Sepsis – newer therapies in management

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Topics of discussion

- Sepsis pathophysiology
- Newer biomarkers
- Newer treatment options
  - Immunomodulators
    - Ivig/GM CSF/Steroids/PD-1,PD-L1/Heparin/TLR 4 inhibitors/Mw
  - Cytokine and endotoxin removal
    - PBFC/Cytosorb/CPFA/Haemofiltration
  - Misc
    - Beta blockers
    - VitC/Hydrocortisone/Thiamine
    - Naloxone

Background

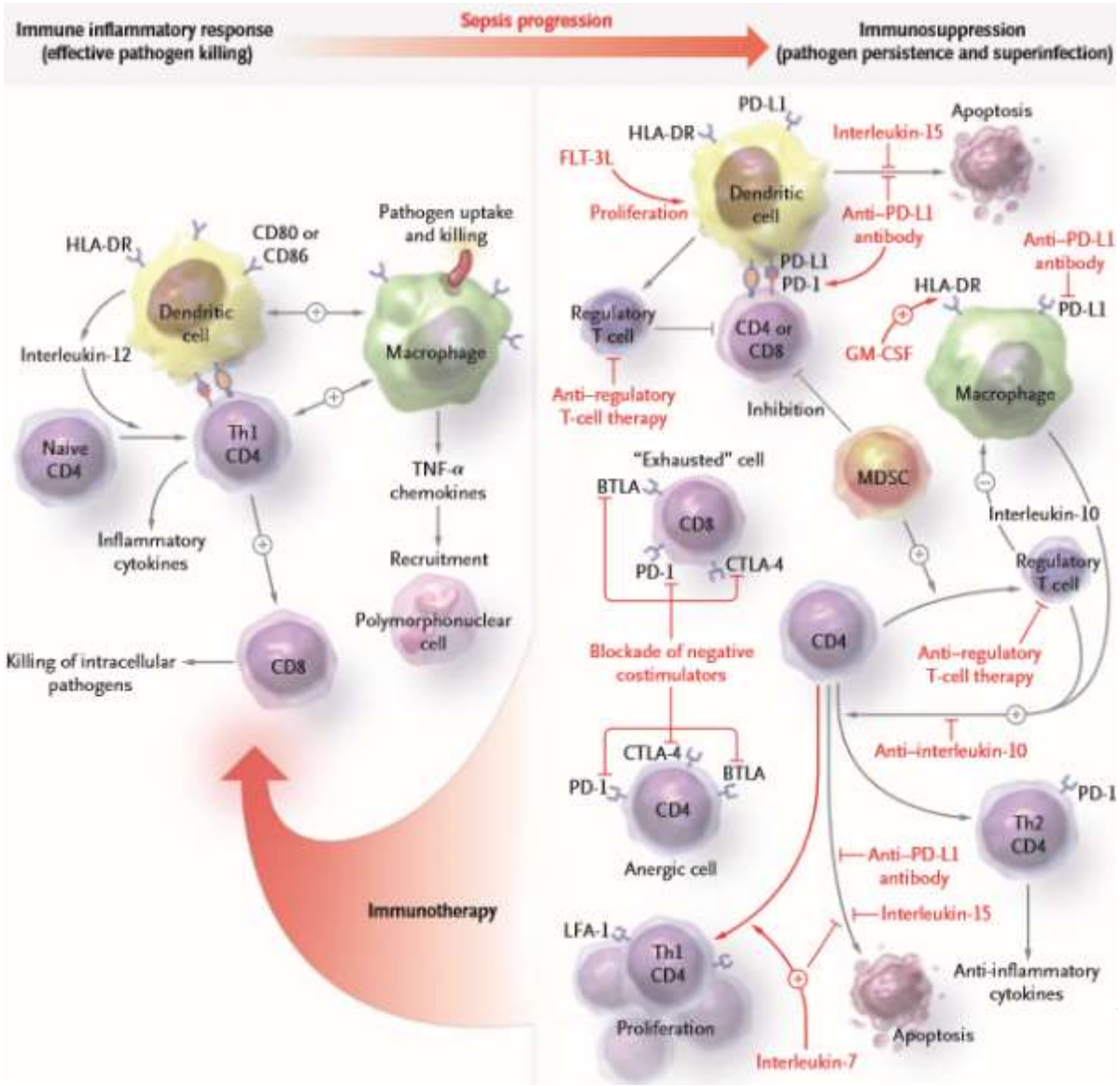
- In last 3 decades more than 200 different compounds were tested for sepsis
- Still no specific therapies have emerged
- Rely on source control, antibiotics and organ support

Sepsis definition

2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[1,3]

Singer et al, JAMA. 2016 Feb 23; 315(8): 801–810

Sepsis – pathogenesis



Increased apoptosis of dendritic cells and lymphocytes

Decreased expression of APC – HLA-DR

Increased expression of negative costimulatory molecules (PD1/PDL1/CTLA4/BTLA)

Regulatory T cells and MDSC are increased→ shift from Th1 to Th2

Sepsis – lab markers

- Lactate
- CRP
- D-dimer
- Procalcitonin
- Proadrenomedullin
- Cytokines

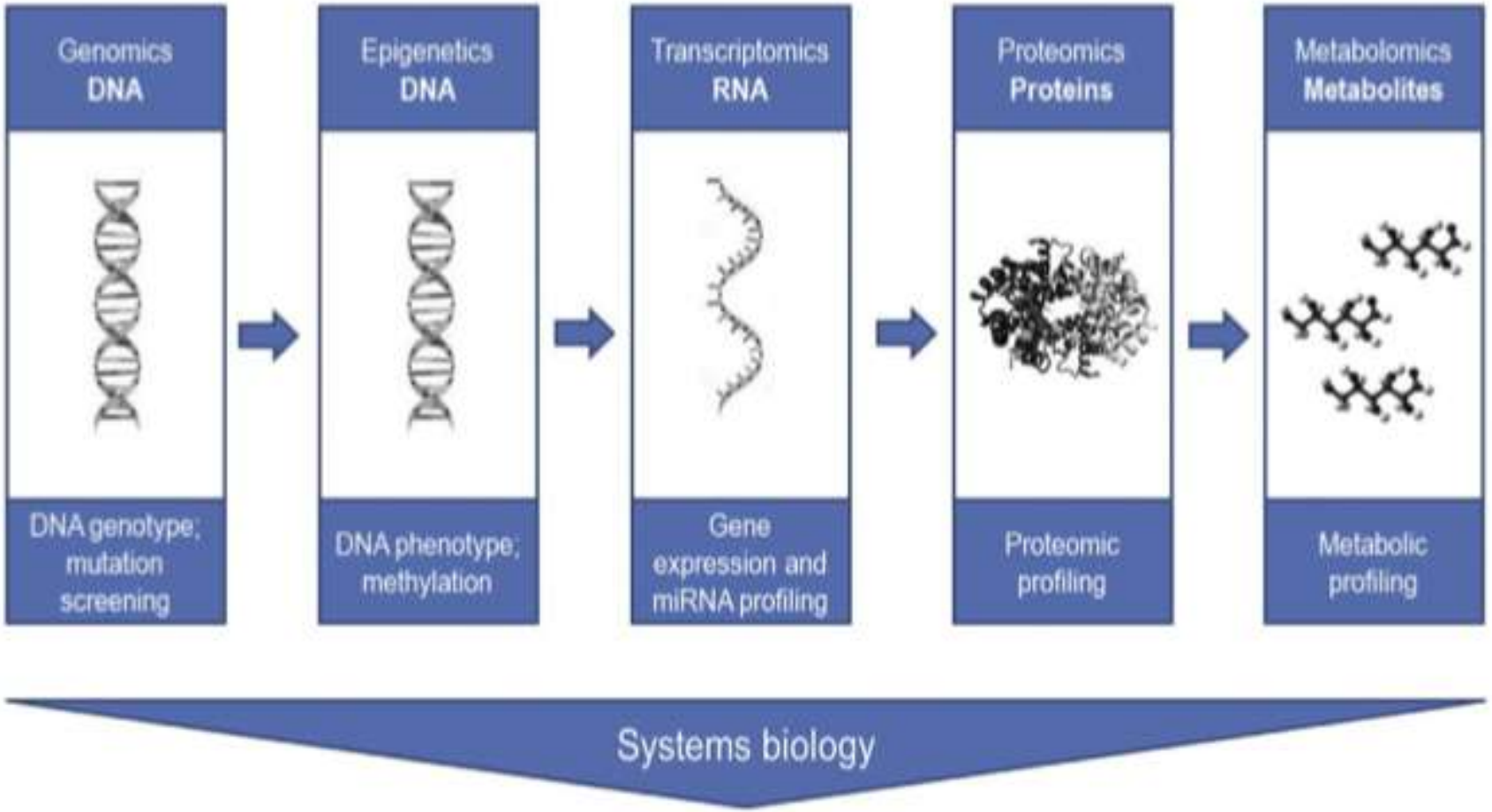
- Multimarker approach
- miRNA
- Omics based

Sepsis – biomarkers

- Blood cultures are positive in 30-40% of sepsis cases

- Biomarkers
  - Identifying sepsis
  - Differentiate between infective and non infective
  - In infective → bacterial vs viral
  - Prognostication

“OMICS”



- Omics is the characterization and quantification of molecules that translate into the structure, function, and dynamics of an organism

Differentiate between infectious and non infectious causes

- RNA biomarkers
  - SeptiCyte LAB
    - US FDA Approved
    - 4 genes (CEACAM4, LAMP1,PLA2G7 and PLAC8)
    - ROC – AUC 0.89 (95% CI, 0.85-0.93)
  - Sepsis MetaScore
    - 11 gene biomarker
    - AUC 0.87(range 0.70-0.98)
  - Newer – mRNA expression profiling
    - 3 upregulagted transcripts(TLR 5,protectin,clusterin)
    - 4 downregulated transcripts(fibrinogenlike2,IL7r, mHLA II, carboxypeptidase,vitellogeniclike)

van Engelen et al, Crit Care Clin 34 (2018) 139–152

To classify cause of illness

- Host gene expression profiling
- Peripheral whole blood gene expression from 273 subjects
- Acute RTI into bacterial/viral/non infectious
- Overall accuracy was 87%
  - Procalcitonin – 78% accuracy for bacterial Vs non bacterial

van Engelen et al, Crit Care Clin 34 (2018) 139–152

May help prognosticate

- Prospective cohort study of ICU patients with sepsis caused by CAP
- N=256
- Trnascriptomics defined 2 sepsis responsive signatures
  - SRS 1- Immunosuppressive phenotype
    - Features of endotoxin tolerance, T-cell exhaustion and downregulation of HLA class II
    - Had higher 14 day mortality; HR 2 ·4, 95% CI 1 ·3–4 ·5, p=0 ·005

Davenport EE et al, Lancet Respir Med. 2016 Apr; 4(4): 259–271

Newer modalities – treatment

- Reversing sepsis induced immunosuppression
- Removal of harmful mediators from blood by extracorporeal methods
- Protecting or restoring endothelial cell function

Intravenous immuno globulin

- These are blood products
- Specifically pooled sera derived from donor blood
- Polyclonal
- Monoclonal

Intravenous immuno globulin

Included 43 trials	
Polyclonal IVIG vs placebo or no treatment	25
Standard IVIG, adults -	10
IgM-enriched, adults -	7
Standard IVIG, neonates -	5
IgM-enriched, neonates -	3
Anti-endotoxins vs placebo	8
Anti-cytokines vs placebo	9
Monoclonal antibody to Enterobacteriaceae	1

Alejandria MM et al,Cochrane Database Syst Rev. 2013

Dose of ivig

Adults

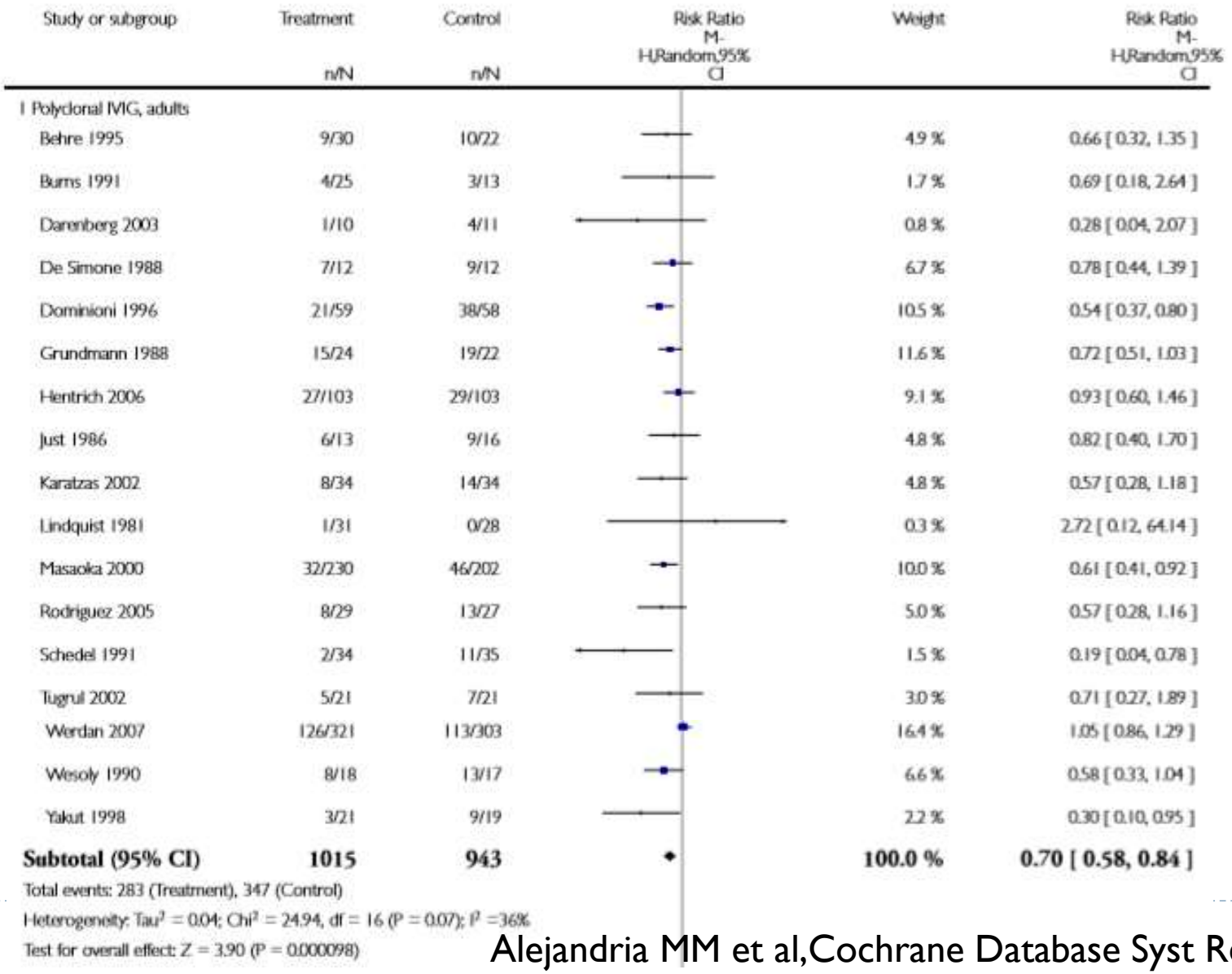
- 250 mg/kg over 2 days
- 400 mg/kg/day for 3 days
- 1 g/kg on first day f/b 500 mg/kg on D2 and D3
- IgM enriched ivIG → 1300 ml over 3 days

Neonates

- 500 mg/kg over 2 hours
- 1 g/kg for 3 days
- IgM enriched ivIG
  - 5 ml/kg/day for three days

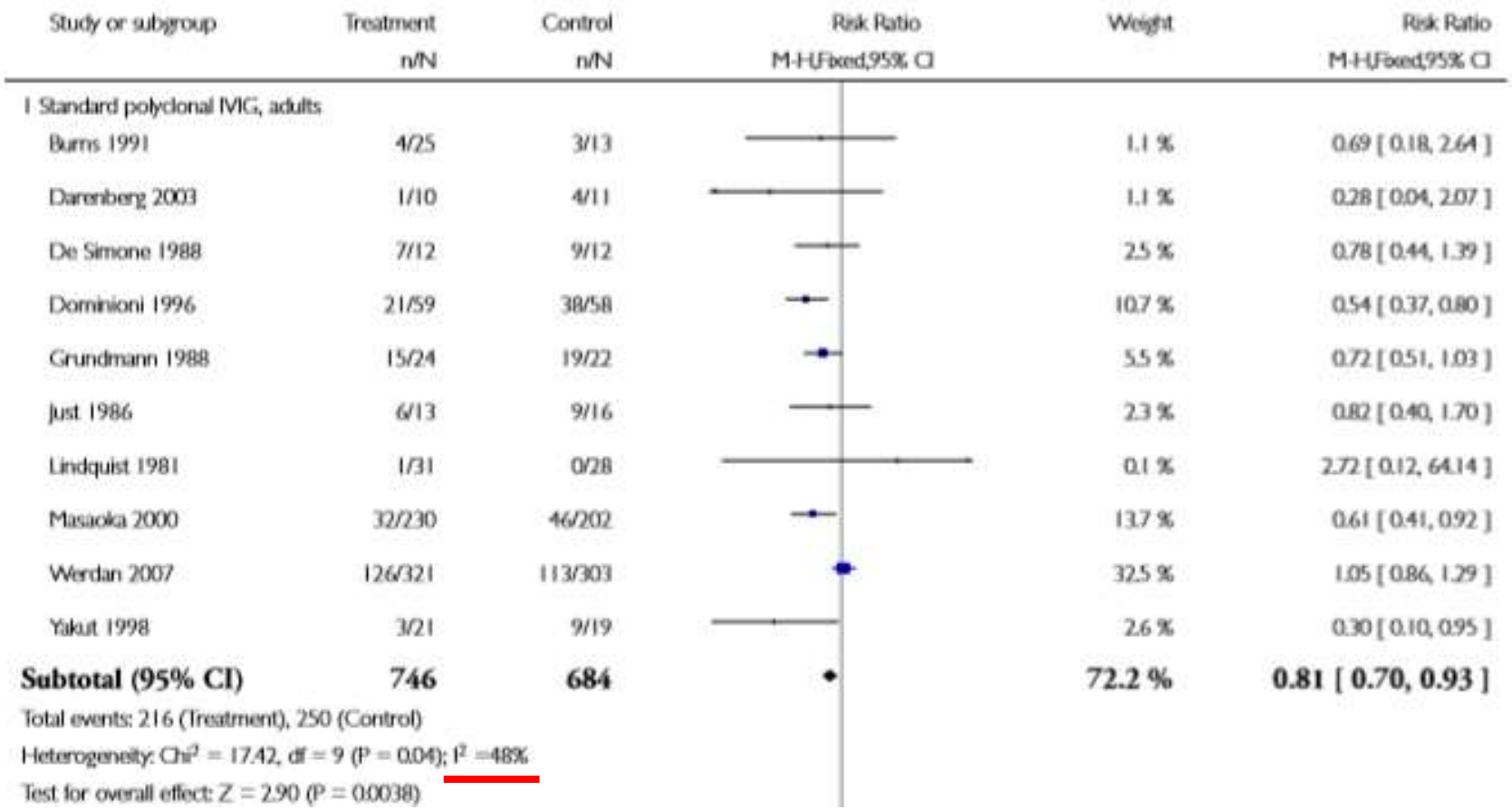
Alejandria MM et al,Cochrane Database Syst Rev. 2013

All ivig studies - adults



Alejandria MM et al,Cochrane Database Syst Rev. 2013

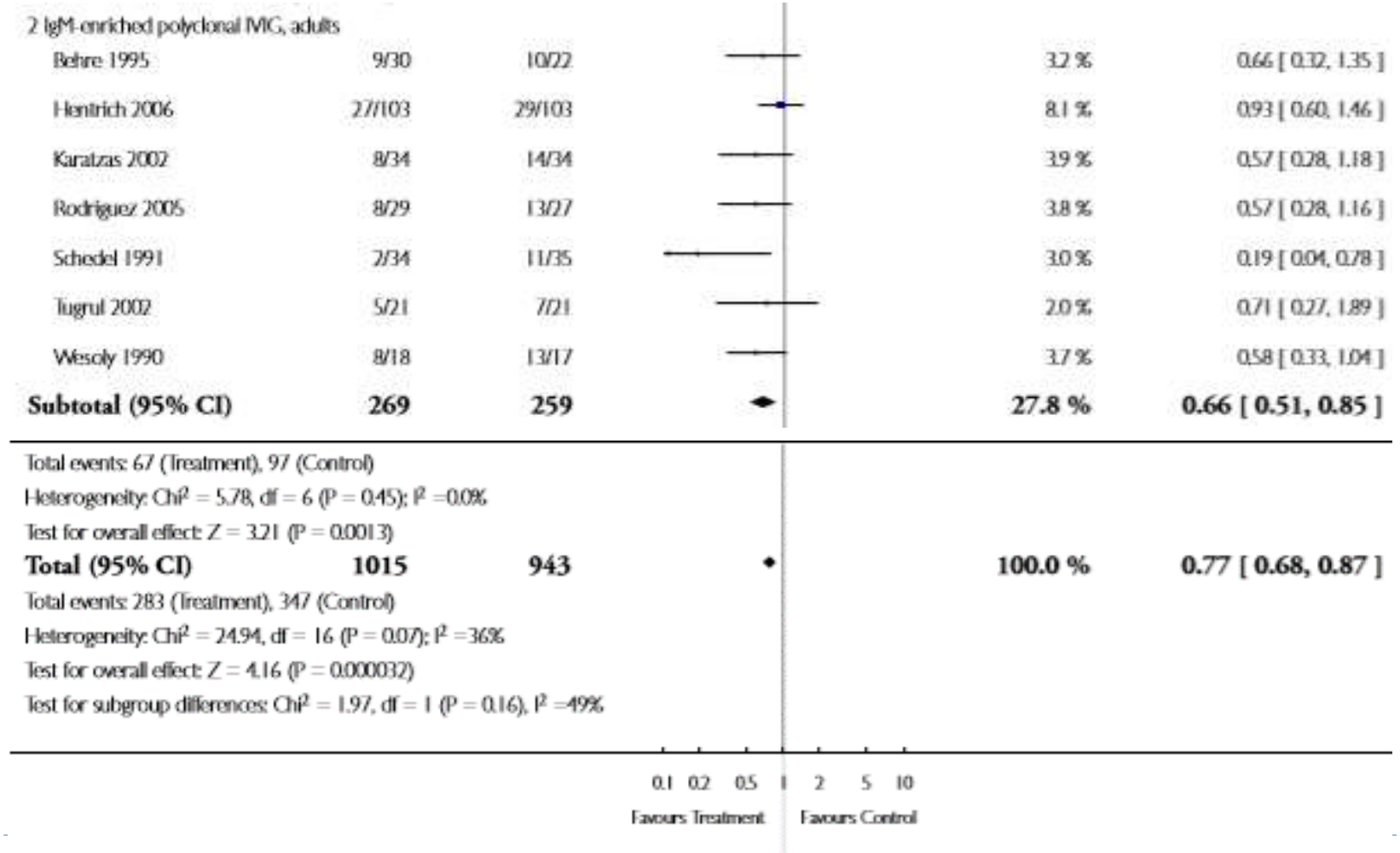
Adults – polyclonal ivig



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Standard polyclonal IVIG, adults					
Burns 1991	4/25	3/13		1.1 %	0.69 [0.18, 2.64]
Darenberg 2003	1/10	4/11		1.1 %	0.28 [0.04, 2.07]
De Simone 1988	7/12	9/12		2.5 %	0.78 [0.44, 1.39]
Dominioni 1996	21/59	38/58		10.7 %	0.54 [0.37, 0.80]
Grundmann 1988	15/24	19/22		5.5 %	0.72 [0.51, 1.03]
Just 1986	6/13	9/16		2.3 %	0.82 [0.40, 1.70]
Lindquist 1981	1/31	0/28		0.1 %	2.72 [0.12, 64.14]
Masaoka 2000	32/230	46/202		13.7 %	0.61 [0.41, 0.92]
Werdan 2007	126/321	113/303		32.5 %	1.05 [0.86, 1.29]
Yakut 1998	3/21	9/19		2.6 %	0.30 [0.10, 0.95]
Subtotal (95% CI)	**746**	**684**		**72.2 %**	**0.81 [0.70, 0.93]**
Total events: 216 (Treatment), 250 (Control)					
Heterogeneity: Chi^2 = 17.42, df = 9 (P = 0.04); I^2 =48%					
Test for overall effect: Z = 2.90 (P = 0.0038)					

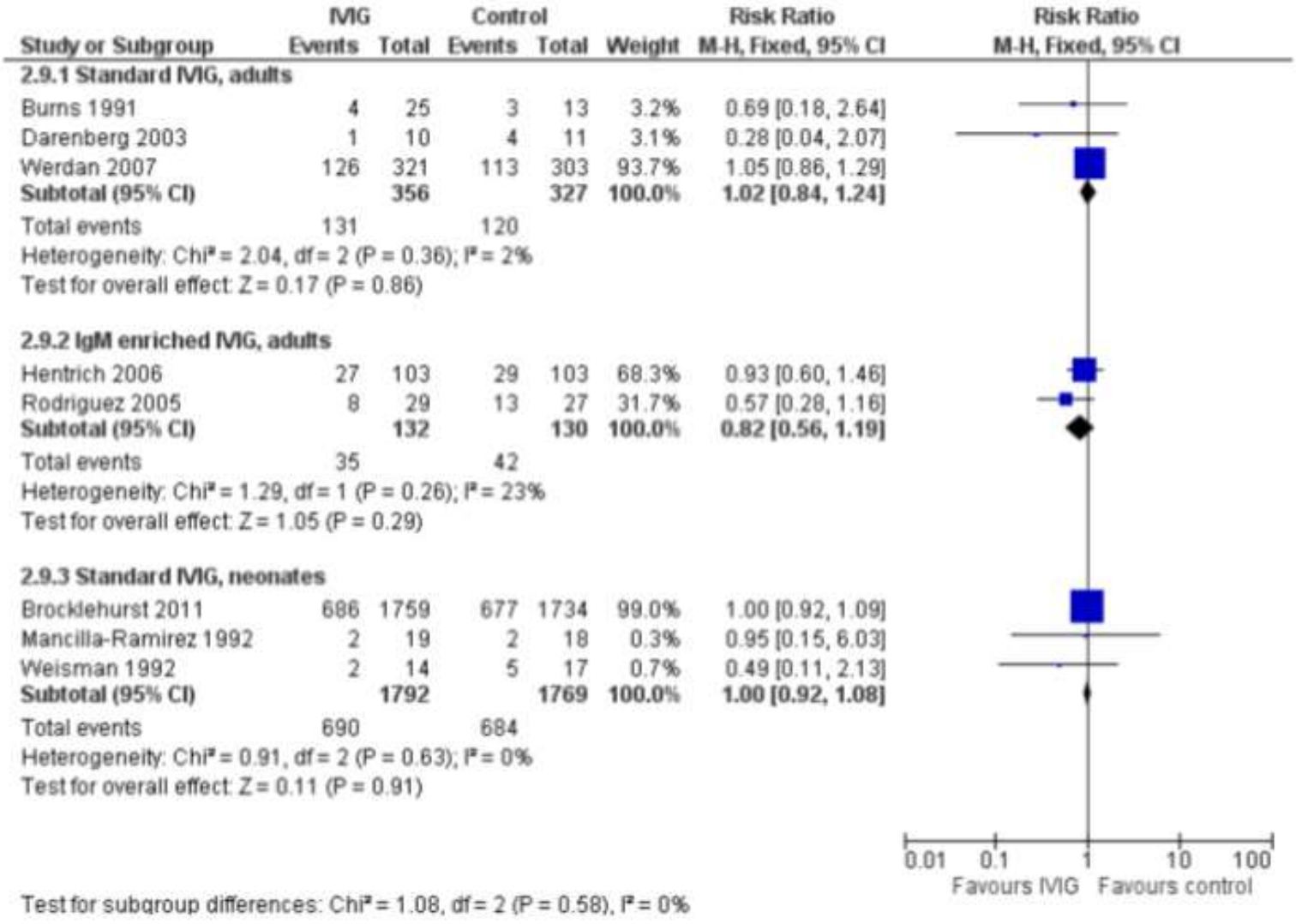
Alejandria MM et al,Cochrane Database Syst Rev. 2013

Adults – IgM enriched



Alejandria MM et al,Cochrane Database Syst Rev. 2013

Figure 4. Polyclonal IVIG versus placebo or no intervention, outcome: all-cause mortality by type of polyclonal IVIG, sensitivity analysis low risk of bias trials.



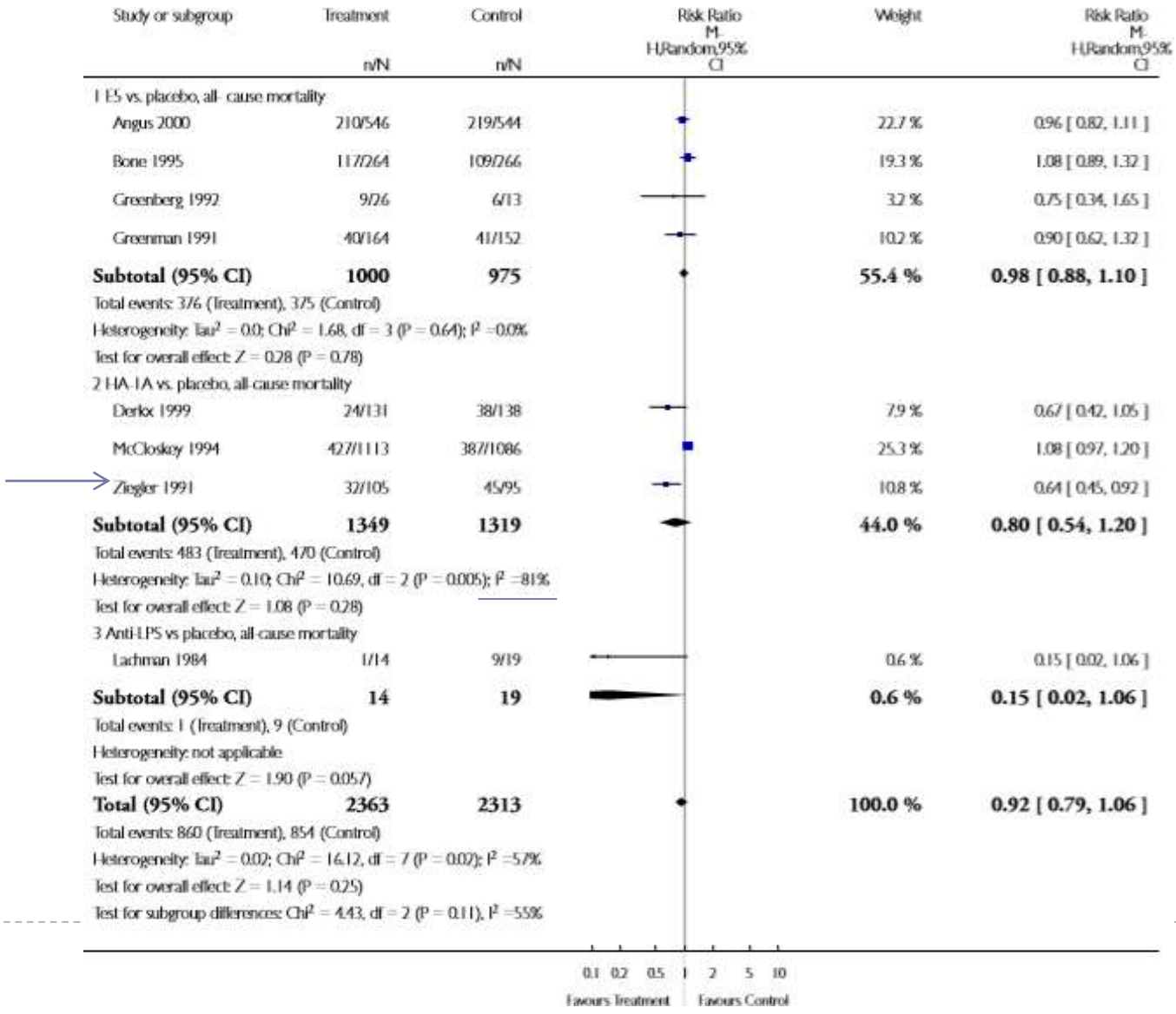
Alejandria MM et al,Cochrane Database Syst Rev. 2013

Result

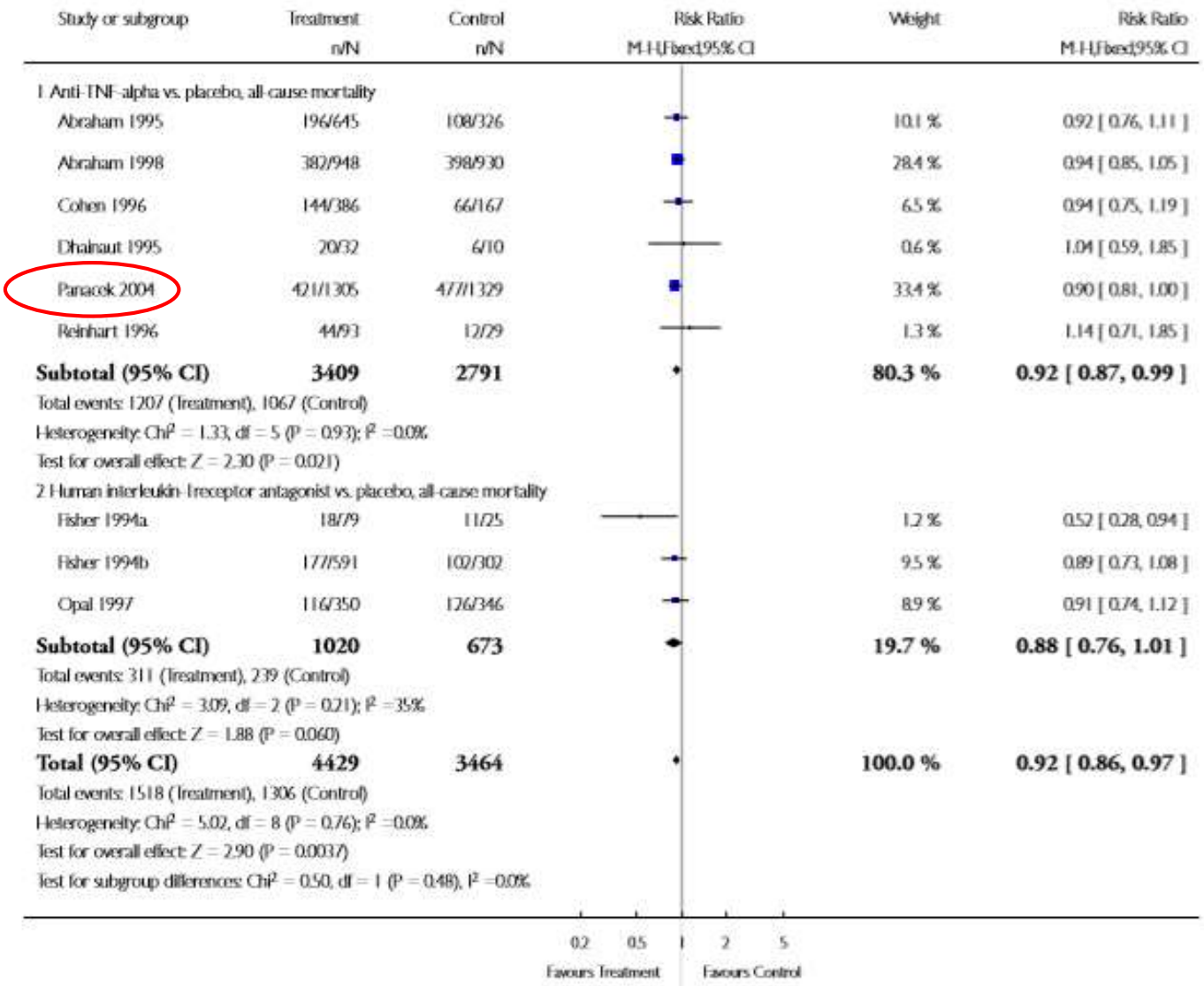
- Neonates
  - No benefit
- Monoclonal antibodies to Enterobacteriacea
  - No benefit
- Anti endotoxins
- Anti cytokines

Alejandria MM et al,Cochrane Database Syst Rev. 2013

Anti endotoxins



Anti cytokines – mortality



Alejandria MM et al,Cochrane Database Syst Rev. 2013

Role of ivig

- At present no strong evidence to support its role
- Larger RCT on IgM enriched ivIG is needed

GM CSF

- How does it help ??
- In state of immunoparalysis
  - Increase HLA DR expression

		Populn	Dose	Benefits	Comments
Presneill JJ et al[1]	RCT, n= 18	≥2 SIRS and paO2 < 60 mmHg at room air or p/F < 287	3mcg/kg iv X 5 days	p/f ratio improved over 5 days	No decrease in 30 day mortality /Duration of ICU stay
Orozco H et al[2]	RCT, n= 58	Generalized peritonitis post surgery and positive peritoneal cultures	3mcg/kg sc X 4 days	Reduced length of stay (9 Vs 13) Duration of antibiotic therapy(9 Vs 13) No of infectious complications(6 Vs 16) All p<0.05	No decrease in mortality
Meisel C et al[3]	RCT, n=38	severe sepsis or septic shock and sepsis induced immunosuppression (mHLA-DR < 8,000 /(mAb)/cell X 2)	4mcg/kg sc X 8 days (8mcg/day)	Shorter duration of MV (148 Vs 207 hours) Shorter hospital stay (59 Vs 69 days) Shorter ICU stay (41 Vs 52 days)	No differcence in mortality/ RRT/ noradr requirement Had increased HLA-DR and TLR cytokines

1- Presneill JJ et al, Am J Respir Crit Care Med. 2002;166(2):138
2- Orozco H et al, Arch Surg. 2006;141(2):150
3- Meisel C et al, Am J Respir Crit Care Med. 2009;180(7):640

GM CSF

- All of these are small studies
- Larger clinical trials are required
  - Multicenter phase III trial is ongoing on patients of sepsis or septic shock (NCT02361528)
- Cannot be recommended at present

Mw

- Sepsis is characterized by initial phase of cytokine storm followed by immune paralysis
- LPS combines with TLR4 receptor
- This initiates two antagonizing pathways
  - MyD88 → proinflammatory
  - TRIF → antiinflammatory

- Mw acts as an immunomodulator acting via TLR4 pathway by involvement of MyD88

In initial study of 50 patients

Table 3
Primary and secondary outcomes of the study

	Mw	Control	Total	*P*
Primary outcome				
Mortality, no. (%)	7 (28)	8 (32)	15 (30)	.505
Secondary outcomes				
→ Days on ventilator	6 (3-7)	9 (5-14)	7 (4-10)	.025
Days on vasopressor drugs	2 (2-3)	3 (2-4)	3 (2-4)	.075
→ Delta SOFA	0 (0-4)	4 (0.5-4.5)		.027
→ ICU length of stay, d	7 (5-10)	12 (9-17)	9 (5-14)	.006
→ Hospital length of stay, d	10 (7-12)	16 (10-20)	12 (8-18)	.007
→ Secondary infection, no. (%)	5 (20)	14 (56)	19 (38)	.009
VAP, no. (%)	5(20)	12 (48)	25 (50)	.037
CRBSI, no. (%)	2 (8)	6 (24)	8 (16)	.123

Sehgal IS,et al, JCritCare(2014) . jcrc.2014.08.012

In next study, Mw(31) & control (29)

Outcomes	Mw (%)	Control (%)	P value
Mortality, n (%)	2 (6)	7 (24)	0.055
Days on mechanical ventilation	6.6 (6.4)	5 (4.6)	0.260
Days on vasopressor drugs	3.4 (4.8)	3.2 (3.9)	0.853
Delta SOFA	1.09 (2.10)	1.1 (1.54)	0.989
ICU length of stay	5 (5.4)	5.4 (4.66)	0.746
Hospital length of stay	15.7 (7.7)	13.4 (6.7)	0.223
Secondary infection	8 (26)	6 (21)	0.558

TLR 4 inhibition

Study	Type	Included pts	Dose	Result	Comments
Opal et al[1]	Multicenter RCT (197 ICU) N=1961	Severe sepsis within 12 hrs of first organ dysfunction	Eritoran 105 mg vs placebo	No differences in 28 day mortality 1 year mortality	No benefit
Rice et al[2]	Multicenter RCT (93 ICU) N= 274	Severe sepsis and shock or respiratory failure	Placebo 200 mg loading f/b 1.2mg/kg/d 2.4 mg/kg/d	No change in IL6 level 28 day mortality 24% VS 22% Vs 17% (p=0.26)	Mortality was low with high dose group but was not significant statistically AE – Methhaemoglobinemia (30.1%)

1-Opal SM et al, JAMA. 2013 Mar;309(11):1154-62
2 -Rice TW et al, Crit Care Med. 2010;38(8):1685

PD-1 and PD-L1

- Negatively regulate immnue system
- Patients with septic shock had increased expression Vs trauma and healthy volunteers
  - In CD4 T cells and monocytes
- Associated with
  - reduced survival
  - greater incidence of secondary nosocomial infections

Boomer JS et al, Crit Care. 2012 Jun 28;16(3):R112

Observational study

- In prospective observational study of 29 healthy controls, 59 patients with sepsis and 76 septic shock patients
- Blood samples obtained on D3-4 of sepsis and analysed PD1 and PD-L1 expression

Baseline Characteristics

Table 1 Baseline characteristics of the patients

Parameters	Control	Sepsis	Septic shock	*P* value
Number	29	59	76	–
Age (years)	68 (66–75)	71 (66–78)	71 (61–78)	0.497
Male, n (%)	18 (62.1 %)	32 (54.2 %)	37 (48.7 %)	0.458
WBC ($\times 10^9$/L)	6.9 (5.6–7.9)	13.3 (10.9–17.8)	14.9 (11.8–17.2)	<0.001
Lymphocyte ($\times 10^9$/L)	2.8 (2.4–3.1)	1.06 (0.73–1.63)	0.76 (0.54–1.07)	<0.001
SOFA score	0	5 (3–7)	11 (9–14)	<0.001
SAPS II	12 (12–15)	26 (24–32)	53 (46–60)	<0.001
Percentage of PD-1$^+$/CD4$^+$ T cells (%)	26.2 (23.2–29.9)	34.1 (28.4–44.4)	38.2 (29.2–47.7)	<0.001
MFI of PD-1 on CD4$^+$ T cells	6.3 (5.8–6.8)	7.1 (5.2–9.2)	7.5 (6.0–9.4)	0.008
Percentage of PD-1$^+$/CD8$^+$ T cells (%)	22.6 (18.7–28.2)	31.6 (23.9–46.6)	36.5 (27.3–51.3)	<0.001
MFI of PD-1 on CD8$^+$ T cells	5.9 (4.8–6.6)	6.4 (4.2–7.5)	6.6 (4.9–8.4)	0.181
Percentage of PD-L1$^+$/CD4$^+$ T cells (%)	18.2 (12.3–22.6)	21.5 (16.5–30.5)	21.0 (9.3–30.6)	0.021
MFI of PD-L1 on CD4$^+$ T cells	1.8 (1.6–2.2)	1.8 (1.6–2.6)	1.8 (1.5–2.0)	0.230
Percentage of PD-L1$^+$/CD8$^+$ T cells (%)	22.6 (17.1–26.2)	18.8 (14.9–37.6)	19.5 (10.3–37.4)	0.645
MFI of PD-L1 on CD8$^+$ T cells	1.5 (1.4–1.7)	1.6 (1.2–2.1)	1.5 (1.4–1.8)	0.596
Percentage of monocytes expressing PD-L1 (%)	12.9 (10.4–15.3)	29.2 (12.1–43.9)	35.9 (20.4–54.7)	<0.001
MFI of PD-L1 on monocytes	3.4 (3.0–3.9)	4.5 (2.2–7.5)	8.3 (7.7–9.7)	<0.001

May help in prognosticating

Table 3 Area under the curve of various parameters for predicting 28-day mortality in patients with septic shock

Variable	AUC	*P* value	95 % Confidence interval	
			Lower limit	Upper limit
Percentage of monocytes expressing PD-L1	0.729	0.001	0.607	0.852
MFI of PD-L1 on monocytes	0.681	0.009	0.548	0.813
SAPS II	0.768	<0.001	0.653	0.883
SOFA score	0.736	0.001	0.610	0.863
Percentage of PD-L1 on monocytes + SAPS II	0.891	<0.001	0.807	0.976
MFI of PD-L1 on monocytes + SAPS II	0.881	<0.001	0.797	0.965
Percentage of PD-L1 on monocytes + SOFA score	0.829	<0.001	0.713	0.944
MFI of PD-L1 on monocytes + SOFA score	0.799	<0.001	0.682	0.917

AUC area under the curve, *MFI* mean of fluorescence intensities, *PD-L1* programmed cell death receptor ligand-1, *SAPS II* simplified acute physiology score II, *SOFA* sepsis-related organ failure assessment

Further …

- Anti PD-1 and anti PD-L1 antibodies have shown to benefit in mouse sepsis model[1,2]
  - Improve immune function
  - Survival

- RCTs are being done in patients of sepsis according to biomarker identified subgroups
  - Phase I &II (NCT02576457,NCT02960854)

1-Shindo Y et al, J Surg Res. 2017 Feb;208:33-39
2-Zhang Y et al, Crit Care. 2010;14(6):R220

Other Immunostimulants

	MOA	Previous evidence	Ongoing trials (phase II)	
IFN gamma	Secreted by Th and NK cells Reduced in sepsis	In series of invasive fungal infections, adjunctive IFN restored immune function	Ongoing trial to determine its effects on sepsis related immunoparalysis (NCT01649921)	Previous trial in unselected patients → there was no benefit
IL 7, IL 15	Activate T cells,NK cells, dendritic cells	Previous trials in animal model improved survival	NCT 02797431 NCT02640807	

Vincent JL et al, Crit Care Clin 34 (2018) 161–173

Role of corticosteroids in sepsis

	Population	Intervention	Result
Annane[1] (2002)	299 patients with septic shock (< 3 hours) and MV	Hydrocortisone 50 mg q 6 hourly + Fludrocortisone 50 microgram tablet for 7 days	**Mortality benefit seen at day 28** Reduced inotropic requirement, reduced ICU stay, reduced hospital stay
CORTICUS TRIAL[2] (2008)	499 patients with septic shock < 72 hours	Hydrocortisone 50mg q 6 hourly for 5 days, then 12 hourly from 6 to day 8 , then 24 hourly from day 9 to day 11	**No mortality benefit at day 28** Reduced inotropic requirement seen

1-Annane D et al,JAMA. 2002 Aug 21;288(7):862-71
2-Toma A et al, CJEM. 2011 Jul;13(4):273-6

	Population	Intervention	Result
HYPRESS TRIAL[1] (2016)	353 sepsis patients (SIRS≥ 2) lasting < 48 hours and not yet progressed to shock	Hydrocortisone infusion 200 mg /day for 5 days	**No significant difference** between placebo and steroids in preventing progression to septic shock **No mortality benefit at day 28** **No benefit in length of stay**
ADRENAL[2] (2018)	3658 patients with septic shock requiring MV < 24 hours (SIRS > 2 + evidence of infection used to define sepsis)	Hydrocortisone infusion 200 mg/day for 7 days	**No mortality benefit at day 90** Reduced duration of shock, increased ventilator free days, reduced ICU stay
APROCCHSS[3] (2018)	1241 patients ≤ 7 days with septic shock ≤ 24 hours, with ≥ 1 infections, with ≥ 2 organ failures (SOFA score ≥ 3)	Hydrocortisone 50 mg iv Q6H + fludrocortisone as 50 µg tab OD for 7 days	**Mortality benefit at 90 day (ARR 6%,NNT 15)** Early weaning from vasopressors, MV, resolution of organ failure

1-Keh D et al, JAMA. 2016 Nov 1;316(17):1775-1785
2-Venkatesh B et al, N Engl J Med. 2018 Mar 1;378(9):797-808
3-Annane D et al, N Engl J Med 2018; 378:809-818

Steroid in sepsis – RICU

- Continue with existing policy to use in double inotrope requiring shock
- But to use combined hydrocortisone and fludrocortisone as per APROCCHSS trial

Cytokine & Endotoxin Removal

- Hemoperfusion through adsorptive materials
- Plasma or whole blood exchange
- Coupled plasma filtration adsorption (CPFA)
- Haemofiltration

Cytokine And Endotoxin Removal

- Perfusion of blood through adsorptive membranes or sorbent containing cartridges can remove harmful circulating cytokines and endotoxin
  - PBFC
  - CytoSorb

Cytokine Adsorbing Columns

- Contain porous, adsorbent polymer beads that target molecules up to 50,000 Da
- IL-1, IL-6, TNF, and IL-10
- Polymer beads are slightly larger than a grain of salt and are compatible with blood

CytoSorb

- Have enormous surface (8,500 m2) when compared with that of classical CRRT membranes (1.5 m2)
- CytoSorb cartridge contains 10 g of polystyrene divinylbenzene copolymer beads with a biocompatible polyvinylpyrrolidone coating
- Each bed is 300–800 μm in size
- Each gram of material has a surface of 850 m2

Honore PM et al,ASAIO J. 2013 Mar-Apr;59(2):99-106

CytoSorb-Animal study

- Rats were subjected to cecal ligation and puncture (CLP)
- This protocol is associated with a control group mortality of 70–90% at 48 hrs
- 20 hrs later were randomized to receive either hemoadsorption (n= 17) or sham treatment(n= 16)

Peng ZY et al, Crit Care Med. 2008 May;36(5):1573-7

CytoSorb

- After 3 hours → treatment was stopped
- Observed for 9 hours
- Surviving animals were killed at 9 hours

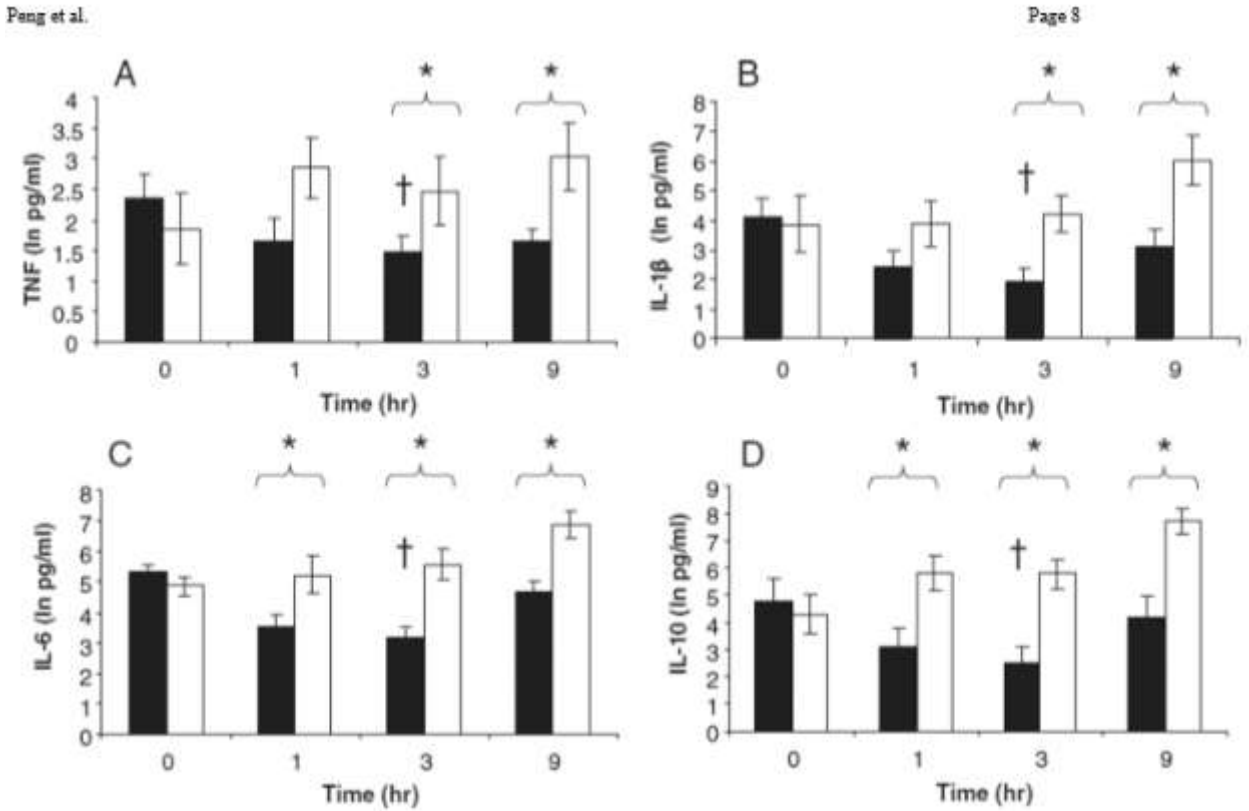
Peng ZY et al, Crit Care Med. 2008 May;36(5):1573-7

Effect on cytokines

Level of cytokines had decreased after 1 hour of treatment

At 9 hours level of cytokines had increased compared to at 3 hours

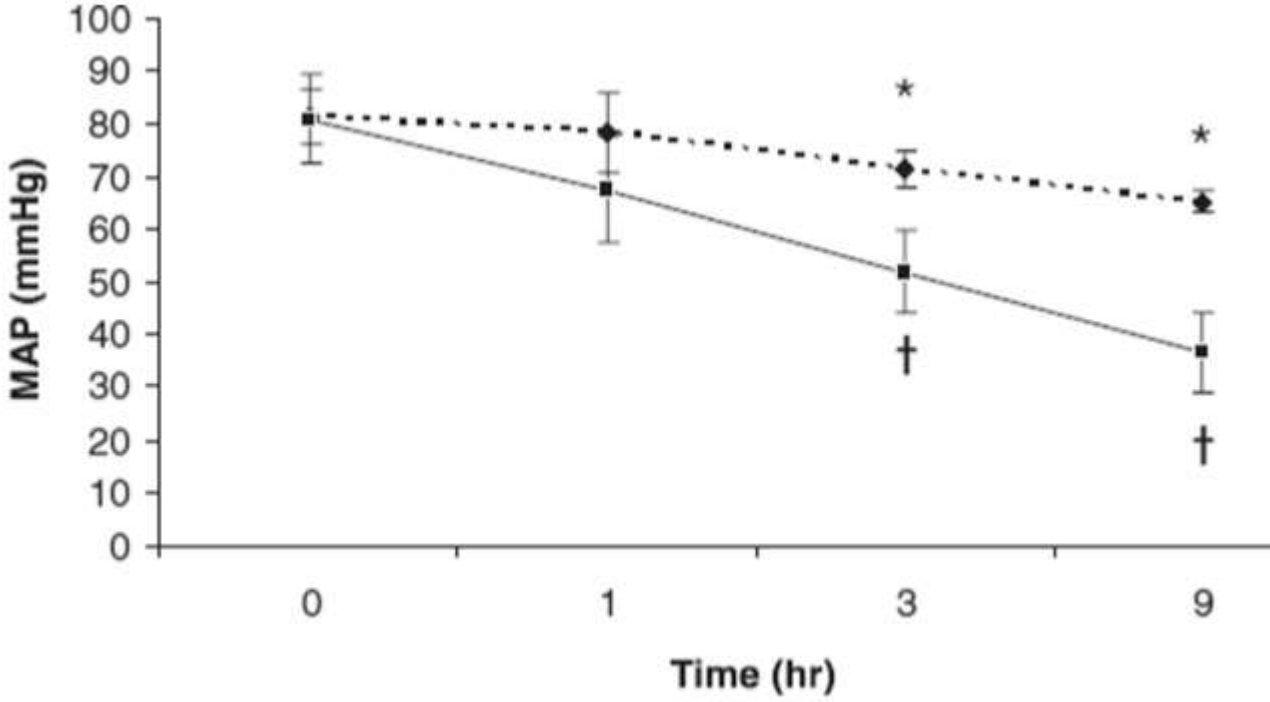
P<0.05



Peng ZY et al, Crit Care Med. 2008 May;36(5):1573-7

Effect on MAP

- MAP gradually decreased in the sham group
- 3 hours : MAP (71.40 vs. 52.00 mmHg)
- 9 hours : MAP (65.25 vs. 36.50 mmHg)
- P<0.05

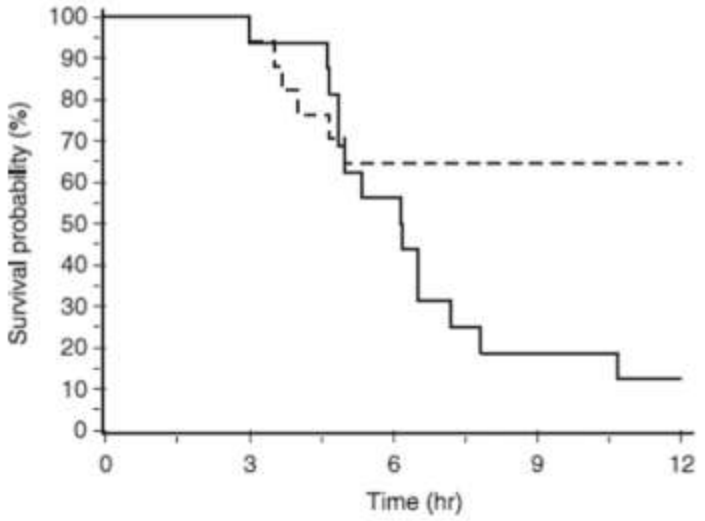


Peng ZY et al, Crit Care Med. 2008 May;36(5):1573-7

Effect on survival

Mean survival time : 720 vs. 381 mins, p = 0.02

Overall survival : 11/17 vs. 2/16;HR: 2.87 [95% CI,1.19 to 7.26], p < .01



Peng ZY et al, Crit Care Med. 2008 May;36(5):1573-7

Pilot study in humans

- Multicenter RCT of 43 patients
- 18 treated; 25 controls
- Included subjects : Severe sepsis and ALI
- Haemoperfusion by Cytosorbents at flow rate of 200 – 300 ml/ min for 6 hours/day for 7 days

Schadler D et al ,Am J Respr Crit Care Med , 2013, pp.A5241

Pilot study in humans

	Treatment	Control	P value
Septic shock	94%	100%	0.42
ARDS	67%	56%	0.33
Renal Failure	39%	24%	0.54

Schadler D et al Am J Respr Crit Care Med , 2013, pp.A5241

CytoSorb-Cytokines

	Decreased by	P value
IL6	- 49.1%	0.01
MCP -1	- 49.5 %	0.002
IL-1ra	- 36.5 %	.001
IL 8	- 30.2%	.002

28 day mortality : 28 % vs 24 % ,p= 0.84
60 day mortality : 39 % vs 32 % , p=0.75

Schadler D et al Am J Respr Crit Care Med , 2013, pp.A5241

Role of cytosorb ?

- May reduce cytokine levels
- But mortality benefit has to be assessed in large scale studies

PBFC

- Polymyxin B - strong affinity to endotoxin
- Clinically applied adsorbent column (Toraymyxin 20-R)
- 5 -7 mg of polymyxin B/gram of polystyrene fiber
- Containing 53 g of polysterene fiber bound covalently to 370 mg of PMX

Vincent et al Shock. 2005;23(5):400

		Population	Intervention	Result (PBFC Vs Control)
Cruz DN et al	Multicenter RCT n= 64 patients	Severe sepsis or septic shock due to intra abdominal infection (post surgery)	For 2 X 2 hours, 24 hours apart, within 24 hrs of Sx	28 day mortality 32% Vs 53% (HR, 0.36; 95% CI, 0.160.80; P=.01) Early improvement in SOFA score/,inotrope and p/F ratio
Iwagami M et al	Propensity matched reteospectiv e analysis N= 1180	nontraumatic perforation of the lower GIT,following surgery and requiring inotropic support	Who underwent PBFC on day 0,1 (maximum of 2 sessions)	No difference in 28 day mortality No difference in noradrenaline requirement, organ dysfunction

1-Cruz DN et al, JAMA. 2009;301(23):2445
2-Iwagami M et al, Crit Care Med. 2014;42(5):1187

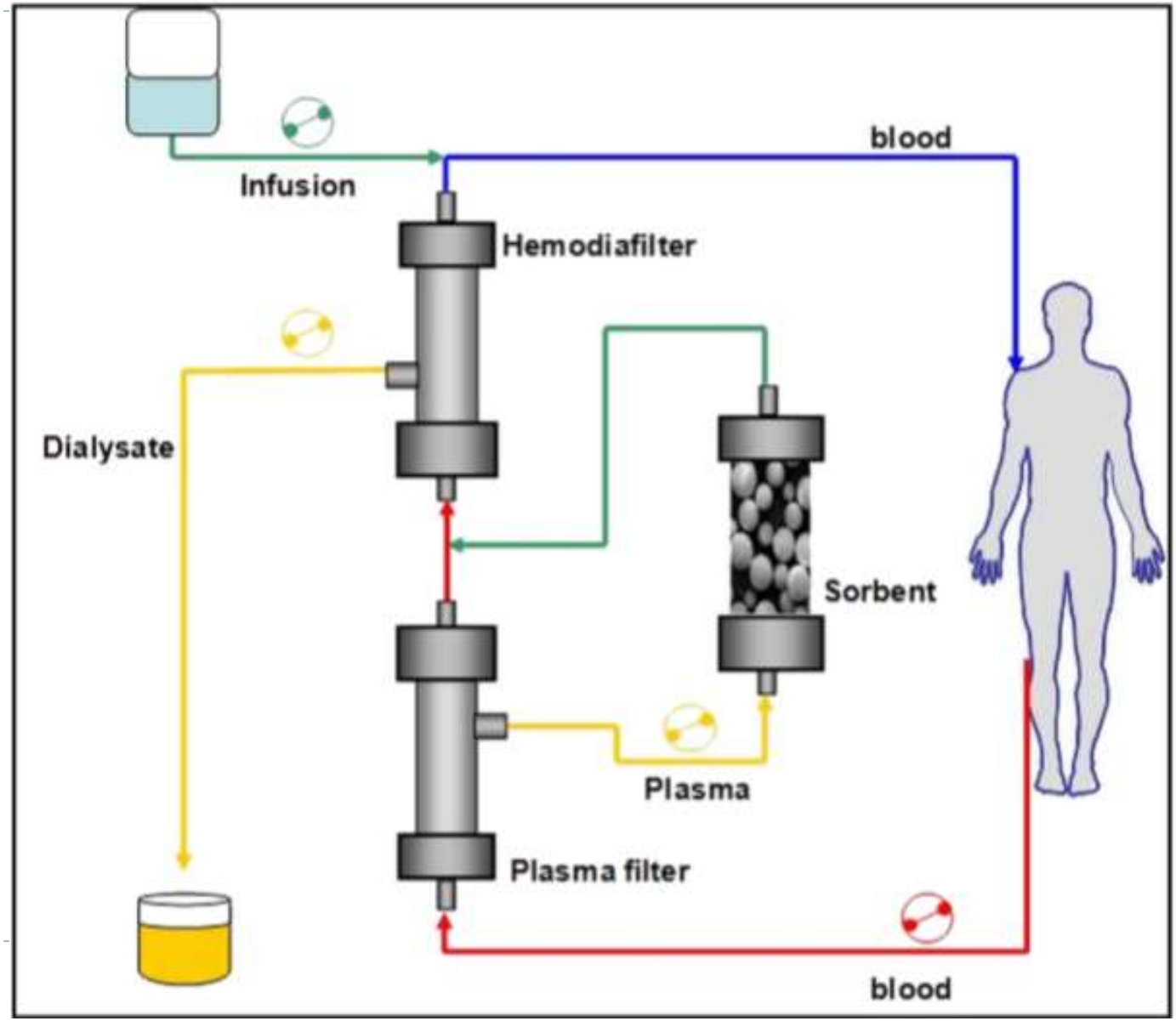
PBFC

- Larger trial – EUPHRATES (NCT01046669)
- 50 ICUs in USA & Canada
- Enrolled 650 patients
- Included patients of septic shock with endotoxin level >0.60

- In interim analysis of 450 patients there was no difference in 28 day mortality

Klein et al. Trials 2014, 15:218

CPFA


Infusion
blood
Hemodiafilter
Dialysate
Sorbent
Plasma
Plasma filter
blood

CPFA

- In multicenter RCT in 18 ICUs
- 192 patients with septic shock were randomized
- CPFA was performed for atleast 5 days, lasting 10 hours/day

Livigni S et al, BMJ Open. 2014 Jan 8;4(1):e003536

CPFA

- Result
  - No difference in primary outcome
    - hospital mortality (47.3% controls Vs 45.1% CPFA, p =0.76)
  - No difference in
    - Occurrence of new organ failures
    - ICU free days
    - 90 day mortality

Livigni S et al, BMJ Open. 2014 Jan 8;4(1):e003536

CPFA- Subgroup

Table 3 Results of the logistic regression model on hospital mortality

Variable	OR	95% CI	p Value
Volume of plasma treated (L/kg/day)			
CPFA, ≤0.18 (1° and 2° tertiles) vs controls	1.52	0.73 to 3.17	0.033
CPFA, >0.18 (3° tertile) vs controls	0.36	0.13 to 0.99	
Age (decades)	1.57	1.19 to 2.07	0.001
Source of admission			
Other ICU vs medical ward	0.28	0.04 to 1.89	
Emergency room vs medical ward	0.27	0.11 to 0.67	0.021
Surgical ward vs medical ward	0.34	0.15 to 0.77	
Renal failure at admission	4.08	1.47 to 11.32	0.007
Cholecystitis or cholangitis on admission	0.18	0.04 to 0.75	0.018

44 of 91 randomized could not be treated for predefined duration

Livigni S et al, BMJ Open. 2014 Jan 8;4(1):e003536

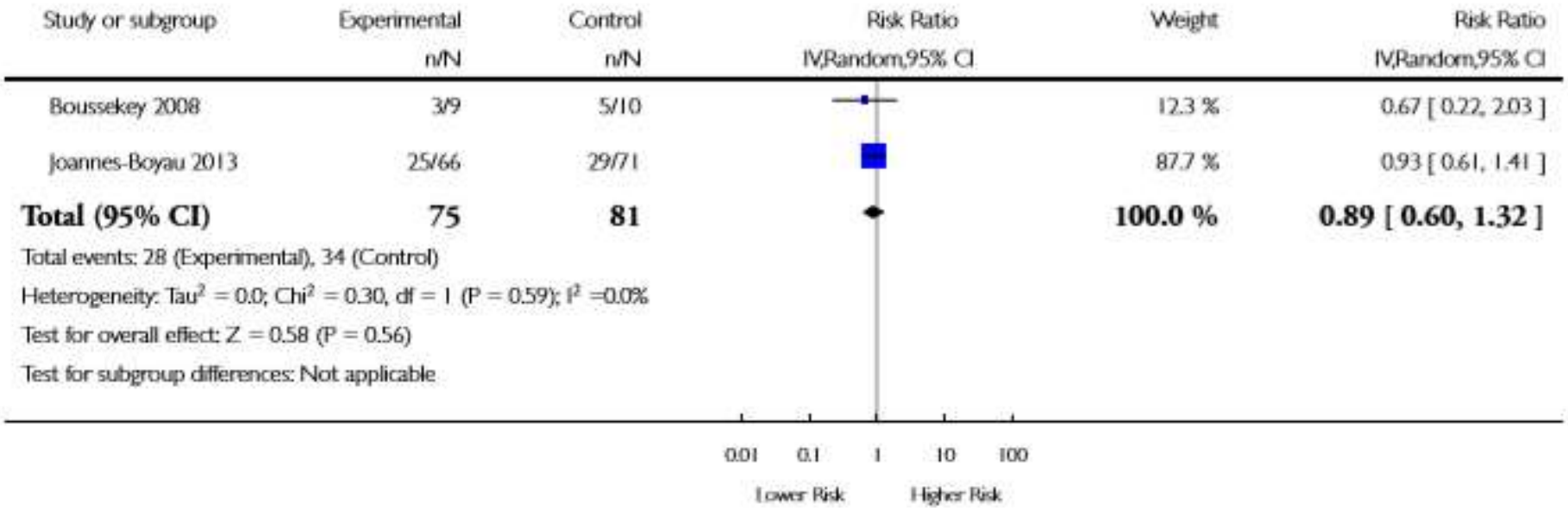
Haemofiltration

- Review of 4 RCTs involving 200 patients
- Compared high volume haemofiltration Vs standard haemofiltration
- Inclusion criteria – Septic shock or severe sepsis
- High volume haemofiltration
  - >35ml/kg/hr

Borthwick EM et al,Cochrane Database Syst Rev. 2017 Jan 31;1:CD008075

Results

Mortality outcome



No difference in length of ICU stay (75 days Vs 74 days, intervention Vs control)

Borthwick EM et al,Cochrane Database Syst Rev. 2017 Jan 31;1:CD008075

Vitamin C/Hydrocortisone/Thiamine

- Vitamin C and hdrocortisone act synergistically
- Inhibit NF-κB
- Downregulate proinflammatory mediators
- Vit C also acts as antioxidant

Marik PE et al, Chest. 2017;151(6):1229

Vitamin C/Hydrocortisone/Thiamine - Setting

- Propensity matched retrospective study
- Intervention group – Jan 2016 to July 2016
- Control group – June 2015 to Dec 2015
- 47 patients in each group
- All patients of sepsis or septic shock and procalcitonin ≥ 2 ng/ml

Marik PE et al, Chest. 2017;151(6):1229

Dosing Used

- Vit C – iv 1.5 gm Q6H X 4 days or ICU discharge over 30 – 60 min
- Hydrocortisone – 50 mg Q6H X 7 days or ICU discharge, tapered over 3 days
- Thiamine – iv 200 mg Q12H X 4 days or ICU discharge

Marik PE et al, Chest. 2017;151(6):1229

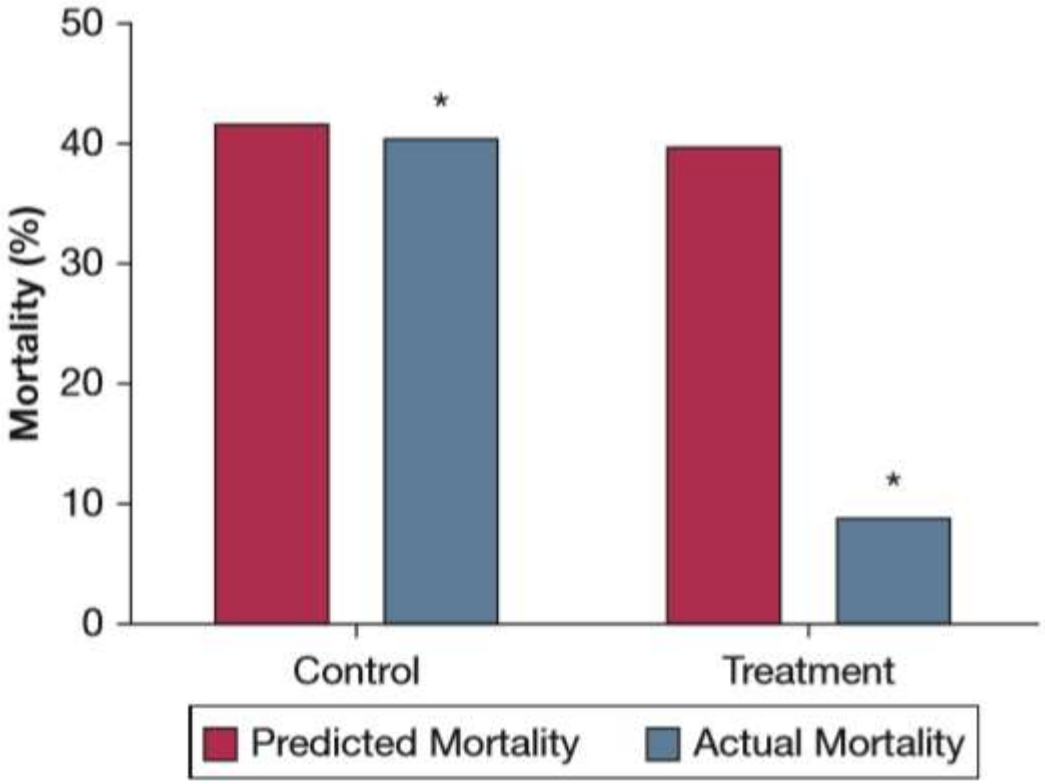
Results

TABLE 2] Outcome and Treatment Variables

Variable	Treated (n = 47)	Control (n = 47)
Hospital mortality, No. (%)	4 (8.5)	19 (40.4)[a]
ICU LOS, median and IQR, d	4 (3-5)	4 (4-10)
Duration of vasopressors, mean ± SD, h	18.3 ± 9.8	54.9 ± 28.4 [a]
RRT for AKI, No. (%)	3 of 31 (10%)	11 of 30 (33%)[b]
ΔSOFA, 72 h	4.8 ± 2.4	0.9 ± 2.7[a]
Procalcitonin clearance, median % and IQR, 72 h	86.4 (80.1-90.8)	33.9 (−62.4 to 64.3)[a]

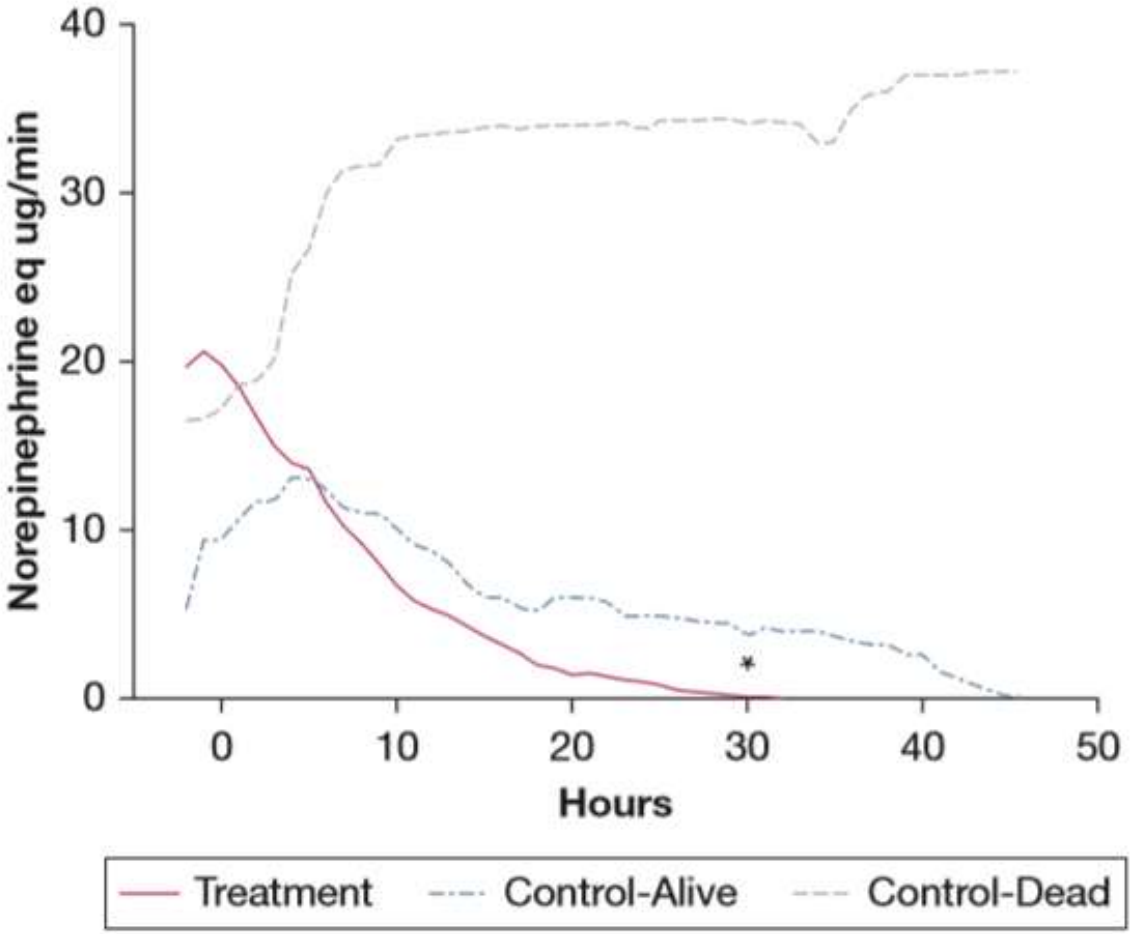
Marik PE et al, Chest. 2017;151(6):1229

Mortality



Marik PE et al, Chest. 2017;151(6):1229

Norepinephrine requirement



Marik PE et al, Chest. 2017;151(6):1229

Results

- In treatment group there were 4 deaths
- Authors claim they died of advanced disease (advanced HF, COPD, cirrhosis, dementia)

  "*were given comfort care in hospital floor*"
- None died of sepsis

Marik PE et al, Chest. 2017;151(6):1229

Drawbacks

- Single centre retrospective study
- Need adequately powered RCT before recommended

Anti coagulants

- Heparin has anti thrombotic and immunomodulating effects

Early intravenous unfractionated heparin and mortality in septic shock

- Retrospective multicenter propensity matched study
- Time interval : 1989 to 2005
- 2365 patients were diagnosed with septic shock and 722 received iv therapeutic dose of heparin
- Excluded patients who died in first 48 hours

Zarychanski R et al Crit Care Med. 2008;36(11):2973

Heparin

- On manual review of 25% of charts
  - ACS as concomitant with septic shock → 71.3%
  - Possible PTE or DVT → 9.6%
  - Chronic AF → 5.2%
  - Possible ischemic bowel → 5.2%
  - Other reasons → 3.6%

Zarychanski R et al Crit Care Med. 2008;36(11):2973

Heparin therapy

- Mean duration of heparin therapy was 4.7 days (±2.9)
- Low dose prophylactic heparin was administered to 73.7% patients in the control group within 48 hrs of shock

Zarychanski R et al Crit Care Med. 2008;36(11):2973

Primary outcome

Table 3. Mortality over 28 days

Septic Shock Cohort	Sample Size, n	Mortality Rate by Heparin Status, No. Deaths/Total No. Patients (%)		Hazard Ratio (95% Confidence Interval)	*p*
		Heparin	Control		
28-day mortality					
Adjusted for propensity score	1390	279/695 (40.1)	307/695 (44.2)	0.85 (0.73–1.00)	0.05
Stratified 28-day mortality analysis in matched cohort (APACHE II quartile)					
5–18	333	41/166 (24.7)	36/167 (21.6)	1.11 (0.70–1.73)	0.65
19–23	381	63/186 (33.9)	68/195 (34.9)	0.93 (0.66–1.342	0.70
24–28	324	81/175 (46.3)	76/149 (51.0)	0.86 (0.63–1.18)	0.34
29–53	352	94/168 (56.0)	127/184 (69.0)	0.70 (0.54–0.92)	0.01

APACHE, Acute Physiology and Chronic Health Evaluation.

Zarychanski R et al,l Crit Care Med. 2008;36(11):2973

Other effects

	Heparin Vs Control	OR	P
Liberation from MV	62.5% vs. 54%	1.42 CI 95% 1.12– 1.79	0.003
Discontinuation from inotrope	74.7% Vs 68.8%	1.34 CI 95% 1.06–1.70	0.01
Median length of hospital stay	19 days (IQR 8–36) vs. 14 days (IQR 5–31)		<0.001

Zarychanski R et al Crit Care Med. 2008;36(11):2973

Adverse events

Table 4. Acquired[a] rates of clinically significant bleeding complications and need for transfusion

	Heparin (n = 695)	Control (n = 695)	*p*
GI hemorrhage, n (%)	36 (5.2)	26 (3.7)	0.19
CNS hemorrhage, n (%)	7 (1.0)	7 (1.0)	1.00
Number of patients transfused PRBC units, n (%)	364 (52.4)	384 (55.3)	0.28
PRBC (units/patient) mean (SD)	5.0 (5.8)	4.7 (5.2)	0.52
Platelets (units/patient) mean (SD)	5.7 (5.5)	6.6 (6.8)	0.19
FFP (units/patient) mean (SD)	16.9 (17.8)	18.4 (19.5)	0.58

GI, gastrointestinal; CNS, central nervous system; PRBC, packed red blood cell; FFP, fresh frozen plasma (approximately 250 mL per donor unit).

[a]Diagnoses and interventions recorded >24 hrs after intensive care unit admission.

Zarychanski R et al Crit Care Med. 2008;36(11):2973

HETRASE Study

- Single centre RCT of 319 patients
- Iv UFH 500 units/hr for 7 days Vs placebo

Jaimes F et al Crit Care Med. 2009;37(4):1185

Inclusion criteria

- Atleast one of each variables in 24 hours of emergency admission

Appendix B
Inclusion criteria

Modified Centers for Disease Control Definitions for Infection	General Variables	Inflammatory Variables
1) Pneumonia	1) Temperature (oral or axillary) >38°C or <36°C	1) White blood cells >12,000 μL^{-1} or <4,000 μL^{-1} or with >10% immature forms
2) Bloodstream infection	2) Heart rate >90 beats/min	2) Plasma C-reactive protein >5 mg/dL
3) Clinical sepsis	3) Respiratory rate >20 breaths/min	
4) Symptomatic urinary tract infection and other infections of urinary tract	4) Altered mental status determined by Glasgow Coma Scale <15	
5) Intra-abdominal infections	5) Systolic blood pressure <90 mm Hg or a decrease >40 mm Hg	
6) Skin infections		
7) Soft tissue infections		
8) Superficial and deep surgical site infections		
9) Joint or bursa infections		

Jaimes F et al Crit Care Med. 2009;37(4):1185

Results

	Heparin	Placebo	p
Median length of stay (days)	12 (IQR 8-19.5)	12.5 (IQR8-20)	0.976
MOD Score (decline/ day)	0.11	0.13	0.240
28 day mortality	14%	16%	0.652

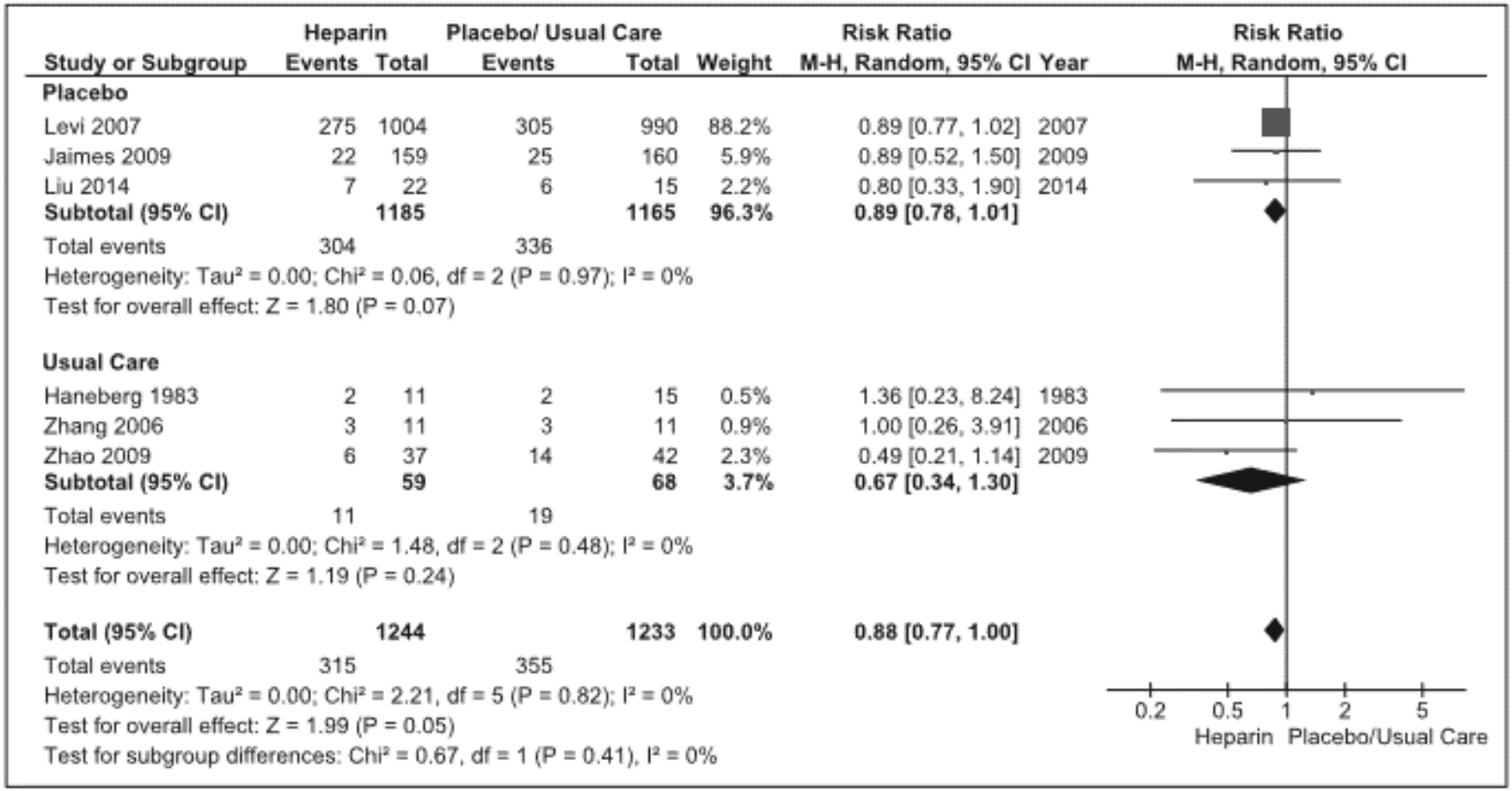
Jaimes F et al Crit Care Med. 2009;37(4):1185

Meta analysis

- 9 trials of 2637 patients
- Patients with sepsis, severe sepsis, septic shock or DIC

Zarychanski R et al, Crit Care Med. 2015 Mar;43(3):511-8

Heparin --- mortality benefit



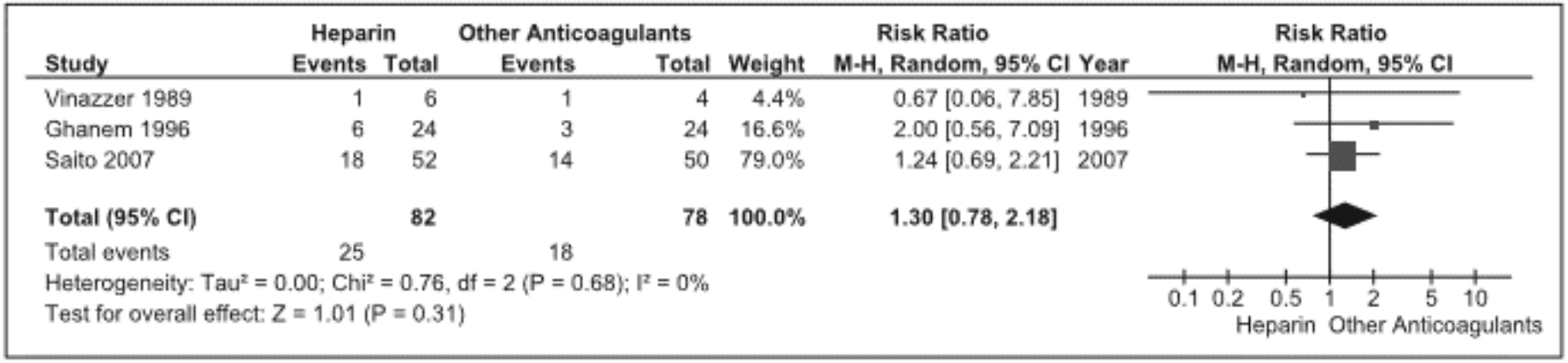
Study or Subgroup	Heparin Events	Heparin Total	Placebo/ Usual Care Events	Placebo/ Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Placebo							
Levi 2007	275	1004	305	990	88.2%	0.89 [0.77, 1.02]	2007
Jaimes 2009	22	159	25	160	5.9%	0.89 [0.52, 1.50]	2009
Liu 2014	7	22	6	15	2.2%	0.80 [0.33, 1.90]	2014
Subtotal (95% CI)		**1185**		**1165**	**96.3%**	**0.89 [0.78, 1.01]**	
Total events	304		336				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%							
Test for overall effect: Z = 1.80 (P = 0.07)							
Usual Care							
Haneberg 1983	2	11	2	15	0.5%	1.36 [0.23, 8.24]	1983
Zhang 2006	3	11	3	11	0.9%	1.00 [0.26, 3.91]	2006
Zhao 2009	6	37	14	42	2.3%	0.49 [0.21, 1.14]	2009
Subtotal (95% CI)		**59**		**68**	**3.7%**	**0.67 [0.34, 1.30]**	
Total events	11		19				
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 2 (P = 0.48); I² = 0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Total (95% CI)		**1244**		**1233**	**100.0%**	**0.88 [0.77, 1.00]**	
Total events	315		355				
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 5 (P = 0.82); I² = 0%							
Test for overall effect: Z = 1.99 (P = 0.05)							
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%							

Figure 3. Mortality in patients randomized to heparin versus placebo or usual care. *Boxes* and *horizontal lines* represent point estimates, varying in size according to the weight in the analysis and 95% CIs. M-H = Mantel-Haenszel.

Zarychanski R et al, Crit Care Med. 2015 Mar;43(3):511-8

Heparin Vs other anticoagulants

- No difference



Study	Heparin Events	Heparin Total	Other Anticoagulants Events	Other Anticoagulants Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Vinazzer 1989	1	6	1	4	4.4%	0.67 [0.06, 7.85]	1989
Ghanem 1996	6	24	3	24	16.6%	2.00 [0.56, 7.09]	1996
Saito 2007	18	52	14	50	79.0%	1.24 [0.69, 2.21]	2007
Total (95% CI)		**82**		**78**	**100.0%**	**1.30 [0.78, 2.18]**	
Total events	25		18				

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)

Figure 4. Mortality in patients randomized to heparin versus other anticoagulants. *Boxes* and *horizontal lines* represent point estimates, varying in size according to the weight in the analysis and 95% CIs. M-H = Mantel-Haenszel.

Zarychanski R et al, Crit Care Med. 2015 Mar;43(3):511-8

Meta analysis of anti coagulants

- Meta analyses of RCT for anticoagulant therapy in 3 different populations
  - overall population with sepsis
  - population with sepsis induced coagulopathy
  - population with sepsis induced DIC

- 24 trials enrolling 14,767 patients

Umemura Y et al J Thromb Haemost. 2016 Mar;14(3):518-30

Defined as

- Sepsis induced coagulopathy → presence of a *single coagulation related parameter change*, such as
  - decreased platelet count
  - prolonged PT
  - decreased AT III activity
  - elevated levels of D-dimer

Umemura Y et al J Thromb Haemost. 2016 Mar;14(3):518-30

Defined as

- Sepsis induced DIC
  - ISTH overt DIC criteria
  - ISTH non overt DIC criteria
  - JMHW DIC criteria
  - JAAM DIC criteria

Umemura Y et al J Thromb Haemost. 2016 Mar;14(3):518-30

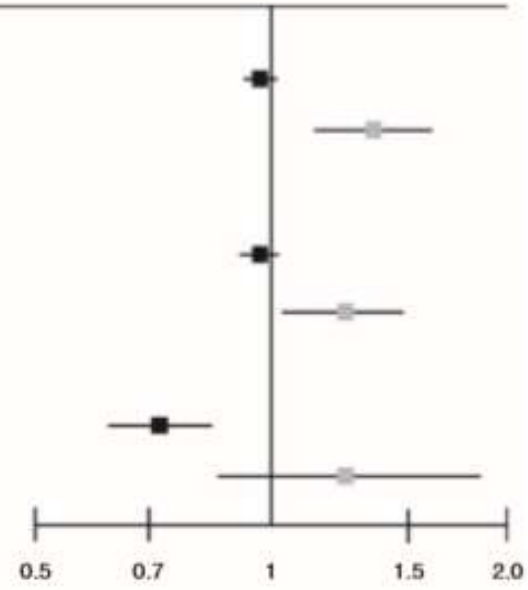
Population groups

- 24 studies for overall sepsis population
- 5 studies for sepsis induced coagulopathy
- 7 studies for sepsis induced DIC

Umemura Y et al J Thromb Haemost. 2016 Mar;14(3):518-30

Results

Outcomes	Illustrative comparative risks [95% CI] Assumed risk Control	Corresponding risk Anticoagulant	Risk ratio M-H, Random, 95% CI	No. of participants [No. of studies]	NNT or NNH [95% CI]
Overall population of sepsis					
All-cause mortality	337 per 1000	327 per 1000 [310, 344]	0.97 [0.92, 1.02]	14767 [24 studies]	not calculated
Bleeding complications	57 per 1000	76 per 1000 [64, 89]	1.33 [1.12, 1.57]	14359 [20 studies]	44 [24, 222]
Population of sepsis-induced coagulopathy					
All-cause mortality	387 per 1000	375 per 1000 [348, 411]	0.97 [0.88, 1.08]	2629 [5 studies]	not calculated
Bleeding complications	155 per 1000	195 per 1000 [164, 232]	1.26 [1.06, 1.50]	1854 [2 studies]	22 [11, ∞]
Population of sepsis-induced DIC					
All-cause mortality	400 per 1000	288 per 1000 [248, 340]	0.72 [0.62, 0.85]	1603 [7 studies]	13 [8, 27]
Bleeding complications	61 per 1000	77 per 1000 [52, 113]	1.26 [0.86, 1.85]	1566 [6 studies]	not calculated



Umemura Y et al J Thromb Haemost. 2016 Mar;14(3):518-30

But ...

Table 2 Characteristics of the 12 trials evaluating mortality in populations with coagulation disorders or with DIC

Author (trials)	Criteria		Sample size, n	
	Sepsis-induced coagulopathy	Sepsis-induced DIC	Treatment	Control
Antithrombin				
F. Fourrier 1993 [16]		Original criteria*	14	18
F. Baudo 1998 [18]	AT III activity < 70%		49	51
B. L. Warren 2001 [21] (KyberSept)		ISTH overt, non-overt DIC, or both	114	115
S. Gando 2013 [23]		JAAM DIC	30	30
Recombinant human activated protein C				
G. R. Bernard 2001 [24] (PROWESS)		ISTH overt DIC	233	221
V. M. Ranieri 2012 [27] (PROWESS-SHOCK)	Platelet count ≤ 100 000/μL		208	181
Tissue factor pathway inhibitor				
E. Abraham 2001 [29]	INR ≥ 1.2		98	48
E. Abraham 2003 [30] (OPTIMIST)	INR ≥ 1.2		880	874
Unfractionated heparin				
F. Jaimes 2009 [34] (HETRASE)	D-dimer > 500 ng/mL		123	117
X. L. Liu 2014 [35]		Original criteria†	22	15
Recombinant human thrombomodulin				
J. L. Vincent 2013 [37]		Modified ISTH overt DIC	371	370
Gabexate mesilate				
J. T. Hsu 2004 [38]		JMHW DIC	25	25

Umemura Y et al J Thromb Haemost. 2016 Mar;14(3):518-30

Should heparin be used ?

- Higher and different doses of heparin is being evaluated
  - NCT01234285
- Larger study for patients with DIC induced septic shock is needed

Beta blockers

- Severe sepsis is characterized by
  - Cardio circulatory abnormalities
  - Sympathetic overactivity
- Meta analysis of 5 RCT's was done
  - 3 studies reported survival rate, MAP, CVP and HR
  - 2 studies reported ScvO2
  - 2 studies reported TnI

Liu P et al, Am J Emerg Med. 2018 Mar;36(3):470-474

Method of admission

- Different in all 5 studies
- From as low as 0.05mcg/kg/min to 0.5 mcg/kg/min
- In 2 of the studies it was titrated to maintain controlled heart rate

Liu P et al, Am J Emerg Med. 2018 Mar;36(3):470-474

Outcomes

- Primary outcome → survival rate
- Secondary outcome →
  - MAP
  - CVP
  - HR
  - ScvO2
  - TnI

Liu P et al, Am J Emerg Med. 2018 Mar;36(3):470-474

MAP / CVP / ScvO2

Study or Subgroup	Esmolol group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Liu 2015	70.9	2.1	24	70.7	1.4	24	32.2%	0.11 [-0.46, 0.68]
Wang 2015	82	16	30	80	19	30	40.3%	0.11 [-0.39, 0.62]
Yang 2014	76	7.9	21	75	8.4	20	27.5%	0.12 [-0.49, 0.73]
Total (95% CI)			**75**			**74**	**100.0%**	**0.11 [-0.21, 0.44]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)

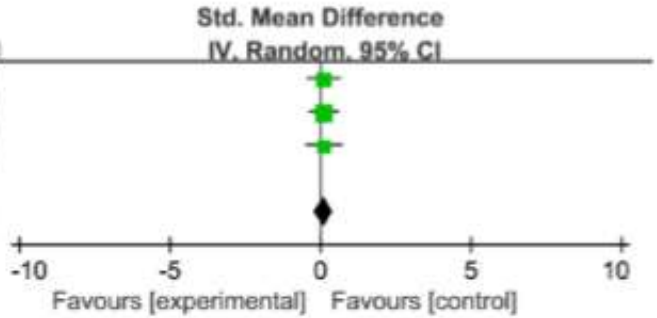
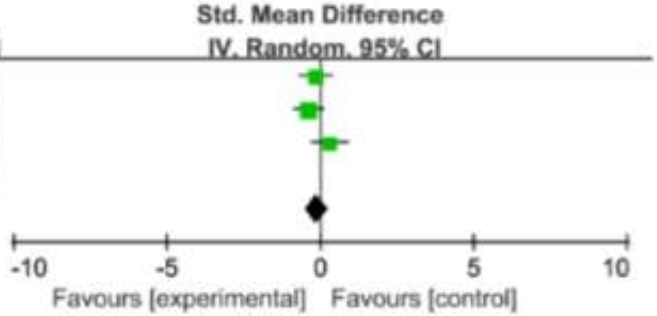


Figure. 3

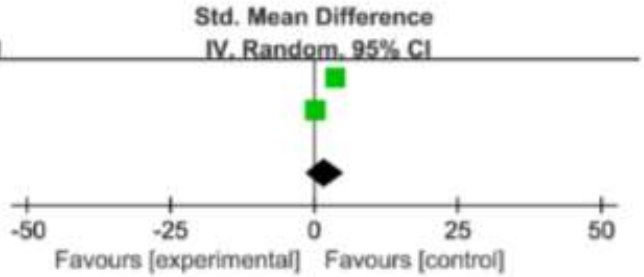
Study or Subgroup	Esmolol group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Liu 2015	12.5	1.3	24	12.7	1.3	24	32.9%	-0.15 [-0.72, 0.42]
Wang 2015	12	2	30	13	3	30	37.9%	-0.39 [-0.90, 0.12]
Yang 2014	11.1	1.3	21	10.7	1.3	20	29.2%	0.30 [-0.31, 0.92]
Total (95% CI)			**75**			**74**	**100.0%**	**-0.11 [-0.50, 0.28]**

Heterogeneity: Tau² = 0.04; Chi² = 2.86, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 0.55 (P = 0.58)



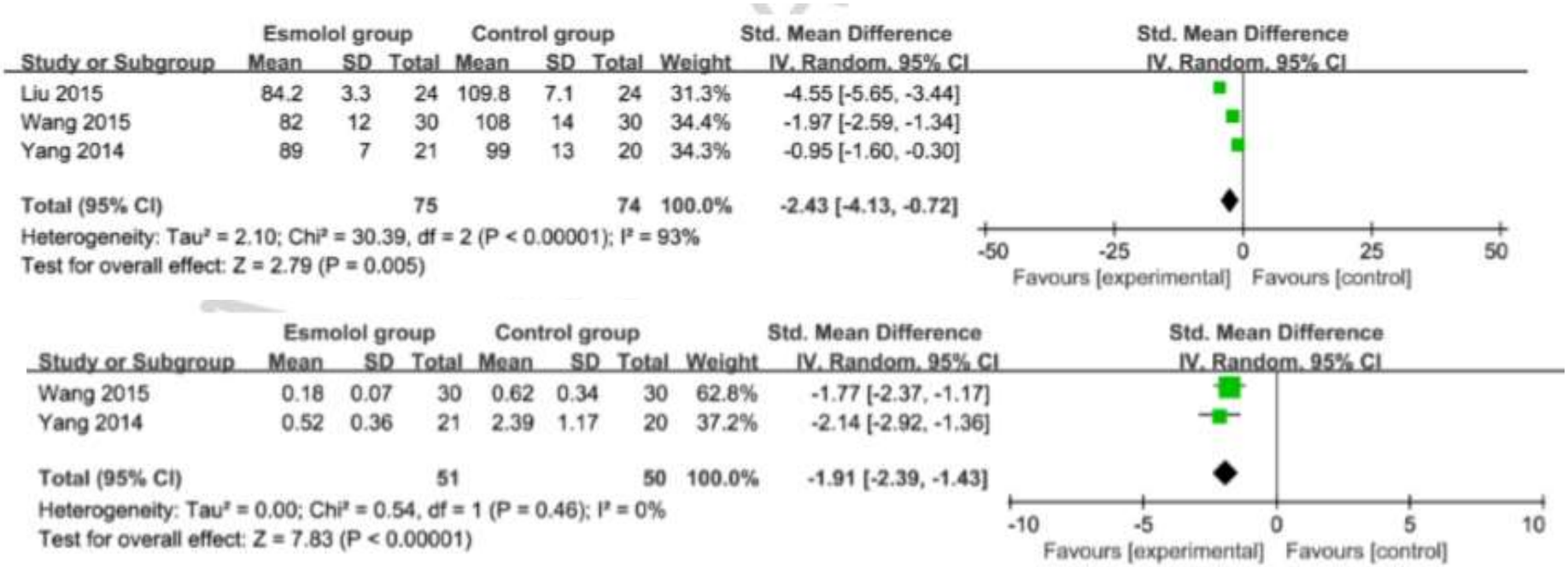
Study or Subgroup	Esmolol group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Liu 2015	0.675	0.02	24	0.61	0.015	24	49.4%	3.62 [2.67, 4.56]
Yang 2014	0.798	0.064	21	0.788	0.065	20	50.6%	0.15 [-0.46, 0.77]
Total (95% CI)			**45**			**44**	**100.0%**	**1.87 [-1.53, 5.26]**

Heterogeneity: Tau² = 5.84; Chi² = 36.41, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.08 (P = 0.28)



Liu P et al, Am J Emerg Med. 2018 Mar;36(3):470-474

HR & TpI



Study or Subgroup	Esmolol group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Liu 2015	84.2	3.3	24	109.8	7.1	24	31.3%	-4.55 [-5.65, -3.44]
Wang 2015	82	12	30	108	14	30	34.4%	-1.97 [-2.59, -1.34]
Yang 2014	89	7	21	99	13	20	34.3%	-0.95 [-1.60, -0.30]
Total (95% CI)			75			74	100.0%	-2.43 [-4.13, -0.72]

Heterogeneity: Tau² = 2.10; Chi² = 30.39, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.79 (P = 0.005)

Std. Mean Difference
IV, Random, 95% CI

-50 -25 0 25 50
Favours [experimental] Favours [control]

Study or Subgroup	Esmolol group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Wang 2015	0.18	0.07	30	0.62	0.34	30	62.8%	-1.77 [-2.37, -1.17]
Yang 2014	0.52	0.36	21	2.39	1.17	20	37.2%	-2.14 [-2.92, -1.36]
Total (95% CI)			51			50	100.0%	-1.91 [-2.39, -1.43]

Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 7.83 (P < 0.00001)

Std. Mean Difference
IV, Random, 95% CI

-10 -5 0 5 10
Favours [experimental] Favours [control]

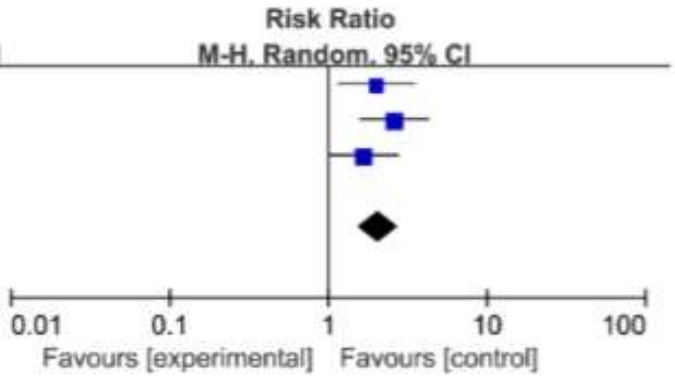
Liu P et al, Am J Emerg Med. 2018 Mar;36(3):470-474

SURVIVAL RATE

Study or Subgroup	Esmolol group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Liu 2015	18	24	9	24	28.5%	2.00 [1.14, 3.52]
Morelli 2013	39	77	15	77	35.8%	2.60 [1.57, 4.31]
Wang 2015	20	30	12	30	35.7%	1.67 [1.00, 2.76]
Total (95% CI)		**131**		**131**	**100.0%**	**2.06 [1.52, 2.79]**
Total events	77		36			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.56$, df = 2 (P = 0.46); $I^2 = 0\%$

Test for overall effect: Z = 4.68 (P < 0.00001)



Liu P et al, Am J Emerg Med. 2018 Mar;36(3):470-474

Clinical implication

- All are small studies with less than 100 patients
- Meta analysis showed marked improvement in survival
- Need an adequately powered RCT before can be recommended

Naloxone

- In cochrane review of 6 CRTs
- No statistically significant benefit
  - Death rate
  - Reduction of dose of vasoactive drug
  - Heart rate
- Statistically significant benefit was seen in MAP
  - mean difference: +9.33 mmHg; 95%CI 7.07-11.59

Boeuf B et al, Cochrane Database Syst Rev. 2003;(4):CD004443

Clinical implication

- Cannot be recommended
- Based on conchrane review authors recommend study of atleast 340 patients
  - To demonstrate difference of mortality for power of 80%

Take home message

- Again none of the studies still show convincing evidence for sepsis
- Reason for these failed trials
  - Lack of clear patient inclusion criteria
  - Heterogeneous population
- Need to better characterize sepsis
  - Better characterize in terms of immune status
  - Biomarkers to identify these groups
  - Targeted new interventions
- Sepsis → personalized treatment approach
  - To identify causative agent
  - Response elicited by person
  - Specific therapies

Sepsis – PIRO concept

Table 2
The predisposition, insult, response, organ dysfunction model

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short-term survival. Cultural or religious beliefs, age, gender.	Genetic polymorphisms in components of inflammatory response (eg, TIR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases.	In the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future).
Insult infection	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.	Assay of microbial products (LPS, mannan, bacterial DNA); gene transcript profiles.	Specific therapies directed against inciting insult require demonstration and characterization of that insult.
Response	SIRS, other signs of sepsis, shock, CRP.	Nonspecific markers of activated inflammation (eg, PCT or IL-6) or impaired host responsiveness (eg, HLA-DR); specific detection of target of therapy (eg, protein C, TNF, PAF).	Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (eg, shock); specific mediator-targeted therapy is predicated on presence and activity of mediator.
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (eg, MODS, SOFA, LOD system, PEMOD, PELOD).	Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.	Response to pre-emptive therapy (eg, targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.

Marshall JC et al, Crit Care Clin 34 (2018) 1–14