Sepsis: nothing really new

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SIRS/Sepsis: ACCP/SCCM Definitions

- Infection: invasion of normally sterile body tissues by microorganisms
- Systemic Inflammatory Response Syndrome (SIRS): systemic response to a variety of insults (burns, trauma, pancreatitis, infection)
- Sepsis is SIRS in the setting of suspected or proven infection

SIRS/Sepsis: Definitions

SIRS: presence of 2 or more of the following criteria

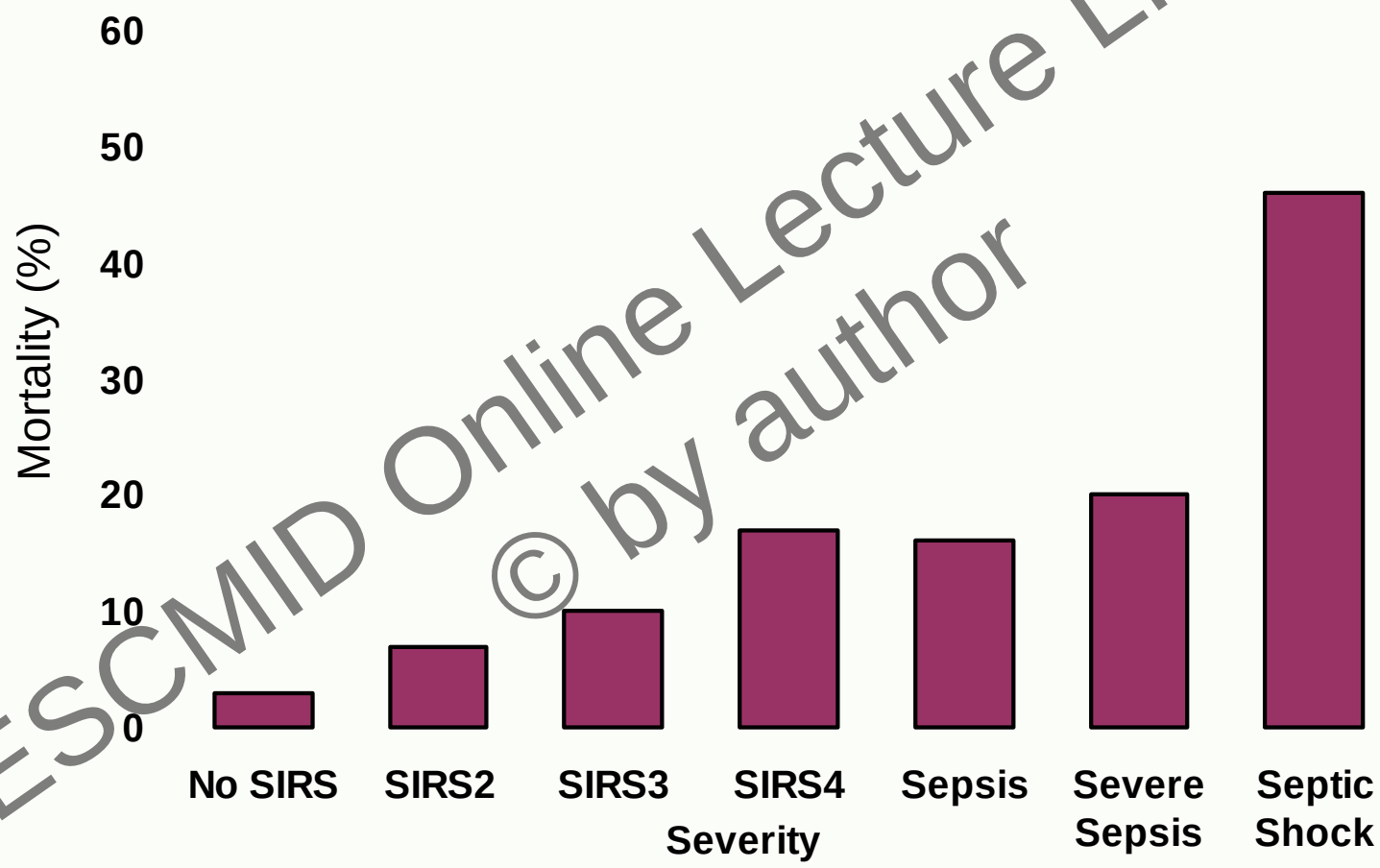
- Fever (core temperature > 38.3 C) or hypothermia (core temperature < 36 C)
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 or need for mechanical ventilation for an acute respiratory process
- WBC > 12,000/mm^3, < 4,000/mm^3, or bands > 10%

Sepsis: ***patient meets the criteria for SIRS and has a suspected or confirmed infection.***

Sepsis and Septic Shock

- Sepsis
  - 2 SIRS criteria plus suspected or documented infection
- Severe sepsis
  - Sepsis plus at least one organ dysfunction (see next slide)
- Septic shock
  - Sepsis plus persistent hypotension despite fluid resuscitation, or
  - Perfusion abnormalities

Increased Mortality Along a Continuum



Rangel-Frausto, et al. *JAMA* 1995;273:117-23.

Management

- Early recognition of a severe bacterial infection
- Fluid resuscitation
- Appropriate, early antibiotic treatment
- Goal-directed management (resources?)
- Steroids
- Vasopressors (?)
- Intervening with the sepsis cascade

Human recombinant protein C for severe sepsis and septic shock in adult and paediatric patients (Cochrane Review)

Martí-Carvajal AJ, Solà I, Gluud C, Lathyris D, Cardona AF

- APC compared with placebo did not significantly affect all-cause mortality at day 28 (780/3435 (22.7%) versus 767/3346 (22.9%); RR 1.00, 95% confidence interval (CI) 0.86 to 1.16; $I^2 = 56\%$).
- APC was associated with an increased risk of serious bleeding (113/3424 (3.3%) versus 74/3343 (2.2%); RR 1.45, 95% CI 1.08 to 1.94; $I^2 = 0\%$).

Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. Haase et al. *BMJ 2013;346:f839*

- Nine trials that randomised 3456 patients with sepsis were included.
- Overall, hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin did not affect the relative risk of death (1.04, 95% confidence interval 0.89 to 1.22, 3414 patients, eight trials).
- In the predefined analysis of trials with low risk of bias the relative risk of death was 1.11 (1.00 to 1.23, trial sequential analysis (TSA) adjusted 95% confidence interval 0.95 to 1.29, 3016 patients, four trials).

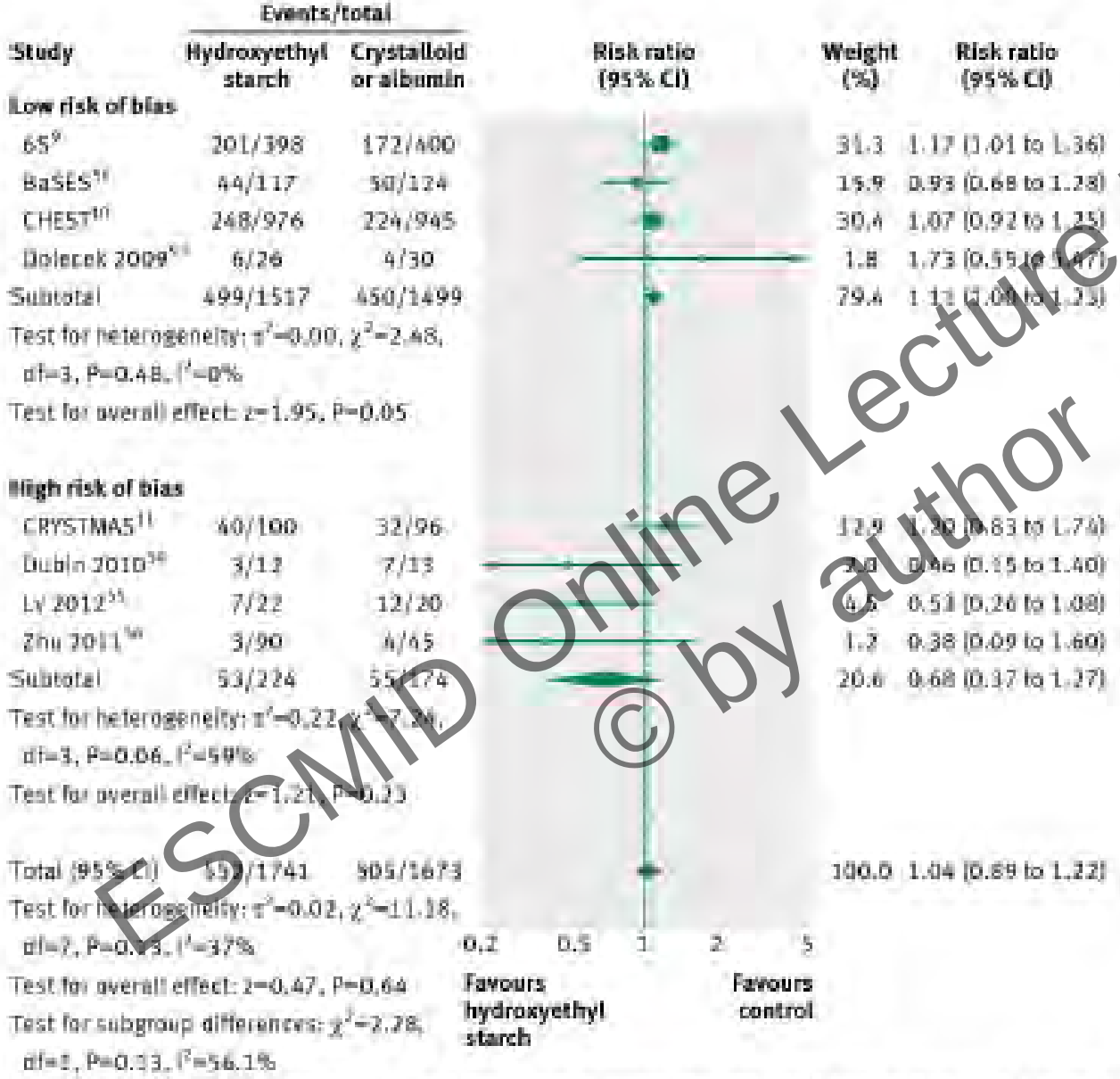


Fig 2 Forest plot of all cause mortality in relation to risk of bias in trials. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals

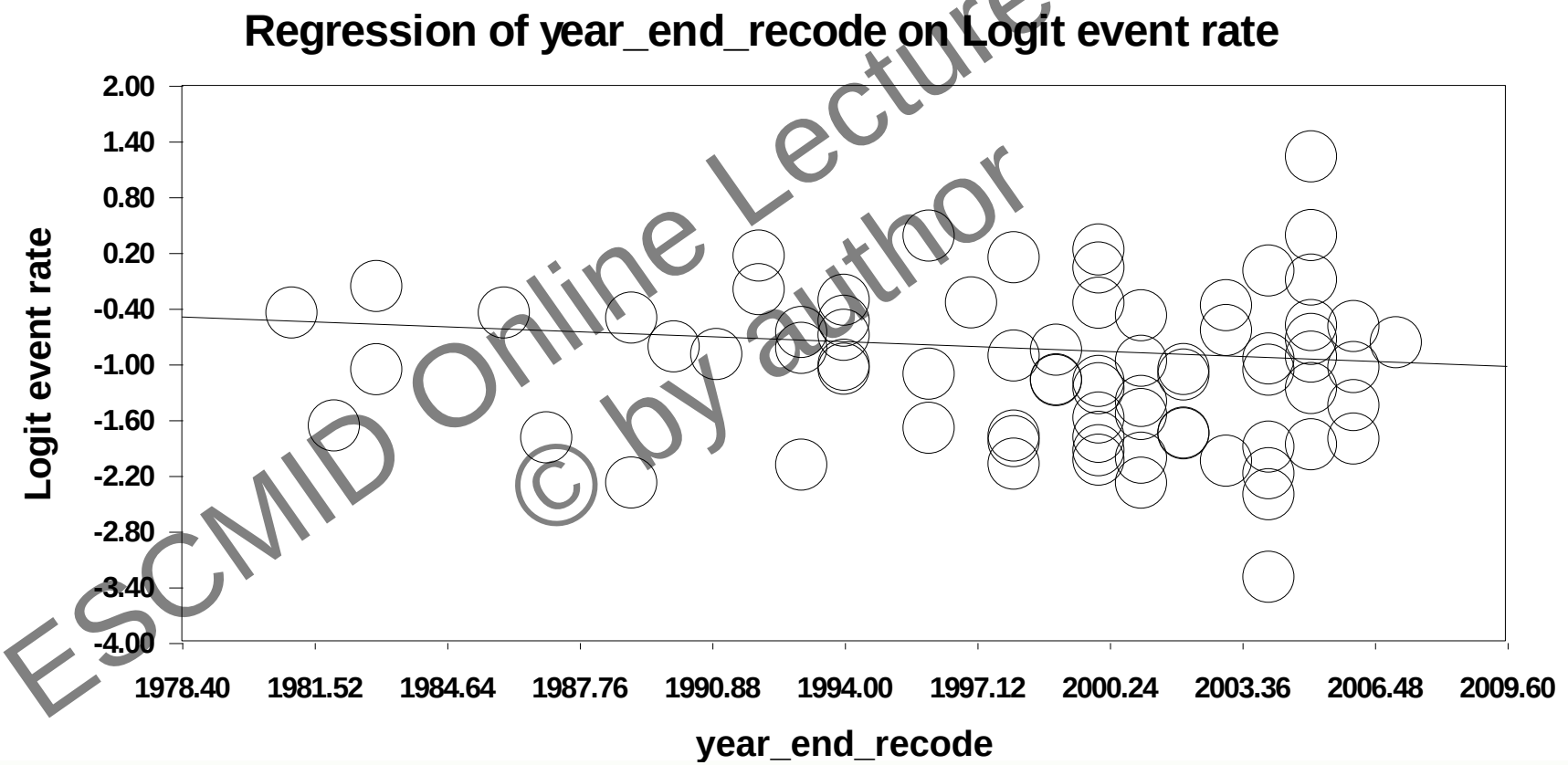
Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis: The ACCESS Randomized Trial. Opal et al. *JAMA. 2013; 309(11): 1154*

- Eritoran is a synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor.
- Patients with severe sepsis (n=1961) were randomized and treated within 12 hours of onset of first organ dysfunction in a 2:1 ratio with a 6-day course of either eritoran tetrasodium (105 mg total) or placebo, with n=1304 and n=657 patients, respectively.
- There was no significant difference in the primary end point of 28-day all-cause mortality with 28.1% (366/1304) in the eritoran group vs 26.9% (177/657) in the placebo group (*P=.59; hazard ratio, 1.05; 95% CI, 0.88-1.26; difference in mortality rate, 1.1; 95%* CI, 5.3 to 3.1)

I. Early empirical antibiotic treatment

- Antibiotic treatment is given empirically before microbiological data are available
- Inappropriate empirical antibiotic treatment is given to 30% of patients with severe infections worldwide
- Inappropriate empirical treatment increases mortality ~X2 in severe infections
- Probabilistic data on the pathogen and its susceptibilities to antibiotics exists, but difficult to use.

Are we improving with time?



Mixed effect meta-regression, slope -0.01 (-0.03-0.01, p=0.23

TREAT

TREAT is a decision support system that uses simple data available within hours to calculate probabilities for site of infection, pathogen, susceptibilities; and advise on antibiotic treatment.

Randomized controlled trial

- Cluster (=department) randomized trial
- Included 2,326 patients in Israel, Germany, Italy
- Departments of medicine, infectious diseases, and specialized medical department

Intervention

TREAT system installed and used. Advice optional.

Control

Local guidelines distributed. Antibiotic use monitored

Paul, Leibovici et al. J Antimicrob Chemother 2006

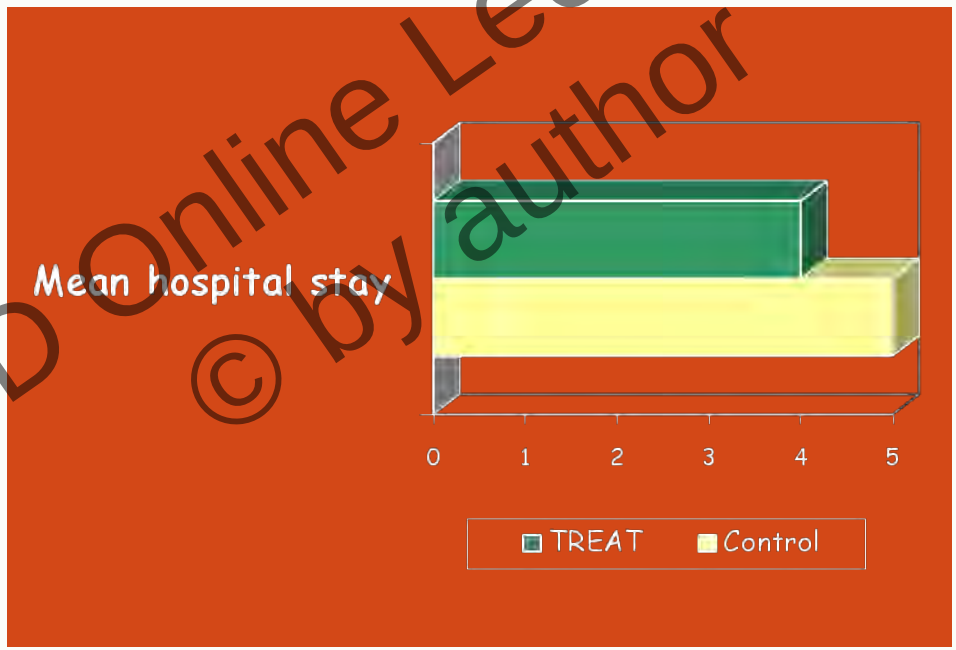
Appropriate empirical treatment

per protocol

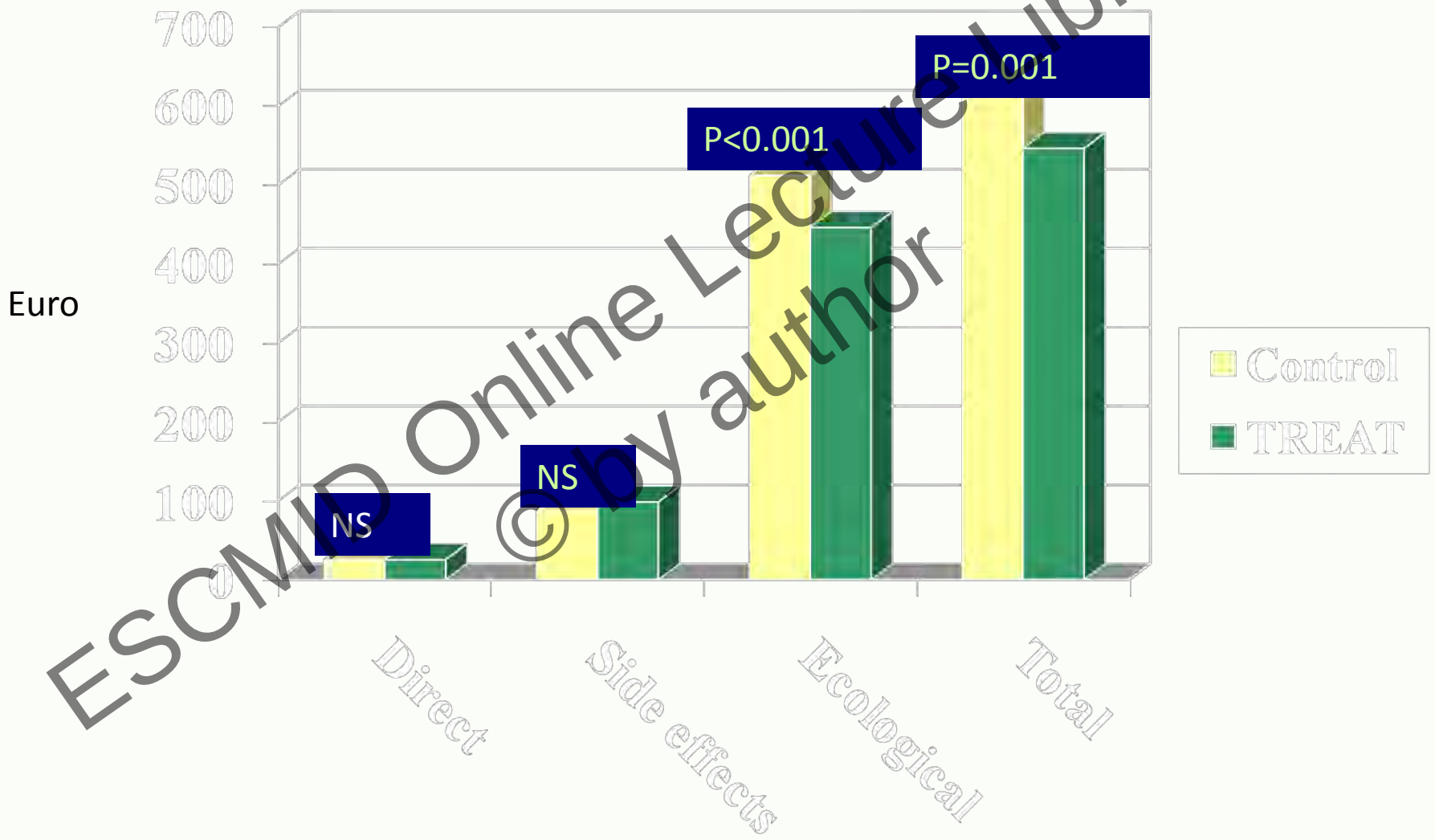
Secondary outcomes

intention to treat

P=0.014



Antibiotic costs - Israel

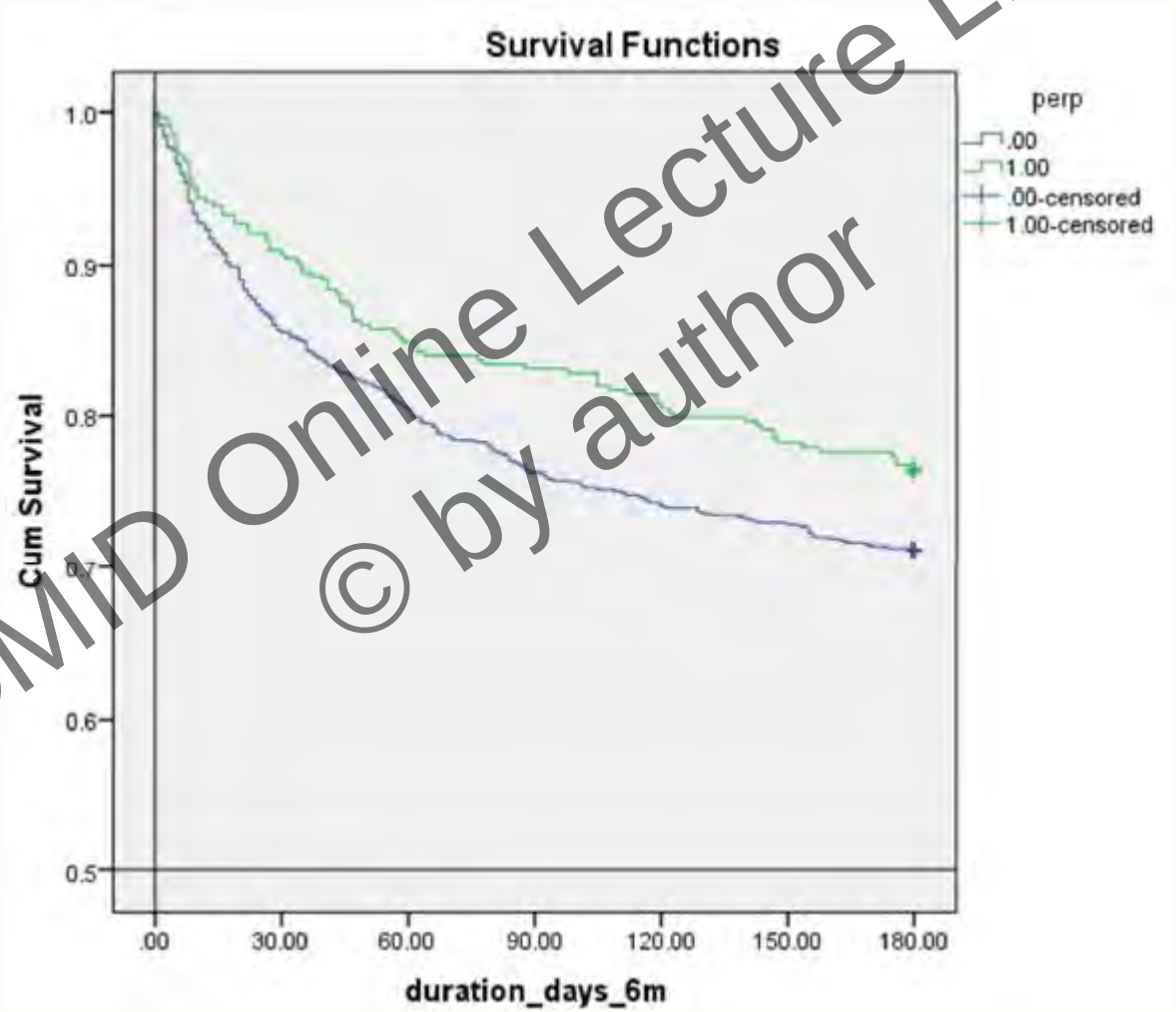


Paul, Leibovici et al. J Antimicrob Chemother 2006

Long-term survival in patients included in a randomized controlled trial of TREAT, a decision support system for antibiotic treatment Leibovici et al. JAC 2013; e-pub before print

- At Beilinson Hospital 1683 patients were included in the study, 860 in the intervention arm and 823 in the control arm.
- In the ITTanalysis180 day survival in control patients was 71% versus 74% in the intervention patients (P=0.2). In the PP analysis the survival percentages were 71% and 77%, respectively (P=0.04).
- In patients with bacterial infections, in the ITT analysis180 day survival in the control group was 68%versus71%i n the intervention patients (P=0.1). In the PP analysis the survival percentages were 68% versus 74% (P=0.04).

Long-term follow-up: survival



Leibovici et al. J Antimicrob Chemother 2013

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Thank you