## Surviving Sepsis Guidelines 2016

IMPLICATIONS FOR THE MANAGEMENT OF SEPSIS IN MYANMAR

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### Surviving sepsis guidelines

- The world's leading cause of preventable death
- Globally, sepsis is estimated to kill at least 6 million people annually
- The Surviving Sepsis Campaign is a global initiative which is committed to reducing mortality from sepsis and septic shock.
- First established in 2008, guidelines are updated as the evidence base evolves

The New England Journal of Medicine

#### EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP\*



Mortality was 30% in the EGDT arm Versus 46% in the usual care arm





Management of Sepsis and Septic Shock

#### Surviving Sepsis Campaign: Association Between Performance Metrics and Outcomes in a 7.5-Year Study

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CCM 2015

#### Falling sepsis related mortality

Figure 1. Mean Annual Mortality in Patients With Severe Sepsis



Kaukonen JAMA 2014

## Surviving Sepsis Guidelines 2016

CrossMark

#### **CONFERENCE REPORTS AND EXPERT PANEL**

#### Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

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#### Recommendations

#### 93 Recommendations

- ► 32 Strong recommendations: "We recommend"
- ► 39 Weak recommendations: "We suggest"
- 18 Best Practice Statements

# So should we apply the 2016 SSG in Myanmar?

#### International Surviving Sepsis Campaign guidelines 2016: the perspective from low-income and middle-income countries

In the most recent international Surviving Sepsis Campaign guidelines, Rhodes and colleagues<sup>1</sup> excellently outline evidence-based management of patients with sepsis and septic shock. Of note, however, is that most of the world's population resides in low-income and middleincome countries (LMICs), where the burden of sepsis is enormous, outcomes are often poor, and socioeconomic consequences are dire.<sup>2</sup> Of the 655 references supporting the new sepsis guidelines, only a few pertain to studies in LMICs (about 10%).<sup>1</sup> This disparity raises concerns that the challenges and problems inherent to LMICs remain inadequately addressed. The guidelines, for example, mainly focus on management of bacterial and fungal sepsis as most frequently encountered in high-income countries. Strikingly, the specific diagnosis and management of sepsis due to pathogens commonly

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### Do the SSG apply in LMIC?

- Fewer trained health care professionals
- Fewer material resources (equipment and drugs)
- Less supporting infrastructure (eg imaging)
- Less laboratory support (lactate, microbiology)
- Basic logistics (water, electricity, oxygen, pressurised air)
- Different pathogens (dengue, TB, influence of HIV)

The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: A prospective intervention study\*

Shevin T. Jacob, MD, MPH; Patrick Banura, MBChB, MPH; Jared M. Baeten, MD, PhD; Christopher C. Moore, MD; David Meya, MMed; Lydia Nakiyingi, MMed; Rebecca Burke, MD; Cheryl Lynn Horton, MD; Boaz Iga, MS, MT (ASCP); Anna Wald, MD, MPH; Steven J. Reynolds, MD, MPH; Harriet Mayanja-Kizza, MMed, MS; W. Michael Scheld, MD; for the Promoting Resource-Limited Interventions for Sepsis Management in Uganda (PRISM-U) Study Group



## Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension A Randomized Clinical Trial

Ben Andrews, MD; Matthew W. Semler, MD, MSc; Levy Muchemwa, MBChB; Paul Kelly, MD, FRCP; Shabir Lakhi, MBChB; Douglas C. Heimburger, MD, MS; Chileshe Mabula, MBChB; Mwango Bwalya, MBChB; Gordon R. Bernard, MD



JAMA 2017



#### Mortality after Fluid Bolus in African Children with Severe Infection



# So should we apply the SSG in Myanmar?

#### Sepsis-3 Definitions

Sepsis: Life-threatening organ dysfunction caused by dysregulated host response to infection

Septic Shock: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality

#### A. Recognition & initial resuscitation

1. Sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately (Best Practice Statement).

## SEPSIS IN ADULTS IS A SERIOUS CONDITION

that can initially look like flu, gastroenteritis or a chest infection. Sepsis affects more than 250,000 people every year in the UK.

The UK Sepsis Trust registered charity number (England & Wales) 1158843 Seek medical help urgently if you develop any or one of the following: lurred speech or confusion xtreme shivering or muscle pain assing no urine (in a day) evere breathlessness t feels like you're going to die kin mottled or discoloured SIAS IT'S A SIMPLE QUESTION, BUT IT COULD SAVE A LIFE

### A. Initial resuscitation

- 2. In the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 h (strong recommendation, low quality of evidence).
- S. Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of hemodynamic status (BPS).
- 4. Further hemodynamic assessment (such as assessing cardiac function) should determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).
- 5. Dynamic over static variables should be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).

#### A. Initial resuscitation

6. The initial target mean arterial pressure (MAP) is 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).



Lehman CCM 2013

#### A. Initial resuscitation

7. Use lactate in patients with elevated lactate levels to guide resuscitation as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).



# B. Screening for sepsis and performance improvement

 1. Hospitals should have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (BPS).

#### Sepsis: defining a disease continuum



Maharaj et al. Critical Care (2015) 19:254 DOI 10.1186/s13054-015-0973-y



#### RESEARCH

#### **Open Access**



## Rapid response systems: a systematic review and meta-analysis

Ritesh Maharaj<sup>1,2,3\*</sup>, Ivan Raffaele<sup>2</sup> and Julia Wendon<sup>1,2</sup>

The implementation of Rapid Response Systems has been associated with an overall reduction in hospital mortality in both the adult (RR 0.87, 95 % CI 0.81–0.95, p<0.001 and paediatric (RR=0.82 95 % CI 0.76–0.89) in-patient population.

## C. Diagnosis

I. Appropriate microbiologic cultures (including blood) should be obtained before starting antimicrobial therapy if doing so results in no substantial delay in the start of antimicrobials (BPS). Journal of Internal Medicine 1998; 244: 379-386

## The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection

L. LEIBOVICI<sup>1</sup>, I. SHRAGA<sup>1</sup>, M. DRUCKER<sup>2</sup>, H. KONIGSBERGER<sup>2</sup>, Z. SAMRA<sup>3</sup> & S. D. PITLIK<sup>1,2</sup> From the <sup>1</sup>Department of Medicine, the <sup>2</sup>Infectious Diseases Unit, and the <sup>3</sup>Microbiology Laboratory, Rabin Medical Center, Beilinson Campus, Petah-Tiqva; and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Mortality was **20%** (436/2158) in those given appropriate antibiotic therapy versus **34%** (432/1255) in those not given appropriate antibiotic therapy (p=0.0001).

 I. IV antimicrobials should be initiated as soon as possible and within 1 hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence).

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

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



CCM 2006

- 2. Empirical broad-spectrum therapy with one or more antimicrobials should be initiated to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).
- S. Empirical antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS).

- 4. Sustained systemic antimicrobial prophylaxis is NOT recommended in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury) (BPS).
- 5. Dosing strategies of antimicrobials should be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock (BPS).

- 6. Empirical combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).
- 7. Combination therapy should not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock (weak recommendation, low quality of evidence).
- 8. Combination therapy is not recommended for the routine treatment of neutropenic sepsis/bacteremia (strong recommendation, moderate quality of evidence).
- 9. If combination therapy is initially used for septic shock, de-escalation is recommended with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. (BPS).

- 10. An antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).
- 11. Longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia (weak recommendation, low quality of evidence).
- 12. Shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (weak recommendation, low quality of evidence).



#### Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans,
C.H. Cook, P.J. O'Neill, J.E. Mazuski, R. Askari, M.A. Wilson, L.M. Napolitano,
N. Namias, P.R. Miller, E.P. Dellinger, C.M. Watson, R. Coimbra, D.L. Dent,
S.F. Lowry,\* C.S. Cocanour, M.A. West, K.L. Banton, W.G. Cheadle,
P.A. Lipsett, C.A. Guidry, and K. Popovsky





- 13. We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (BPS).
- 14. We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence).

#### E. Source control

- 1. A specific anatomic diagnosis of infection should be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made (BPS).
- 2. Prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established (BPS).

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### F. Fluid therapy

- 1. A fluid challenge technique should be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS).
- Crystalloids are the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
- S. Balanced crystalloids or saline are recommended for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).

### F. Fluid therapy

- 4. Consider albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).
- 5. Hydroxyethyl starches (HESs) should not be used for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
- 6. Crystalloids are recommended over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence)

#### G. Vasoactive medications

- 1. Noradrenaline is the first choice vasopressor (strong recommendation, moderate quality of evidence).
- 2. Vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or adrenaline (weak recommendation, low quality of evidence) should be added to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.

Solution 3. Dopamine should only be used as an alternative vasopressor agent to noradrenaline in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation, low quality of evidence).

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#### Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators\*



#### G. Vasoactive medications

- 4. Don't use low-dose dopamine for renal protection (strong recommendation, high quality of evidence).
- 5. Consider dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).
- 6. All patients requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available (weak recommendation, very low quality of evidence).

#### H. Corticosteroids

1. Don't use IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).



Gibbinson Crit Care 2017

#### The NEW ENGLAND JOURNAL of MEDICINE

#### ORIGINAL ARTICLE

#### Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot,
M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes,
K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators
and the Australian–New Zealand Intensive Care Society Clinical Trials Group\*

There were no significant between-group differences with respect to mortality at 28 days, the rate of recurrence of shock, the number of days alive and out of the ICU, the number of days alive and out of the hospital, the recurrence of mechanical ventilation, the rate of renal replacement therapy, and the incidence of new-onset bacteremia or fungemia.

#### I. Blood products

- 1. RBC transfusion should only occur when haemoglobin concentration decreases to <7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute haemorrhage (strong recommendation, high quality of evidence).
- 2. Don't use erythropoietin for treatment of anaemia associated with sepsis (strong recommendation, moderate quality of evidence).
- 3. Don't use fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures (weak recommendation, very low quality of evidence).

#### I. Blood products

4. Use prophylactic platelet transfusion when counts are <10,000/mm<sup>3</sup> (10 × 10<sup>9</sup>/L) in the absence of apparent bleeding and when counts are <20,000/mm<sup>3</sup> (20 × 10<sup>9</sup>/L) if the patient has a significant risk of bleeding. Higher platelet counts [≥50,000/mm<sup>3</sup> (50 × 10<sup>9</sup>/L)] are advised for active bleeding, surgery, or invasive procedures (weak recommendation, very low quality of evidence).

#### J. Immunoglobulins

1. Don't use IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).

## K. Blood purification

1. No recommendation regarding the use of blood purification techniques.



## L. Anticoagulants

1. Don't use of antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence).

#### **ORIGINAL ARTICLE**

## Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis

Gordon R. Bernard, M.D., Jean-Louis Vincent, M.D., Ph.D., Pierre-Francois Laterre, M.D., Steven P. LaRosa, M.D., Jean-Francois Dhainaut, M.D., Ph.D., Angel Lopez-Rodriguez, M.D., Jay S. Steingrub, M.D., Gary E. Garber, M.D., Jeffrey D. Helterbrand, Ph.D., E. Wesley Ely, M.D., M.P.H., and Charles J. Fisher, Jr., M.D., for the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group<sup>\*</sup> N Engl J Med 2001; 344:699-709 | March 8, 2001 | DOI: 10.1056/NEJM200103083441001



- 1. Use a target tidal volume of 6 mL/kg predicted body weight (PBW) compared with 12 mL/kg in adult patients with sepsis induced ARDS (strong recommendation, high quality of evidence).
- 2. Use an upper limit goal for plateau pressures of 30 cmH<sub>2</sub>O rather than higher plateau pressures in adult patients with sepsis-induced severe ARDS (strong recommendation, moderate quality of evidence).

- 3. Use higher PEEP over lower PEEP in adult patients with sepsisinduced moderate to severe ARDS (weak recommendation, moderate quality of evidence).
- 4. Use recruitment manoeuvres in adult patients with sepsis-induced, severe ARDS (weak recommendation, moderate quality of evidence).
- 5. Use a prone rather than a supine position in adult patients with sepsis-induced ARDS and a PaO<sub>2</sub>/FiO<sub>2</sub> ratio <150 (strong recommendation, moderate quality of evidence).

- 6. Use high-frequency oscillatory ventilation (HFOV) in adult patients with sepsis-induced ARDS (strong recommendation, moderate quality of evidence).
- 7. No recommendation regarding the use of non-invasive ventilation (NIV) for patients with sepsis-induced ARDS.
- ► 8. Use neuromuscular blocking agents (NMBAs) for ≤48 h in adult patients with sepsis induced ARDS and a PaO<sub>2</sub>/FiO<sub>2</sub> ratio <150 mm Hg (weak recommendation, moderate quality of evidence).

- 9. Use a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (strong recommendation, moderate quality of evidence).
- 10. Don't use of β-2 agonists for the treatment of patients with sepsisinduced ARDS without bronchospasm (strong recommendation, moderate quality of evidence).
- 11. Don't use a PA catheter for patients with sepsis-induced ARDS (strong recommendation, high quality of evidence).

- 12. Use lower tidal volumes over higher tidal volumes in adult patients with sepsis induced respiratory failure without ARDS (weak recommendation, low quality of evidence).
- 13. Mechanically ventilated sepsis patients should be maintained with the head of the bed elevated between 30° and 45° to limit aspiration risk and to prevent the development of VAP (strong recommendation, low quality of evidence).

#### N. Sedation and analgesia

I. We recommend that continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration end points (BPS).

#### O. Glucose control

1. Use a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤180 mg/dL rather than an upper target blood glucose level ≤110 mg/dL (strong recommendation, high quality of evidence).

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#### Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators\*

Increased mortality in patients with intensive blood sugar control (81-108mg/dL) versus conventional control (<180mg/dL) (odds ratio1.14; 95% confidence interval, 1.02 to 1.28; P=0.02)

#### O. Glucose control

- 2. Blood glucose values should be monitored every 1–2 h until glucose values and insulin infusion rates are stable, then every 4 h thereafter in patients receiving insulin infusions (BPS).
- Solution 3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (BPS).

#### P. Renal replacement therapy

- 1. Continuous RRT (CRRT) or intermittent RRT should be used in patients with sepsis and acute kidney injury (weak recommendation, moderate quality of evidence).
- 2. CRRT should be used to facilitate management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence).
- 3. Don't use RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis (weak recommendation, low quality of evidence).

#### Q. Bicarbonate therapy

► 1. Don't use sodium bicarbonate therapy to improve haemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15 (weak recommendation, moderate quality of evidence).

# R. Venous thromboembolism prophylaxis

- I. Use pharmacologic prophylaxis [unfractionated heparin (UFH) or low-molecular- weight heparin (LMWH)] against venous thromboembolism (VTE) in the absence of contraindications to the use of these agents (strong recommendation, moderate quality of evidence).
- 2. Use LMWH rather than UFH for VTE prophylaxis in the absence of contraindications to the use of LMWH (strong recommendation, moderate quality of evidence).
- 3. Use combination pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible (weak recommendation, low quality of evidence).
- 4. Use mechanical VTE prophylaxis when pharmacologic VTE is contraindicated (weak recommendation, low quality of evidence).

#### S. Stress ulcer prophylaxis

- 1. Use stress ulcer prophylaxis in patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding (strong recommendation, low quality of evidence).
- 2. We suggest using either proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) when stress ulcer prophylaxis is indicated (weak recommendation, low quality of evidence).

## T. Nutrition

I. We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally (strong recommendation, moderate quality of evidence).

2. We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible (strong recommendation, moderate quality of evidence).

## U. Setting goals of care

- I. Goals of care and prognosis should be discussed with patients and families (BPS).
- 2. Goals of care should be incorporated into treatment and end-oflife care planning, utilizing palliative care principles where appropriate (strong recommendation, moderate quality of evidence).
- 3. Goals of care should be addressed as early as feasible, but no later than within 72 h of ICU admission (weak recommendation, low quality of evidence).

#### So should we apply the SSG in Myanmar?

Many of these interventions would be expected to have a benefit in Myanmar

## Suggestions

- Early recognition and monitoring
- Microbiological diagnosis
- An understanding of local resistance patterns
- Early, broad-spectrum antibiotics
- Cautious fluids
- Identify source for source control
- Stress ulcer and DVT prophylaxis
- Enteral nutrition
- Communication with families

#### Myanmar Sepsis Guidelines

Myanmar clinicians develop guidelines using local data that take into account the specific challenges of caring for patients in Myanmar