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Supplemental Digital Content (SDC)

Supplemental Digital Content 1

SSC Conflict of Interest Policy

The Surviving Sepsis Campaign (SSC) Guidelines Committee developed and adopted a comprehensive conflict of interest (COI) policy at the commencement of the current update process. This policy was established to ensure that SSC managed real and potential COI (both financial and non-financial) in an open and effective manner in order to secure and preserve transparency and public trust in the integrity of SSC processes and products. The comprehensive policies and standards for the management of COI applied to all subcommittees, work groups, task forces, evidence process panels, and writing panels as well as individual volunteers, liaisons, staff, and others involved in SSC Guidelines Committee work.

The goals of the COI policy were:1) to enhance the objectivity, scientific rigor, and transparency of official SSC statements, guidelines, and documents by providing an explicit methodology for individuals and participating organizations to identify and disclose all personal or institutional "competing interests" that may cause, or be perceived as causing, a COI affecting the individual's participation in the activity, and resolve all conflicts of interest; and 2) to provide for disclosure and resolution of COI in a manner respectful of the SSC participating organizations and other individuals essential to SSC activities, and respectful of confidentiality to the extent appropriate.

Individual participants were required to provide a written disclosure of all potential COI (both financial and non-financial) by completing the International Committee of Medical Journal Editors (ICMJE) Uniform Disclosure Form for Potential Conflicts of Interest. Although committee members were encouraged to specify remuneration of any dollar amounts, this was not mandatory. A separate questionnaire was developed to record non-financial COI, including

an assessment of each participant's approach to the use of guidelines and incorporation of evidence into clinical decision making in sepsis.

Updates were required whenever material changes occurred in an individual's status. Processes were established for review and adjudication of COI (Appendix B of guideline document). Individuals with COI in a particular area or topic who were selected for a leadership role with oversight or responsibility for that area or topic were subject to heightened adjudication by the Executive Committee. The Executive Committeereviewed initial disclosures before deciding on participants, and excluded participants if there was a conflict that could not be resolved. The chair of each subgroup and more than 50% of the members of each subgroup were required to be free of any relevant relationship with industry and of any significant nonfinancial COI or competing organizational relationship. Any chair of a writing group with any relevant COI was asked to step down as chair.

During in-person meetings and telephone conference calls, each individual all participants were required to make a verbal statement each time they spoke regarding their potential COI. Any individuals with a financial conflict relative to the subject matter about to be discussed were asked to recuse themselves from the deliberation, unless they had special information of a technical nature. Formal abstention from all votes and actions was required for any individual with a potential recorded COI.

Authors' Disclosure Information

Dr. Aitken has not disclosed any potential conflicts of interest. Her non-financial disclosures include publications on protocol-directed sedation and nursing considerations to complement the Surviving Sepsis Campaign guidelines.

Dr. Al Rahma disclosed that he has no potential conflicts of interest.

Dr. Angus consulted for Eli Lilly (member of the Data Safety Monitoring Board, multicenter trial of a PC for septic shock); Eisai, Inc. (anti-TLR4 therapy for severe sepsis); and Idaho Technology (sepsis biomarkers). He received grant support (investigator, long-term follow-up of phase III trial of an anti-TLR4 agent in severe sepsis) and received a consulting income (anti-TRL4 therapy for severe sepsis) from Eisai, Inc. Travel/accommodation expenses were reimbursed by Eisai, Inc. Additionally, he is the primary investigator for an ongoing National Institutes of Health-funded study comparing early resuscitation strategies for sepsis-induced tissue hypoperfusion.

Dr. Annane participated on the Fresenius Kabi International Advisory Board (honorarium €2000). His non-financial disclosures include being the principal investigator of a completed investigator-led multicenter randomized controlled trial assessing the early guided benefit to risk of NIRS tissue oxygen saturation. He was the principal investigator of an investigator-led randomized controlled trial of epinephrine versus norepinephrine (CATS study;*Lancet* 2007). He also is the principal investigator of an ongoing investigator-led multinational randomized controlled trial of crystalloids versus colloids (Crystal Study).

Dr. Beale received compensation for his participation as board member for Eisai, Inc., Applied Physiology, bioMérieux, Covidien, SIRS-Lab, and Novartis. Consulting income was paid to his institution by PriceSpective Ltd, Easton Associates (soluble guanylatecyclase activator in acute respiratory distress syndrome/acute lung injury adjunct therapy to supportive care and ventilation strategies), Eisai (eritoran), and Philips (Respironics). He provided expert testimony for Eli Lilly and Company (paid to his institution). He received honoraria (paid to his institution) from Applied Physiology (Applied Physiology PL SAB, Applied Physiology SAB, Brussels, Satellite Symposium at the ISICEM, Brussels); bioMérieux (GeneXpert Focus Group, France); SIRS-Lab (SIRS-LAB SAB Forum, Brussels and SIRS-LAB SAB, Lisbon); Eli Lilly (CHMP Hearing); Eisai (eritoran through leader touch plan in Brussels); Eli Lilly (Lunchtime Symposium, Vienna); Covidien (adult monitoring advisory board meeting, Frankfurt); Covidien (Global Advisory Board CNIBP Boulder USA); Eli Lilly and Company (development of educational presentations including service on speakers bureaus (intensive care school hosted in department). Travel/accommodations were reimbursed from bioMérieux (GeneXpert Focus Group, France);LiDCO (Winter Anaesthetic and Critical Care Review Conference); Surviving Sepsis Campaign (Publications Meeting, New York; Care Bundles Conference, Manchester; SSC Publication Committee Meeting and SSC Executive Committee Meeting, Nashville; SSC Meeting, Manchester); Novartis (Advisory Board Meeting, Zurich); Institute of Biomedical Engineering (Hospital of the Future Grand Challenge Kick-Off Meeting; Hospital of the Future Grand Challenge Interviews EPSRC Headquarters, Swindon); Philips (Kick-Off Meeting, Boeblingen, Germany; MET Conference, Copenhagen); Covidien (Adult Monitoring Advisory

Board Meeting, Frankfurt); and Eisai (ACCESS Investigators Meeting, Barcelona).His non-financial disclosures include authorship of the position statement on fluid resuscitation from the ESICM task force on colloids (yet to be finalized).

Dr. Bernard received compensation for his participation as a board member of Cumberland Pharmaceuticals, Nashville, TN ($50,000-$100,000; no known conflict with any topic area) and AstraZeneca ($1,000-$5,000; paid consultancy ended in 2009). He received grant support from AstraZeneca ($100,000; grant is in support of the study on statins in the treatment of H1N1 influenza). He has stock/stock options in Cumberland Pharmaceuticals (no known conflict with topic area). Vanderbilt University was the coordinating center for the PROWESS Shock trial (Eli Lilly; income support commensurate with 1% to 5% effort on the project). His non-financial disclosures includeinitial authorship of the PROWESS trial of activated protein C in sepsis.

Dr. Biban disclosed that he has no potential conflicts of interest.

Dr. Bion received grant support for being the senior clinical leader of the National Patient Safety Agency's Matching Michigan project.

Dr. Calandra reports grant support from Baxter (research grant on testing of anti-migration inhibitory factormonoclonal antibodies for treatment of sepsis); bioMérieux (development of diagnostic tests for fungal infections; money to research foundation); Merck Sharp &Dohme-Chibret AG (grant for medical mycology); and Roche Diagnostics (research grant for SeptiFast). He consulted for Astellas (speaker and chairperson at company-sponsored symposium [ESICM 2009 and ISICEM 2010; antifungal therapy]); Baxter (anti-migration inhibitory factor monoclonal antibodies for treatment of sepsis); bioMérieux (diagnostic tests for infectious diseases); Essex Chemie AG (advisory board); Evolva (advisory board); Merck Sharp &Dohme-Chibret AG (antifungal agents, and was on the advisory board of a chairperson meeting); and Pfizer (speaker at meeting). He also reports monetary compensation for his participation in review activities (data monitoring boards, statistical analysis, endpoint committees [Eisai - steering committee; Eritoran Clinical Trial; PPD; Novartis]). His institution received grant support from the Swiss National Science Foundation. Furthermore, he is a member of the Research Council of the Swiss National Science Foundation. His non-financial disclosures includeauthorship of review articles on the use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis.

Dr. Carcillo received grant support from the National Institutes of Health and holds a patent from the University of Pittsburgh. His non-financial disclosures includeauthorship of the American College of Critical Care Medicine pediatric advanced life support guideline and publications on the management of sepsis and shock in children.

Dr. Clemmer has non-financial conflicts as a member of ARDSNet since its inception and is a contributor to many of its publications. He developed a protocol for the standard use of airway pressure release ventilation for local use. Additionally, he has published and lectured on the removal of sedation and early ambulation of mechanically ventilated patients.

Dr. Dellinger consulted for Biotest (immunoglobulin concentrate available in Europe for potential use in sepsis) and AstraZeneca (anti-TNF compound unsuccessful in recently completed sepsis clinical trial); his institution received consulting income from IKARIA for new product development (Ikaria has inhaled nitric oxide available for off label use in ARDS) and grant support from Spectral Diagnostics Inc (current endotoxin removal clinical trial) and Ferring (vasopressin analog clinical trial-ongoing), as well as serving on the speakers bureau for Eisai (anti-endotoxin compound that failed to show benefit in clinical trial).

Dr. Deutschman has non-financial involvement as a coauthor of the Society of Critical Care Medicine's glycemic control guidelines.

Dr. Divatia received unrestricted education grants to his institution (Edwards India, USD $8,000). He also received income from Asia Ventilation Forum (workshop/symposium speaker; Covidien paid honoraria). Travel/accommodations were reimbursed by Edwards India, AstraZeneca India, and MSD India. His non-financial involvement includes being a board member of the Asia Ventilation Forum (a working group to enhance ventilatory management in Asian countries).

Dr. Douglas received grants paid to his institution from Eli Lilly (PROWESS Shock site); Eisai (study site); National Institutes of Health (ARDS Network); Accelr8 (ventilator-associated pneumonia diagnostics); CCCTG (Oscillate Study); and Hospira (Dexmedetomidine in Alcohol Withdrawal randomized controlled trial). His institution received an honorarium from the Society of Critical Care Medicine (Paragon ICU Improvement).He consulted for Eli Lilly (PROWESS Shock Steering Committee and Sepsis Genomics Study) in accordance with institutional policy. He received payment for providing expert testimony (Smith Moore Leatherwood LLP). Travel/accommodations reimbursed by Eli Lilly and Company (PROWESS Shock Steering Committee)and the Society of Critical Care Medicine (Hospital Quality Alliance, Washington DC; four times per year 2009-2011). He received honoraria from Covidien (non-CME lecture 2010, US $500) and the University of Minnesota Center for Excellence in Critical Care CME program (2009, 2010). In addition, he has a pending patent for a bed backrest elevation monitor.

Dr. Duncan disclosed that he has no potential conflicts of interest.

Dr. Fujishima disclosed that he has no potential conflicts of interest.

Dr. Gando received grant support for Grants-in-Aid for Science Research from the Ministry of Education, Science, Sports, and Culture in Japan (Grant # 2007-19390456). He is an author of a review on the use of activated protein C in surgical patients (published in the *New England Journal of Medicine*, 2009).

Dr. Gerlach is an author of a review on the use of activated protein C in surgical patients (published in the *New England Journal of Medicine*, 2009).He disclosed that he has no potential conflicts of interest.

Dr. Goodyear disclosed that he has no potential conflicts of interest.

Dr. Guyatt disclosed that he has no potential conflicts of interest.

Dr. Hazelzet received travel/accommodations reimbursement from ESPNIC and EMEA (EC or expert meeting). He is the Medical President of ESPNIC and a member of the European Pediatric Genetic Study consortium.

Dr. Hirasawa reports income to his institution from the Surviving Sepsis Campaign Guideline Committee ($10,000-$25,000). He received honoraria from the Surviving Sepsis Campaign Guideline Committee ($1,000-$5,000). He is the senior author of a manuscript describing the efficacy of continuous hemodiafiltration with cytokine-absorbing hemofilter on sepsis mediator removal.

Dr. Hollenberg consulted for Eisai (eritoran).

Dr. Jacobi reports grant support to her institution from Eli Lilly (Project Mercury; experience with DAA and an unrestricted educational grant in 2009: $1,000-$5,000). She reports income to her institution for the development of educational presentations including service on speakers bureaus (Eli Lilly 2001-2006; CareFusion Center for Clinical Safety 2007).Travel/accommodations reimbursed to her institution from Eli Lilly's speakers bureau (SCCM traveluntil 2006). She and her husband own stock in healthcare companies (managed by a broker): Abbott Labs (no sepsis-specific related products); Cardinal Health (distributor of products only, no sepsis therapies of their own); Baxter International (150 shares ~ $8,000; fluids used for resuscitation, may be used in sepsis patients); Edwards Lifesciences (30 shares ~ $2,500; monitoring devices used in sepsis patients); Merck Medco (no sepsis-related products); Pfizer (179 shares ~ $3,400; antimicrobial products used in sepsis patients; no sepsis-specific therapies). She is the past president of the Society of Critical Care Medicine, and chairs the Society of Critical Care Medicine's task force completing the glycemic control guidelines. She is a coauthor of the Project Mercury paper (retrospective evaluation of drotrecogin alfa activated that demonstrated a higher risk of bleeding compared with the prior research populations in randomized controlled trials).

Dr. Jaeschke disclosed that he has no potential conflicts of interest.

Dr. Jenkins received income for speakers bureau activities related to deep venous thrombosis prevention from Medavera and Haymarket Medical Education and Quintiles. He is an author of a sepsis review article (published in the *Journal of Hospital Medicine*, 2006).

Dr. Jimenez received grants paid to his institution from CareFusion (mechanical ventilation research); KCI (abdominal compartment syndrome device research); and Hamilton (mechanical ventilation research). He received income from CareFusion (mechanical ventilation talks related to ongoing research) and KCI (moderator of kinetic therapy symposium). Travel/accommodations reimbursement came from CareFusion (travel expenses while giving talks/workshops overseas).

Dr. Jones received grant support from HTI. He is an elected board member of SAEM and EMF.

In addition he is the primary author on a manuscript comparing lactate clearance with central venous oxygen saturation.

Dr. Kacmarek is the author of original research papers, editorials, and chapters showing the benefit of lung protective ventilation.

Dr. Kern consulted for Pfizer and received grant support paid to his institution from Pfizer. He received honoraria from Pfizer, Janssen-Cilag, Astellas, and Novartis. Travel/accommodations were reimbursed by Bayer.

Dr. Kissoon disclosed that he has no potential conflicts of interest.

Dr. Kleinpell received monetary compensation for providing expert testimony (four depositions and one trial in the past year). Her institution receives grants from the Agency for Healthcare Research and Quality and the Prince Foundation (4-year R01 grant, principal investigator; 3-year foundation grant, co-investigator). She received honoraria from the Cleveland Clinic and the American Association of Critical-Care Nurses for keynote speeches at conferences. She received royalties from McGraw-Hill (co-editor of critical care review book). Travel/accommodations were reimbursed from the American Academy of Nurse Practitioners, Society of Critical Care Medicine, and American Association of Critical-Care Nurses (one night hotel coverage at national conference).

Dr. Koh disclosed that she has no potential conflicts of interest.

Dr. Kotani reports grant support paid to his institution from AstraZeneca, Asahi Kasei Pharma, EBMs, Kaken Pharmaceutical, Nihon Pharmaceutical, Teijin Pharma Limited, CSL Behring, Torii Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer Japan Inc., Daiichi Sankyo, Benesis, Mochida Pharmaceutical, Terumo, Abbott Japan, Otsuka Pharmaceutical Inc., Ono Pharmaceutical, Shionogi Inc., and Toray Medical.

Dr. Levy reports grant support from Eisai (Ocean State Clinical Coordinating Center to fund clinical trial,$500K). He received honoraria from Eli Lilly (lectures in India, $8,000). He has been involved with the Surviving Sepsis Campaign guideline from its beginning.

Dr. Machado reports unrestricted grant support paid to her institution for Surviving Sepsis Campaign implementation in Brazil (Eli Lilly do Brasil). She is the primary investigator for an ongoing study involving vasopressin.

Dr. Mangia disclosed that she has no potential conflicts of interest.

Dr. Marini consulted for GE Healthcare (Scientific Advisory Committee). He reports research grant support was paid to his institution from GE Healthcare. In addition, he is the investigator for research studies in pandemic influenza (principal investigator for ongoing study of statins as adjuvant therapy) and antibiotics in acquired infection (principal investigator of randomized clinical trial of empiric antibiotics vs. placebo for suspected ICU-acquired infection).

Dr. Marshall reports consulting income deposited to university division group practice for work

as a Steering Committee member for the PROWESS Shock Study (Eli Lilly); Steering Committee and Clinical Evaluation Committee; ACCESS Study (Eisai); Steering Committee member for EUPHRATES study (Spectral Diagnostics; DMC; Artisan Therapeutics; DMC, Leo Pharma). He consulted for Idaho Technologies, Bayer, Roche Diagnostics, Pfizer, Daiichi Sankyo, and Vertex Pharmaceuticals. Travel/accommodations were reimbursed by Spectral Diagnostics for travel as a speaker at a meeting in Moscow (bioMérieux meeting in Paris). Dr. Marshall is the Chair of the Canadian Critical Care Trials Group that has undertaken some of the primary research underlying the SSC guidelines; Chair of the International Forum of Acute Care Trialists, an umbrella organization whose members include a number of investigator-led and run consortia that have published work forming the basis for the SSC guidelines. He is also a member and past chair of the International Sepsis Forum (received a stipend while chair). He is the primary investigator for an ongoing study of statins as adjuvant therapy and is the primary investigator of a randomized clinical trial of empiric antibiotics vs. placebo for suspected ICU-acquired infection.

Dr. Masur disclosed that he has no potential conflicts of interest.

Dr. Mehta reports grant support paid to her institution for a sedation-related research grant from the Canadian Institutes of Health Research. She received honoraria from Hospira (Advisory Board member, $1,500).

Dr. Moreno consulted for bioMérieux (expert meeting). He is a coauthor of a paper on corticosteroids in patients with septic shock. He is the author of several manuscripts defining sepsis and stratification of the patient with sepsis. He is also the author of several manuscripts contesting the utility of sepsis bundles.

Dr. Muscedere reports grant support to his institution for the ventilator-associated pneumonia (VAP) knowledge translation study ($10,000-$25,000). He received honoraria from Astellas (advisory board for doripenem, $1,000-$5,000). He was the site investigator for a multicenter study on surfactant for ARDS ($10,000-$25,000) from PneumaPharma and was the site investigator for a multicenter study on the treatment of VAP with tygecycline (ongoing study, no funds received) from Wyeth. He is a contributing author on a systemic review and meta-analysis of procalcitoninuse. He is also is the lead author for a systematic review and meta-analysis of subglottic secretion drainage for the prevention of VAP.

Dr. Napolitano consulted as an advisory board member for Wyeth, Pfizer, and Ortho-McNeil. She received honoraria from medical educational companies (CME lectures and national meetings). Travel/accommodations were reimbursed by Pfizer, Wyeth, and Ortho-McNeil.

Dr. Nunnally received a stipend for a chapter on diabetes mellitus. Additionally, he is an author of editorials contesting classic tight glucose control.

Dr. Opal consulted for Genzyme Transgenics (consultant on transgenic antithrombin, $1,000); Pfizer (consultant on TLR4 inhibitor project, $3,000); British Therapeutics (consultant on polyclonal antibody project, $1,000); and Biotest A (consultant on immunoglobin project, $2,000). His institution received grant support from Novartis (Clinical Coordinating Center to

assist in patient enrollment in a phase III trial with the use of tissue factor pathway inhibitor [TFPI] in severe community-acquired pneumonia [SCAP], $30,000 for 2 years); Eisai ($30,000 for 3 years); AstraZeneca ($30,000 for 1 year); Aggenix ($30,000 for 1 year); Inimex ($10,000); Eisai ($10,000); AtoxBio ($10,000); Wyeth ($20,000); Sirtris (preclinical research, $50,000); and Cellular Bioengineering Inc. ($500). He received honoraria from Novartis (clinical evaluation committee TFPI study for SCAP, $20,000) and Eisai ($25,000). Travel/accommodations were reimbursed from Sangart (data and safety monitoring, $2,000); Spectral Diagnostics (data and safety monitoring, $2,000); Takeda (data and safety monitoring, $2,000); and Canadian trials group ROSII oseltamivir study (Data And Safety Monitoring Board, no money). Additionally, he is also on the Data Safety Monitoring Board for Tetraphase (US$600 in 2012).

Dr. Osborn consulted for Sui Generis Health ($200). Her institution receives grant support from the National Institutes of Health Research (NIHR), Health Technology Assessment Programme-United Kingdom (trial doctor for sepsis-related randomized controlled trial). Salary paid through the NIHR government-funded (non-industry) grant. Grant awarded to chief investigator from Intensive Care National Audit & Research Centre. She is a trial clinician for ProMISe.

Dr. Parker provided expert testimony for Amer Cunningham Co. (June 2010).

Dr. Parrillo consulted for Artisan, Philips, and Cytosorbents Inc. and Sangart Data Safety Monitoring Boards. His institution received grants from the Robert Wood Johnson Foundation (New Jersey Health Initiative: Heart Failure) and the Salem Health and Wellness Foundation. He is board member of the National Heart, Blood, and Lung Institute's Heart Failure Network.

Dr. Qiu's institution received grants from Pfizer (US$30,000 for methicillin-resistant *Staphylococcus aureus* survey); MSD China (US$10,000 for candidemia survey in China); and Xian-Janssen Pharmaceutical Ltd (US$8,000 for pharmacokinetics/pharmacodynamics of itraconazole in severe fungal infection). He received honoraria from Pfizer, MSD China, Eli Lilly, AstraZeneca, and Drager(money paid to his institution). He received travel reimbursement from Pfizer (to attend annual ESICM meeting in 2011) and MSD China (to attend SCCM's 41st Congress).

Dr. Randolph consulted for Eisai Pharmaceuticals and Discovery Labs.

Dr. Reinhart consulted for Eisai (Steering Committee member,less than US$10,000); BRAHMS Diagnostics (less than US$10,000); and SIRS-Lab Jena (founding member, less than US$10,000). He received honoraria for lectures, including service on the speakers bureau from Biosyn Germany (less than €10,000) and Braun Melsungen (less than €10,000). He received royalties from Edwards Lifesciences for sales of central venous oxygen catheters (~ US $100,000).

Dr. Rello consulted for Intercell (board member), Pasteur-Sanofi, Polyphor, and Roche. He has received grant support from Intercell and Jansen-Cilag. He also received income from Pfizer (lectures) and Wyeth and Pfizer (development of educational presentations).

Dr. Resende received monetary support from Edwards Lifesciences Brazil (development of educational presentation). He is the primary author of a scientific paper about epidemiology of severe sepsis in the emergency department.

Dr. Rhodes consulted for Eli Lilly (monetary compensation paid to himself as well as his institution; Steering Committee for the PROWESS Shock trial) and LiDCO. Travel/accommodation reimbursement was received from Eli Lilly and LiDCO. He received income for participation in review activities such as data monitoring boards, statistical analysis from Orion, and for Eli Lilly. He is an author on manuscripts describing early goal-directed therapy, and he believes in the concept of minimally invasive hemodynamic monitoring.

Dr. Rivers has been a one-time consultant for AstraZeneca; bioMérieux; Aggenix; Idaho Technologies; Massimo; Philips Electronics; and Eisai Pharmaceuticals (receiving less $5,000). He is an unpaid consultant for the Institute of Medicine, National Academies of Sciences, and Catholic Health Partners. His institution (Henry Ford Health Systems) has received research grant support from Biosite, Inc. ($180,000); National Institutes of Health ($500,000); Agennix ($100,000); Hutchinson's Technologies ($150,000); and Alere ($150,000). He has received lecture honoraria from the Volunteer Hospital Association and Merck ($4,000). Over 15 years ago, a patent for a modification to central venous oximetry was registered under Henry Ford Health Systems; however, Dr. Rivers has never received remuneration, royalties, or financial benefit. The early goal-directed therapy study in severe sepsis and septic shock was performed without industry or extramural support or funding. Dr. Rivers currently is the investigator on cortisol levels in sepsis, early markers of renal failure, and the pathogenesis of early inflammatory diseases.

Dr. Rubenfeld received grant support from nonprofit agencies or foundations, including National Institutes of Health ($10 million); Robert Wood Johnson Foundation ($500,000); and Canadian Institutes of Health Research ($200,000). His institution received grants from for-profit companies, including Advanced Lifeline System ($150,000); Siemens ($50,000); Bayer ($10,000); Byk Gulden ($15,000); AstraZeneca ($10,000); Faron Pharmaceuticals ($5,000); and Cerus Corporation ($11,000). He received honoraria, consulting, editorship, royalties, and Data and Safety Monitoring Board membership fees paid to him from Bayer ($500); DHD ($1,000); Eli Lilly ($5,000); Oxford University Press ($10,000); Hospira ($15,000); Cerner ($5,000); Pfizer ($1,000); KCI ($7,500); American Association for Respiratory Care ($10,000); American Thoracic Society ($7,500); BioMed Central ($1,000); National Institutes of Health ($1,500); and the Alberta Heritage Foundation for Medical Research ($250). He has database access or other intellectual (non-financial) support from Cerner.

Ms. Schorr reports travel support from the Society of Critical Care Medicine (faculty member of SSC Phase III). She is a coauthor of a prospective cohort study of 15,022 patients studying an intervention to facilitate compliance with the SSC guidelines (specifically SSC bundle performance improvement). She is the coauthor of a multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis.

Dr. Sevransky reports grant support to his institution from Sirius Genomics Inc. He has consulted for Idaho Technology ($1,500). He is the co-principal investigator of a multicenter study evaluating the association between ICU organizational and structural factors, including protocols

and in-patient mortality. He maintains that protocols serve as useful reminders to busy clinicians to consider certain therapies in patients with sepsis or other life-threatening illness.

Dr. Shukri disclosed that he has no potential conflicts of interest.

Dr. Silva consulted for MSD ($3,000).

Dr. Soth received honoraria from Wyeth ($2,000 resident review).

Dr. Sprung reports grants paid to his institution from Artisan Pharma ($25,000-$50,000); Eisai Corporation ($1,000-$5,000, ACCESS); Ferring Pharmaceuticals A/S ($5,000-$10,000); Hutchinson Technology Incorporated ($1,000-$5,000); Novartis Corp. (<$1,000). His institution receives grant support for patients enrolled in clinical studies from Eisai Corporation (principal investigator,patients enrolled in the ACCESS study, $50,000-$100,000); Takeda (principal investigator,study terminated before patients enrolled). He received grants paid to his institution and consulting income from Artisan Pharma/Asahi Kasei Pharma America Corp. ($25,000-$50,000). He also consulted for Eli Lilly (sabbatical consulting fee $10,000-$25,000), and received honoraria from Eli Lilly (lecture $1,000-$5,000). He is a member of the Australia and New Zealand Intensive Care Society Clinical Trials Group for the NICE SUGAR Study (no money received). He is a council member of the International Sepsis Forum (as of October 2010). He has held long-time research interests in steroids in sepsis, principal investigator of CORTICUS study, end-of-life decision making, and principal investigator of ETHICUS, ETHICATT and WELPICUS studies.

Dr. Thompsondisclosed that she has no potential conflicts of interest.

Dr. Townsend is an advocate for healthcare quality improvement.

Dr. Vender receives honoraria and consulting income from Edwards Lifesciences and Hospira (lectures on hemodynamic monitoring and for consulting on new technologies).

Dr. Vincent reports consulting income paid to his institution from Astellas, AstraZeneca, Curacyte, Eli Lilly, Eisai, Ferring, GlaxoSmithKline, Merck, and Pfizer. His institution received honoraria on his behalf from Astellas, AstraZeneca, Curacyte, Eli Lilly, Eisai, Ferring, Merck, and Pfizer. His institution received grant support from Astellas, Curacyte, Eli Lilly, Eisai, Ferring, and Pfizer. His institution received payment for educational presentations from Astellas, AstraZeneca, Curacyte, Eli Lilly, Eisai, Ferring, Merck, and Pfizer.

Dr. Webb consulted for AstraZeneca (anti-infectives $1,000-$5,000) and Jansen-Cilag (anti-infectives $1,000-$5,000). He received grant support from a National Health and Medical Research Council (NHMRC) project grant (ARISE randomized controlled trial [RCT] of early goal-directed therapy [EGDT]; NHMRC project grant and Freseniusunrestricted grant (CHEST RCT of Voluven vs saline; RCT of steroid vs placebo for septic shock); NHMRC project grant (BLISS study of bacteria detection by polymerase chain reaction [PCR] in septic shock); Intensive Care Foundation-ANZ (BLING pilot RCT of beta-lactam administration by infusion); Hospira (SPICE programme of sedation delirium research); NHMRC Centres for Research

Excellence Grant (critical illness microbiology observational studies); and Hospira unrestricted grant (DAHlia RCT of dexmedetomidine for agitated delirium). He received travel/accommodations reimbursement from Jansen-Cilag ($5,000-$10,000) and AstraZeneca ($1,000-$5,000). He has a patent for a meningococcal vaccine. He is chair of the ANZICS Clinical Trials Group and is an investigator in trials of EGDT, PCR for determining bacterial load, and a steroid in septic shock trial.

Dr. Welte consulted for Novartis, MSD, Bayer, AstraZeneca, Astellas, and Pfizer. His institution received grant support from Novartis and Bayer. He received honoraria from Intercell, Pari (Data Monitoring Board), GlaxoSmithKline, Nycomed, Novartis (COPD) and MED Update (Pneumo and ICU Update development).

Dr. Zimmerman disclosed that she has no potential conflicts of interest.

Supplemental Digital Content 2

Supplemental Bibliography

Observational studies showing improved outcomes with early quantitative resuscitation between 2001 and 2011

References

Observational studies showing improved outcomes with early quantitative resuscitation between 2001 and 2011

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Supplemental Digital Content 3

Combined topical digestive tract antibiotics (includes chlorhexidine) versus no prophylaxis for mechanical ventilation > 48 hours

Patients: Adults intubated >48 hours
Settings: Intensive care unit
Intervention: Topical digestive tract antimicrobials, including chlorhexidine
Comparison: No prophylaxis
Sources: Analysis performed by M. Nunnally and S. Opal for Surviving Sepsis Campaign, using following publications: Liberati A. Cochrane Database of Systematic Reviews 2010 Issue 9; de Smet AMGA. *N Engl J Med* 2009;360(1):20-31; Chan E. *BMJ* 2007;334:889-900; Bellisimo-Rodrigues F. *Infect Control Hosp Epidemiol* 2009;30(10):952-958; Cabov T. *Wien Klin Wochenschr* 2010;122:397-404; Panchabhai TS. *Chest* 2009;135:1150-1156; Scannapieco FA. *Crit Care* 2009;13(4):R117;Tantipong H. *Infect Control Hosp Epidemiol* 2008;29(2):131-136.

Outcomes	Illustrative comparative risks (95% CI) Assumed risk Control	Corresponding risk Topical antimicrobials	Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
Overall mortality, all studies	**269 per 1000**	**266 per 1000** (250 to 285)	**RR 0.99** (0.93 to 1.06)	8530 (25 studies)	⊕⊕⊕⊖ **moderate**[1,2,3]	
Overall mortality –chlorhexidinevs no prophylaxis	**178 per 1000**	**188 per 1000** (164 to 215)	**RR 1.06** (0.92 to 1.21)	2853 (11 studies)	⊕⊕⊕⊖ **moderate**[2,3,4]	
Overall mortality −topical antibiotics vs no prophylaxis	**313 per 1000**	**303 per 1000** (281 to 328)	**RR 0.97** (0.9 to 1.05)	5677 (14 studies)	⊕⊕⊕⊖ **moderate**[2,3,5]	
Respiratory tract infection, all studies	**221 per 1000**	**124 per 1000** (99 to 152)	**RR 0.56** (0.45 to 0.69)	4588 (23 studies)	⊕⊕⊕⊖ **moderate**[2,6]	
Respiratory tract infection−chlorhexidinevs no prophylaxis	**156 per 1000**	**100 per 1000** (80 to 127)	**RR 0.64** (0.51 to 0.81)	2853 (11 studies)	⊕⊕⊕⊖ **moderate**[2,7]	
Respiratory tract infection−topical antibiotic vs no prophylaxis	**321 per 1000**	**154 per 1000** (106 to 218)	**RR 0.48** (0.33 to 0.68)	1735 (12 studies)	⊕⊕⊕⊖ **moderate**[2,8]	

CI = confidence interval, **RR** = risk ratio.
The **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[1] I^2= 0%; test for subgroup differences, I^2 = 15%.
[2] Patient population includes all critically ill patients, not just septic patients.
[3] Several studies suggest harm, but we did not lower the quality of evidence for imprecision.
[4]I^2 = 11% (*P* = 0.34).
[5]I^2 = 0%.
[6]I^2 = 52% (*P* = 0.002). Test for subgroup differences I^2 = 46.6% (*P* = 0.17). We did not lower for heterogeneity, because the issue is only the degree of benefit.
[7]I^2= 20% (*P* = 0.26).
[8]I^2= 68% (*P* = 0.0003). We did not lower for heterogeneity, because the issue is only the degree of benefit.

Supplemental Digital Content 4

Low-dose long-term glucocorticosteroids for severe sepsis and septic shock

Patient or population: Patients with severe sepsis and septic shock
Settings: Intensive care unit
Intervention: Low-dose long-term glucocorticosteroids
Comparison: No corticosteroid
Source: Analysis performed by H. Gerlach for the Surviving Sepsis Campaign, using following publication: Patel GP. *Am J Respir Crit Care Med* 2012;185:133-139

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	**Low-dose long-term glucocortico-steroids**				
Mortality Follow-up: mean 28 days	**432 per 1000**	**394 per 1000** (329 to 467)	**RR 0.91** (0.76 to 1.08)	968 (6 studies)	⊕⊕⊖⊖ **low**[1,2]	
Mortality in higher baseline mortality studies Follow-up: mean 28 days	**612 per 1000**	**471 per 1000** (343 to 642)	**RR 0.77** (0.56 to 1.05)	381 (3 studies)	⊕⊕⊕⊖ **moderate**[3,4]	
Mortality in lower baseline mortality studies Follow-up: mean 28 days	**317 per 1000**	**336 per 1000** (270 to 425)	**RR 1.06** (0.85 to 1.34)	587 (3 studies)	⊕⊕⊕⊖ **moderate**[5]	

CI = confidence interval, **RR** = risk ratio.
The **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[1] Some suggestion of heterogeneity between three studies with higher baseline mortality and three with lower.
[2] Results are not statistically significant and include large benefit and small harm.
[3] I^2= 31%, but concerns size of benefit and not direction.
[4] Imprecision. With the use of fixed effect model RR 0.82 (0.69–0.99).
[5] Imprecision as confidence intervals include harm.

Supplemental Digital Content 5

Neuromuscular blocking agents (NMBA) compared to placebo in patients with acute respiratory distress syndrome (ARDS)

Patient or population: Patients with ARDS
Settings: Intensive care unit (ICU)
Intervention: NMBA
Comparison: Placebo
Sources: Analysis performed by W. Alhazzani and J. Sevransky for the Surviving Sepsis Campaign, using following publications: Papazian L. *N Engl J Med* 2010;363:1107-1116; Gainnier M. *Crit Care Med* 2004;32:113-119; Forel JM. *Crit Care Med* 2006;34:2749-2757.

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	**NMBA**				
Mortality at 28 days	**Study population**		**RR 0.66** (0.50 to 0.87)	431 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	389 per 1000	**257 per 1000** (195 to 339)				
Mortality in ICU	**447 per 1000**	**313 per 1000** (246 to 398)	**RR 0.70** (0.55 to 0.89)	431 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Ventilator-free days Follow-up: 28 days		The mean ventilator-free days in intervention groups was **1.91 higher** (0.28 to 3.55 higher)		431 (3 studies)	⊕⊕⊕⊕ **high**[3]	
ICU-acquired weakness	**298 per 1000**	**322 per 1000** (247 to 420)	**RR 1.08** (0.83 to 1.41)	431 (3 studies)	⊕⊕⊖⊖ **low**[1,2,4]	
Barotrauma	**96 per 1000**	**41 per 1000** (19 to 87)	**RR 0.43** (0.20 to 0.90)	431 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	

CI = confidence interval, **RR** = risk ratio.
The **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

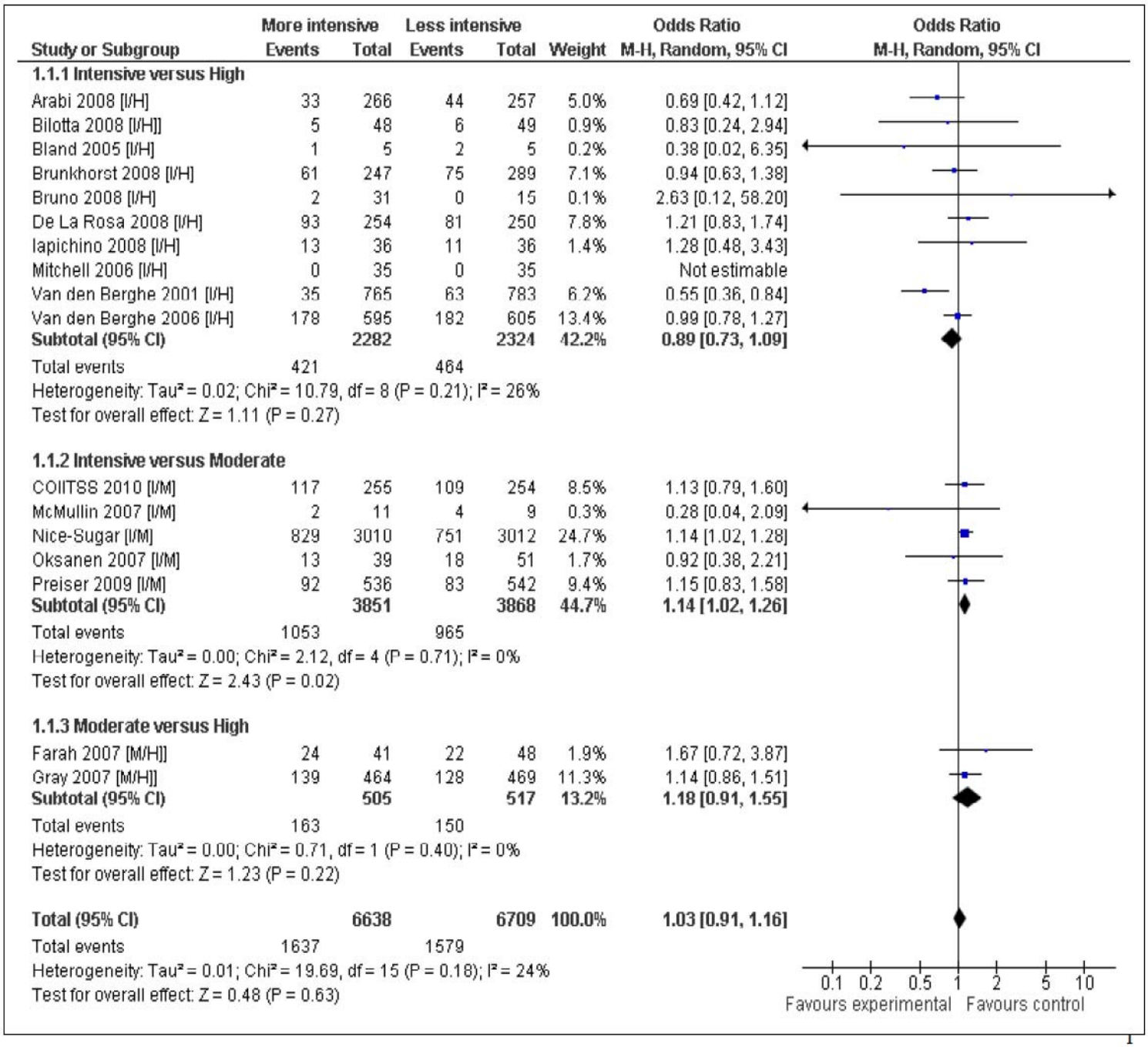
[1] Two trials lacked appropriate blinding.
[2] Due to small number of available trials, we could not assess for publication bias.

[3] Ventilator-free days correlate with survival.
[4] Wide confidence interval crossing equivalence and including significant harm.

Supplemental Digital Content 6

Mortality in Clinical Trials of Intensive Insulin Therapy by High or Moderate Glucose Level Control Groups

Figure 1 – Mortality in clinical trials of intensive insulin therapy by high or moderate control groups



Supplemental Digital Content 7

Histamine-2 receptor antagonists (H2RA) compared to placebo or no treatment for prevention of gastrointestinal (GI) bleeding

Patient or population: Critically ill patients
Settings: Intensive care units
Intervention: H2RA
Comparison: Placebo or no treatment
Sources: Prepared by W. Alhazzaniand C. Sprungfor the Surviving Sepsis Campaign using the following studies: Marik PE. *Crit Care Med* 2010;38:2222-2228; Leonard J. *Am J Gastroenterol* 2007;102:2047-2056.

Outcomes	Illustrative comparative risks (95% CI) Assumed risk Control	Corresponding risk H2RA	Relative effect (95% CI)	No of Participants (studies)	Quality of evidence (GRADE)	Comments
Clinically important GI bleeding (CIB)	**Low**[1]		**OR 0.47** (0.29 to 0.76)	1836 (17 studies)	⊕⊕⊕⊖ **moderate**[2,3,4]	
	5 per 1000	**2 per 1000** (1 to 4)				
	High[1]					
	50 per 1000	**24 per 1000** (15 to 38)				
Overall mortality	**164 per 1000**	**168 per 1000** (132 to 211)	**OR 1.03** (0.78 to 1.37)	1540 (14 studies)	⊕⊕⊕⊖ **moderate**[4,5]	
Nosocomial (hospital-acquired) pneumonia	**114 per 1000**	**165 per 1000** (103 to 252)	**OR 1.53** (0.89 to 2.61)	1157 (9 studies)	⊕⊕⊕⊖ **moderate**[4,6]	
***Clostridium difficile* infection (**in studies examining any antisecretory therapy[7])	**50 per 1000**	**93 per 1000** (72 to 120)	**OR 1.95** (1.48 to 2.58)	18468 (19 studies)	⊕⊖⊖⊖ **very low**[7]	

OR = odds ratio, CI = confidence interval.
[1] Frequency of clinically important GI bleeding varies: 1.5% (observational study; Cook, *NEnglJMed* 1994;330:377), 3.8% (group receiving sucralfate in Cook. *N Engl J Med* 1998,338:791). In the first study, patients without need for mechanical ventilation for more than 48hr and without coagulopathy (platelet count <50,000 or international normalized ratio >1.5 or activated partial thromboplastin time more than two times normal) had 0.1% risk of bleeding. Other authors list number of other potential risk factors of less-established significance, including burn, brain or multiple trauma, hypotension, renal or liver failure, steroid use, etc.
[2] All studies used randomization, most used blinding. Quality of evidence not lowered.
[3] Benefits not present in studies using enteral nutrition for all or most of the patients (OR for

mortality 1.89 [1.04−3.44, total of 65 events]); for pneumonia OR 2.81 (1.2−6.56, 41 events) and for CIB 1.26 (0.43−3.7, 28 events). We consider this an exploratory finding and, while lowering the quality of evidence, decided to provide one recommendation. We acknowledge the possibility of a different interpretation.

[4] Most studies are old and may be of limited applicability today. Quality of evidence not lowered.

[5] Overall no difference, possible harm in studies using enteral nutrition.

[6] Unable to exclude harm.

[7] From Leonard J, et al. *Am J Gastroenterol* 2007;102: 2047. Observational studies with indirectness to critically ill patients. The association was numerically greater for proton pump inhibitor (OR 2.05 [1.47−2.85]) than for H2RA (OR 1.48 [1.06−2.06]) without statistically significant difference between those two classes of drugs (*P*=0.17). We did not consider this outcome critical, but we acknowledge the possibility of a different interpretation.

Supplemental Digital Content 8

Proton pump inhibitors (PPI) compared to histamine-2 receptor antagonists (H2RA) for prevention of gastrointestinal (GI) bleeding

Patient or population: Critically ill patients
Settings: Intensive care units
Intervention: PPI
Comparison: H2RA
Sources: Prepared by W. Alhazzaniand C. Sprungfor the Surviving Sepsis Campaign using the following studies: Alhazzani. *Pol Arch Med Wewn* 2012;122:107-114; Leonard J. *Am J Gastroenterol* 2007;102:2047-2056.

Outcomes	Illustrative comparative risks (95% CI) Assumed risk H2RA	Corresponding risk PPI	Relative effect (95% CI)	No of Participants (studies)	Quality of evidence (GRADE)	Comments
Clinically important GI bleeding	**Low**		**RR 0.36** (0.19 to 0.67)[1]	1274 (11 studies)	⊕⊕⊖⊖ **low**[2,3,4]	
	10 per 1000	**4 per 1000** (2 to 7)				
	High					
	50 per 1000	**18 per 1000** (10 to 34)				
Overall mortality	**223 per 1000**	**223 per 1000** (181 to 275)	**RR 1.00** (0.81 to 1.23)	1007 (7 studies)	⊕⊕⊕⊖ **moderate**[5]	
Nosocomial pneumonia	**105 per 1000**	**112 per 1000** (77 to 160)	**RR 1.06** (0.73 to 1.52)[6]	1100 (8 studies)	⊕⊕⊕⊖ **moderate**[2,7]	
***Clostridium difficile* infection** (in studies examining any antisecretory therapy)	**50 per 1000**	**93 per 1000** (72 to 120)	**OR 1.95** (1.48 to 2.58)	18,468 (19 studies)	⊕⊖⊖⊖[8] **very low**	

CI = confidence interval, RR = relative risk, OR = odds ratio.
[1] In two recent meta-analyses (Pongprasobchai. *J Med Assoc Thai* 2009;92:632; Lin. *Crit Care Med* 2010;38:1197): OR 0.42 (95% CI, 0.2–0.91) and risk difference (RD) -4% (95% CI, -9 to +1%).
[2] Only three studies were in low bias risk category. For the remainder, the bias risk was mostly due to unclear blinding and unclear concealment of randomization. This is less important for mortality (not downgraded for that outcome).
[3] High or unknown risk of bias studies (lower quality) provided larger estimate of PPI efficacy than studies of higher quality (RR 0.16 [0.07-0.39] versus 0.6 [0.27-1.35]).

[4] Some asymmetry of funnel plot noted; quality of evidence is not lowered for possibility of publication bias. Quality lowered due to imprecision (data based on <50 events).
[5] A minority of the studies was in the low bias risk category. Most studies had unclear blinding and concealment of randomization.
[6] Two recent meta-analyses (Pongprasobchai 2009; Lin 2010): RD +1% (-9 to +11%), OR 1.02 (0.59−1.75).
[7] Imprecision: Wide confidence interval.
[8] From Leonard J et al. *Am J Gastroenterol* 2007;102: 2047. Observational studies with indirectness to critically ill patients. The association was numerically greater for PPI (OR 2.05 [1.47−2.85]) than for H2RA (OR 1.48 [1.06−2.06]) without statistically significant difference between those two classes of drugs (*P*=0.17). We did not consider this outcome critical, but we acknowledge the possibility of a different interpretation.