

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maurene Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee

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We recommend that intravenous antibiotic therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (1D). Appropriate cultures should be obtained before initiating antibiotic therapy but should not prevent prompt administration of antimicrobial therapy (grade 1D).

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Crit Care Med 2008; 36:296–327

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Because patients with severe sepsis or septic shock have little margin for error in the choice of therapy, the initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens. There is ample evidence that failure to initiate appropriate therapy (i.e., therapy with activity against the pathogen that is subsequently identified as the causative agent) correlates with increased morbidity and mortality (45–48).

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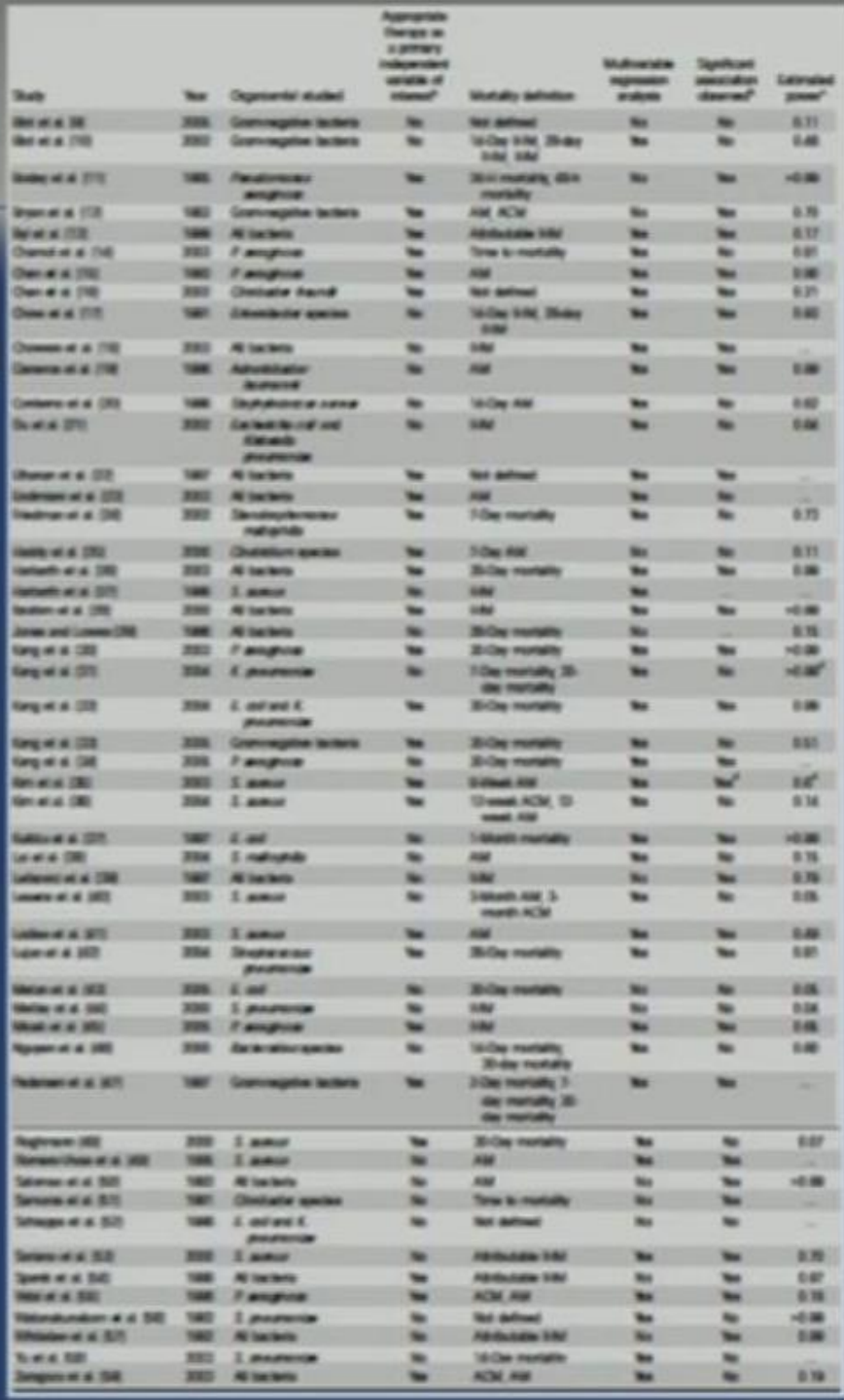
IS THIS TRUE???

Crit Care Med 2008; 36:296–327

A Systematic Review of the Methods Used to Assess the Association between Appropriate Antibiotic Therapy and Mortality in Bacteremic Patients

Jessina C. McGregor,[1] Shayna E. Rich,[1] Anthony D. Harris,[1,2] Eli N. Perencevich,[1,2] Regina Osih,[1] Thomas P. Lodise, Jr.,[3] Ram R. Miller,[4] and Jon P. Furuno[1]

Clinical Infectious Diseases 2007; 45:329–37



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Clinical Infectious Diseases 2007; 45:329–37

nearly half the studies showed no association

all studies heavily criticised

- weak methodologies
- multiple limitations

Impact of Inactive Empiric Antimicrobial Therapy on Inpatient Mortality and Length of Stay

Kimberly K. Scarsi,[1]* Joe M. Feinglass,[2] Marc H. Scheetz,[1] Michael J. Postelnick,[1] Maureen K. Bolon,[3] and Gary A. Noskin[3]

Inpatient mortality. Regardless of initial empiric therapy, the crude mortality rates were similar for both inactive- and active-therapy groups (13.6% and 16.1%, respectively; $P = 0.48$). No significant mortality difference was found between patients receiving inactive versus active therapy after controlling for other clinically significant mortality risk factors (OR = 0.61, $P = 0.14$) (Table 2).

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2006, p. 3355–3360

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Inpatient mortality. Regar
the crude mortali
active-th

TABLE 2. Multiple logistic regression results for the effects of active versus inactive empiric therapy on inpatient mortality for patients with GNBI (n = 884)

Patient characteristic	OR (95% CI[a])	P value
Inactive empiric antimicrobial therapy	0.61 (0.31, 1.18)	0.14

y,
n
control-
risk factors (OR =

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2006, p. 3355–3360

Empiric Antibiotic Therapy for *Staphylococcus aureus* Bacteremia May Not Reduce In-Hospital Mortality: A Retrospective Cohort Study

Marin L. Schweizer[1,2]*, Jon P. Furuno[1], Anthony D. Harris[1], J. Kristie Johnson[3], Michelle D. Shardell[1], Jessina C. McGregor[4], Kerri A. Thom[1], George Sakoulas[5], Eli N. Perencevich[2,6]

Principal Findings: Among 814 admissions, 537 (66%) received appropriate empiric therapy. Those who received appropriate empiric therapy had a higher hazard of 30-day in-hospital mortality (Hazard Ratio (HR): 1.52; 95% confidence interval (CI): 0.99, 2.34). A longer time to appropriate therapy was protective against mortality (HR: 0.79; 95% CI: 0.60, 1.03) except among the healthiest quartile of patients (HR: 1.44; 95% CI: 0.66, 3.15).

Conclusions/Significance: Appropriate empiric therapy was not associated with decreased mortality in patients with *S. aureus* bacteremia except in the least ill patients. Initial broad antibiotic selection may not be widely beneficial.

PLoS ONE July 2010 | Volume 5 | Issue 7 | e11432

Corticosteroids for Septic Shock

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for the CORTICUS Study Group

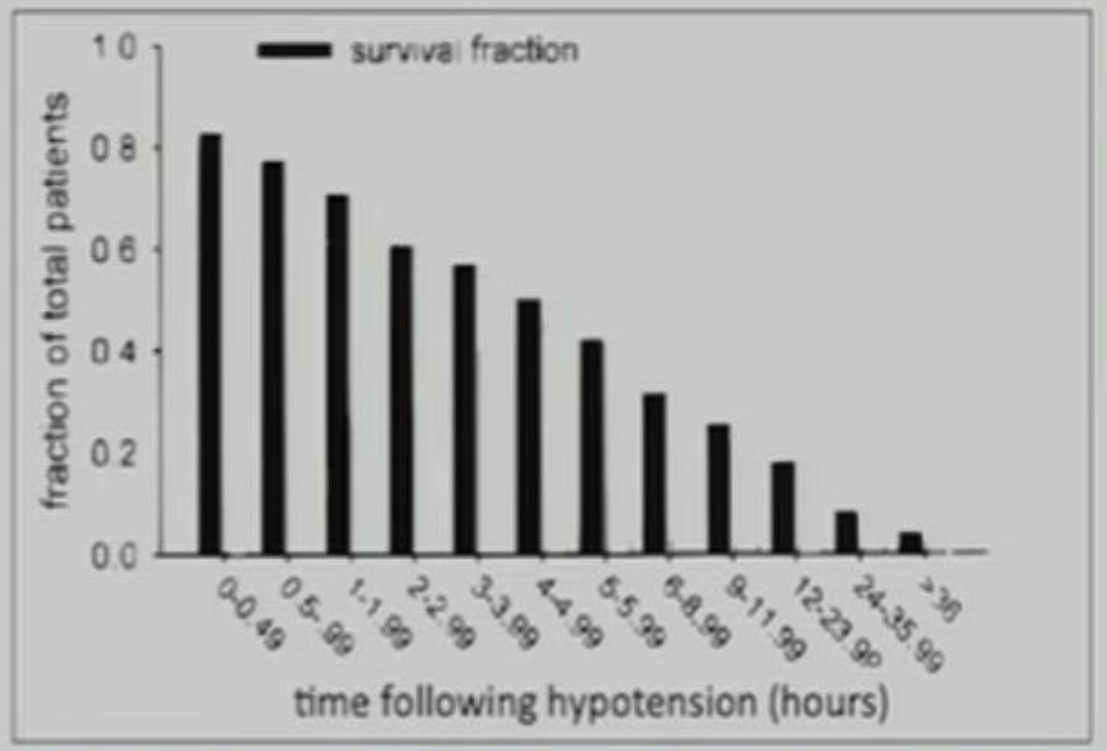
A higher mortality was seen among patients classified as receiving appropriate antimicrobial agents as compared with those not receiving appropriate antibiotics (35% vs. 23%).

N ENGL J MED 358;19 WWW.NEJM.ORG MAY 8, 2008

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

Crit Care Med 2006; 34:1589–1596



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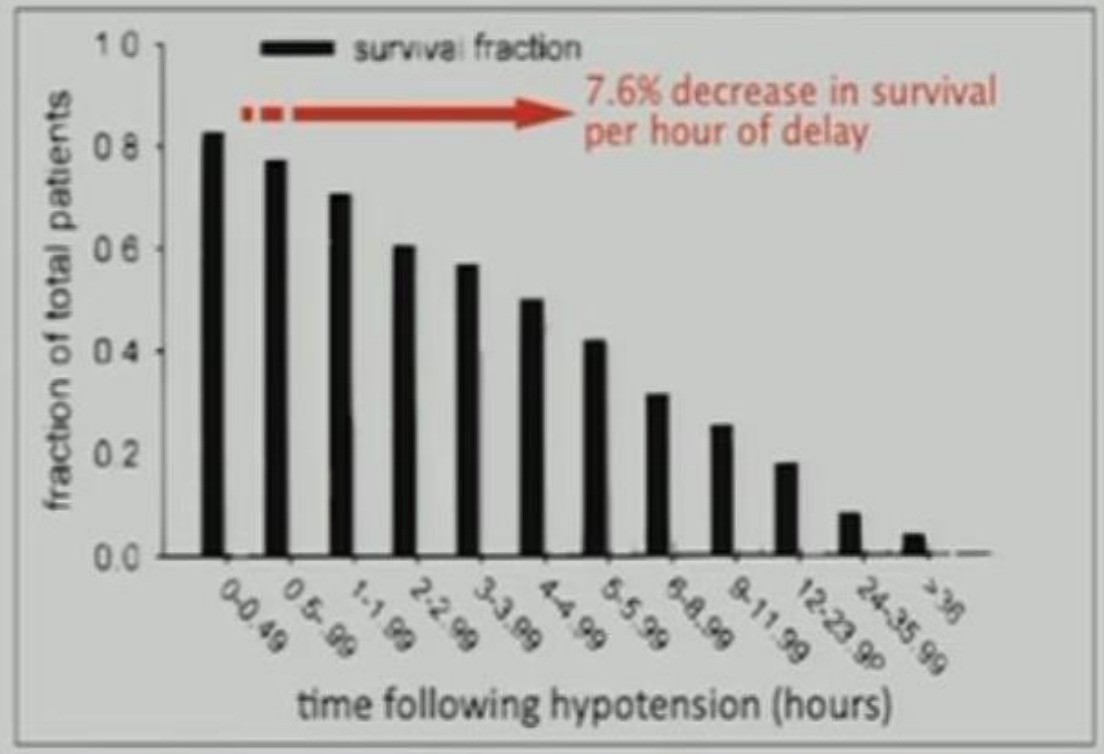

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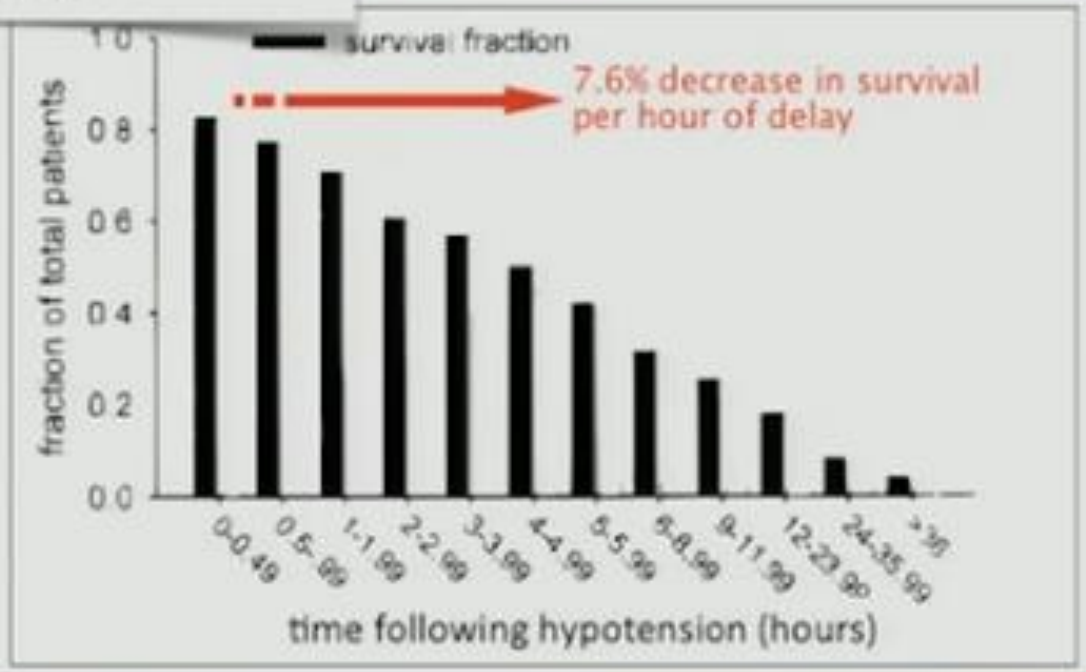

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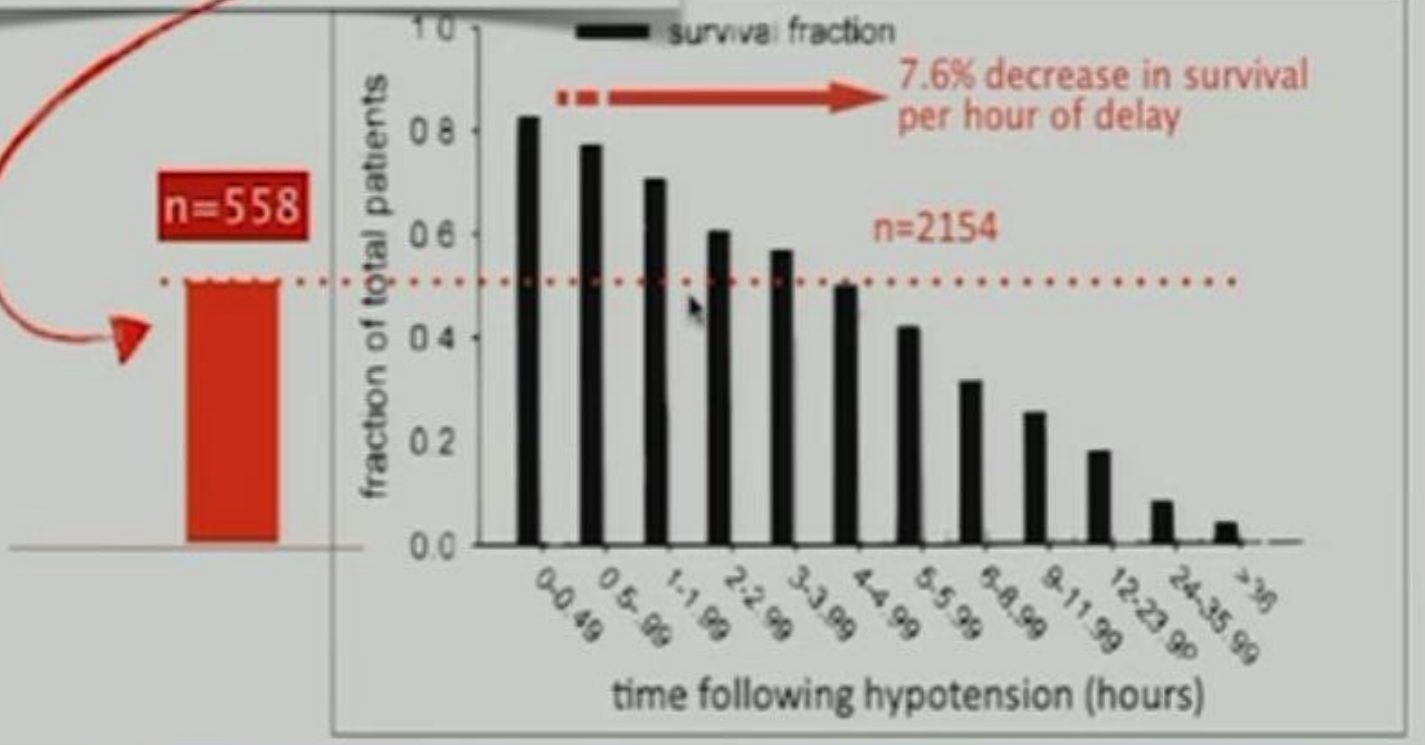

Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study

Tjasa Hranjec, Laura H Rosenberger, Brian Swenson, Rosemarie Metzger, Tanya R Flohr, Amani D Politano, Lin M Riccio, Kimberley A Popovsky, Robert G Sawyer

- 2 year before-after observational study of 1483 patients admitted to Surgical ICU of Univ of Virginia
- Year 1: "aggressive Rx"
  - clinical suspicion of infection -> cultures + antibiotics
- Year 2: "conservative Rx"
  - clinical suspicion of infection -> antibiotics started only after objectively confirmed infection
- ITT analysis
- 1° outcome: hospital mortality

Lancet Infect Dis 2012; 12:774-80

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Any patient who was unstable and needed vasoactive drugs after appropriate resuscitation and who was suspected of harbouring an infection could have empirical antimicrobial drugs started immediately at the discretion of the attending intensivist. These patients were nonetheless included in all analyses. Patients with a mean arterial pressure (MAP) of less than 60 mm Hg after volume resuscitation were treated with vasoactive drugs.

Lancet Infect Dis 2012; 12: 774–80

	Aggressive (n=247)	Conservative (n=237)	p value
Time from blood culture to start of treatment (h)			
Number	189	206	
Mean (SE)	20·9 (24·4)	34·8 (34·4)	<0·0001
Median (IQR)	12 (3–30)	22 (7–58)	<0·0001
Time from fever to start of treatment (h)			
Number	103	139	
Mean (SD)	11·1 (14·9)	35·2 (37·4)	<0·0001
Median (IQR)	6 (3–14)	24 (9–44)	<0·0001
Duration of antimicrobial treatment (days)			
Mean (SD)	17·7 (28·1)	12·5 (10·7)	<0·008
Median (IQR)	11 (7–8)	10 (7–14)	0·015
Appropriate antimicrobials (number [%])			
Initial*	144 (62%)	158 (74%)	0·0095
Switched	64 (28%)	48 (23·5%)	0·17
Overall	208 (90%)	206 (96%)	0·010

Not all patients had blood cultures drawn or had fever (temperature ≥38·5°C). Antibiotics were generally switched to appropriate coverage 3 days after cultures were sent when sensitivities returned. *Data for appropriate initial therapy were available from 214 patients in the aggressive group, and 231 in the conservative group.

Table 4: Time to start of treatment and appropriateness of antibiotic therapy

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	Aggressive	Conservative	p value
Infections associated with MAP <60 mm Hg			
Number	95	110	0·077
APACHE II score			
Mean (SD)	22·0 (6·9)	22·4 (6·4)	0·71
Median (IQR)	21 (17–29)	22 (17–27)	0·79
Time from blood culture to initiation of treatment (h)			
Mean (SD)	9·2 (14·0)	31·8 (37·6)	<0·0001
Median (IQR)	4 (3–12·5)	20 (8–39)	<0·0001

MAP=mean arterial pressure.

Table 8: Distribution of mean arterial pressures and descriptive statistics and outcomes for infections treated with MAP less than 60 mm Hg

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Mean (SD)	9·2 (14·0)	31·8 (37·6)	<0·0001
Median (IQR)	4 (3–12·5)	20 (8–39)	<0·0001
Deaths	63 (66%)	29 (26%)	0·0004

MAP=mean arterial pressure.

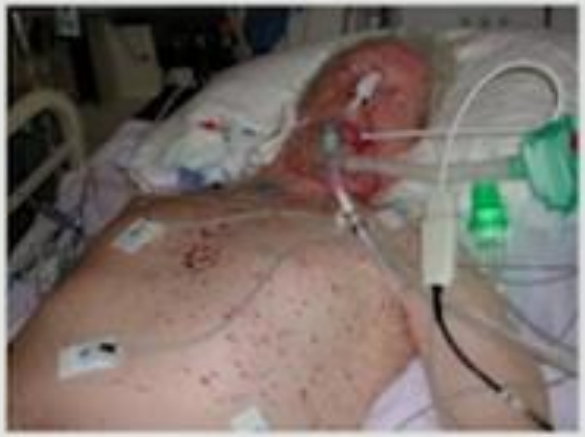
Table 8: Distribution of mean arterial pressures and descriptive statistics and outcomes for infections treated with MAP less than 60 mm Hg

Lancet Infect Dis 2012; 12: 774–80

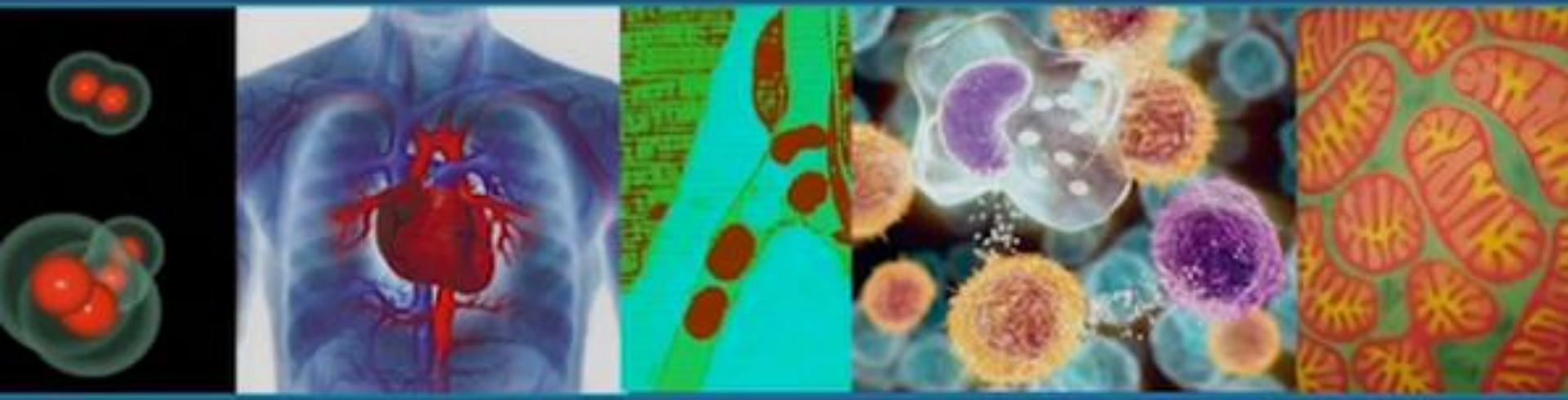
Where does this leave us????

- Surviving Sepsis, IHI, bundles, lawyers ...
  versus strong contrary evidence
- ideally need good quality RCTs – will this happen??
- my advice:
  - still treat early if patient deteriorating but STOP quickly (my practice 4–5 days for most infections)

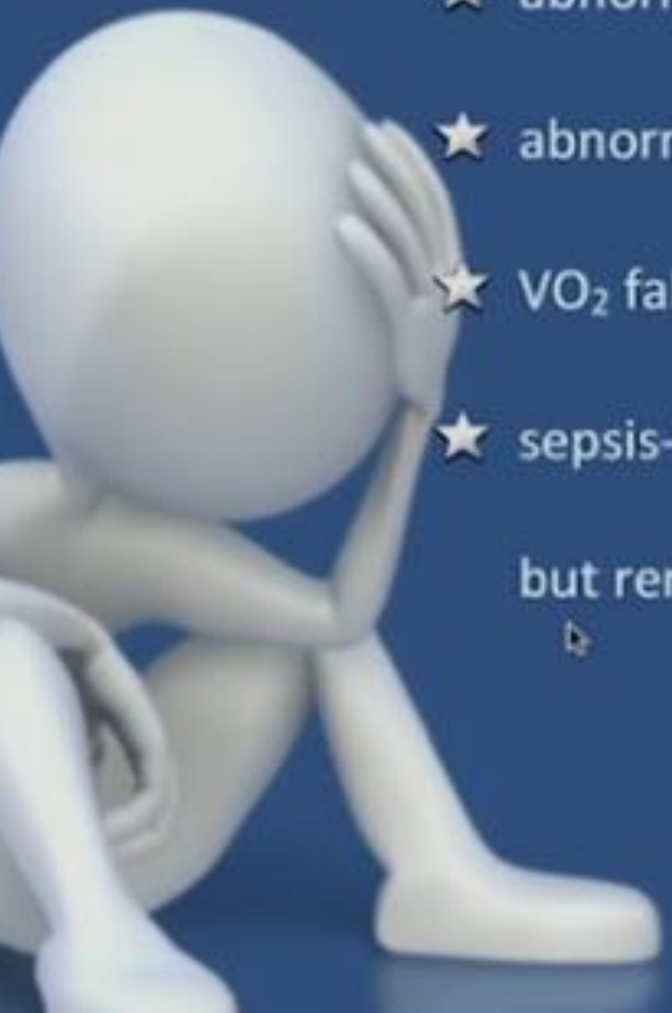
How do we get from inflammation to MOF?



What causes MOF?



Multiple organ failure, multiple paradoxes



- abnormal coagulation .. but minimal clots (even with DIC)
- abnormal microcirculation .. but normal/high tissue O_2
- VO_2 falls with increasing severity (& rises on recovery)
- sepsis-induced MOF characterized by functional 'failure'

  but remarkably little structural damage (cell death)

Organs look normal in patients dying of MOF ...

Hotchkiss RS, Karl IE. N Engl J Med 2003; 348:138-50

"An intriguing finding was discordance between histology findings and the degree of organ dysfunction in patients dying of sepsis"

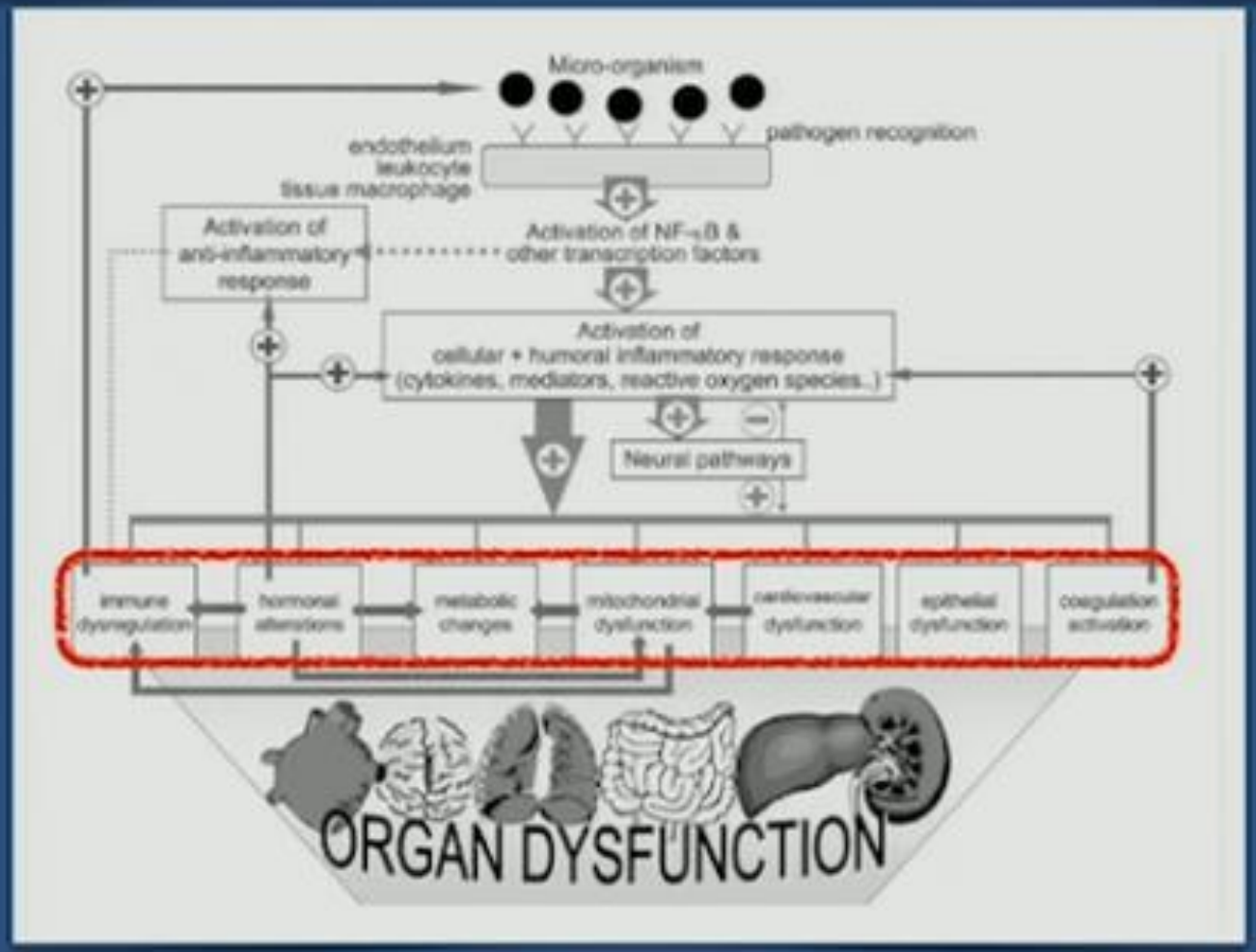
"Cell death in heart, kidney, liver, & lung was relatively minor & did not reflect the clinical evidence of more profound organ dysfunction

".. no evidence of injury to cardiac myocytes in patients with sepsis who had myocardial depression."

".. in patients with sepsis and acute renal failure only focal injury with preservation of normal glomeruli and tubules."

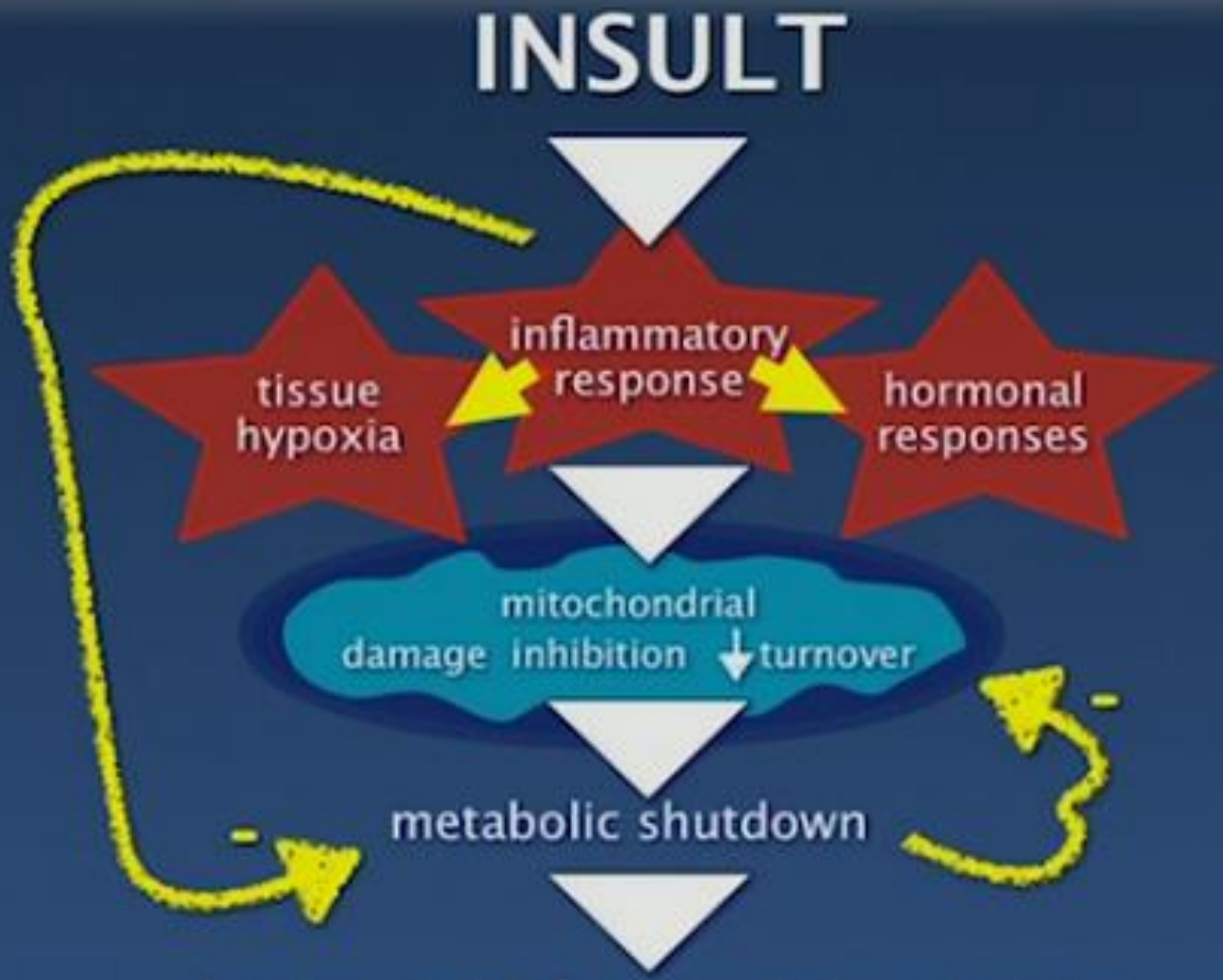
Mechanisms of sepsis-induced organ dysfunction

Edward Abraham, MD; Mervyn Singer, MD, FRCP



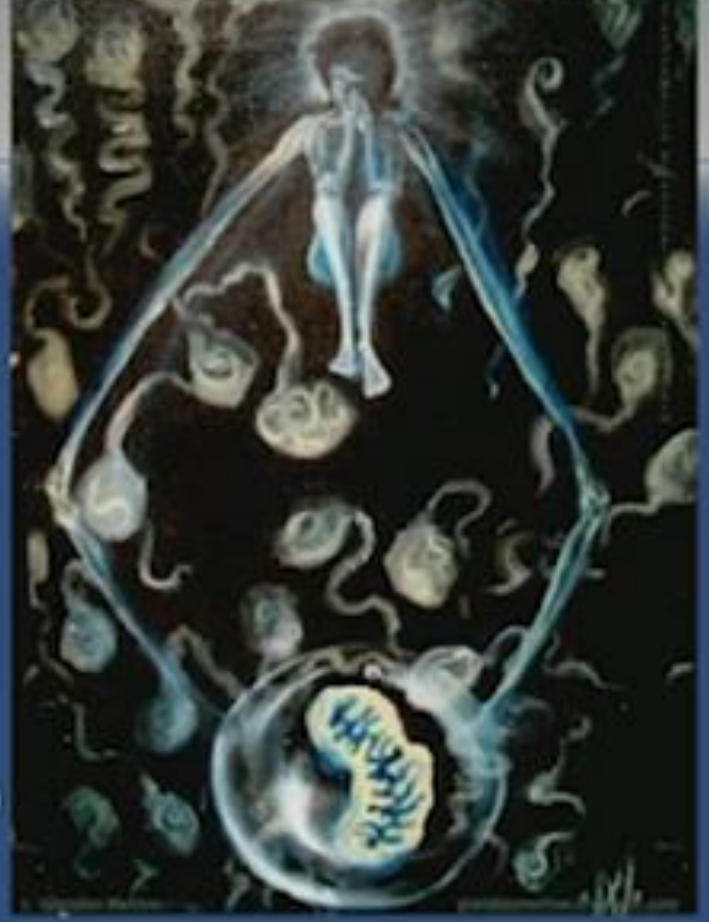
Crit Care Med 2007; 35:2408–2416

Is this how MOF happens?...



Δ: multiple organ failure

Mitochondria

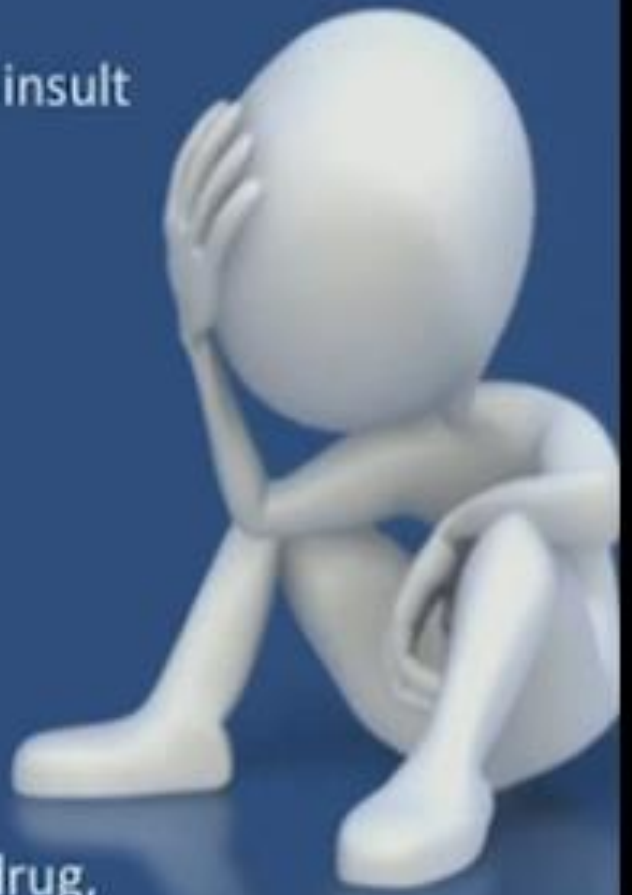


- ★ present in almost all cell types
- ★ primary provider of energy (ATP)
- ★ major provider of body heat
- ★ use >90% of total body VO_2
- ★ major source of free radicals in body
- ★ major target of nitric oxide (+ CO, H_2S)
- ★ major role in triggering cell death
- ★ major role in intracellular calcium regulation
- ★ major site of action & production of hormones (e.g.cortisol)
- ★ major role in lipid metabolism (e.g. HMG CoA reductase)
- ★ likely role in ageing


Less is best ...
Blood
gastric acid inhibitors
OXYGEN
parenteral nutrition
sedatives
inotropes
antibiotics
(immuno)nutrition
renal replacement therapy
Hyperglycaemia
PRESSORS
analgesics
mechanical ventilation

Final thoughts (1)

- we don't yet fully understand the pathophysiology
- over-extrapolation from animal models to man
  - generally give before, at, or soon after septic insult
  - .. to young, healthy animals
- in man:
  - wrong timing
  - wrong dosing
  - wrong duration
- one size cannot fit all
  - lack of bedside biomarkers to select correct drug, optimize dosing and duration



Final thoughts (ii)

- ★ outcomes are improving due to earlier recognition

  .. and less/better guided intervention ("first do no harm")

- ★ near-term future -> far superior diagnostics for early pathogen recognition and sepsis detection

  -> better guided treatment (type, dose, duration)

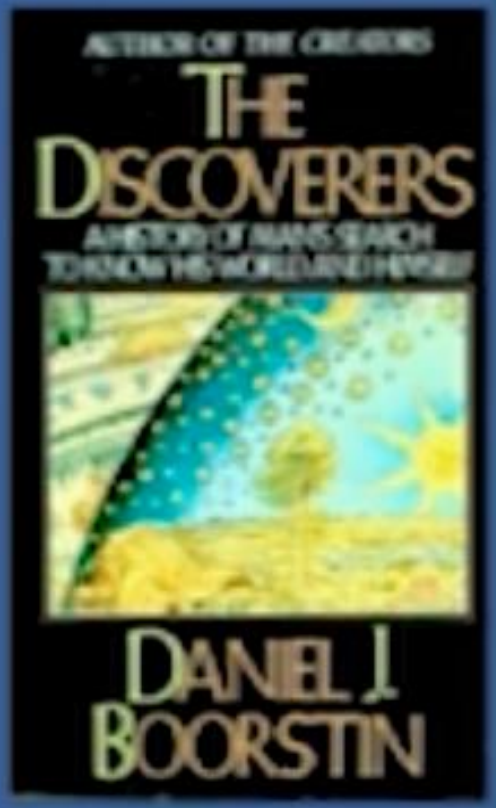
  -> better outcomes

- ★ theragnostics -'stratified medicine' to identify who should get immunomodulatory Rx, when, how much, and for how long

- ★ more attention on accelerating recovery and preventing the long-term sequelae of sepsis

Daniel J. Boorstin

"The greatest obstacle
to discovery is not ignorance
– it is the illusion of knowledge"



RAS EL TEEN Palace , Alexandria

Thank You