Editorial

The management of sepsis: science & fiction

This special edition of the *Journal of Thoracic Disease* (*JTD*) explores emerging concepts in the management of patients with sepsis and septic shock. Sepsis has been a leading cause of death in humans since the dawn of mankind. Data suggests that almost half the entire population of Europe and Asia were wiped out in the Black Death plague of the early 15th century. More recently between 50–100 million patients were estimated to have died during the 1918 influenza pandemic (1); most of these deaths being due to bacterial pneumonia (2). The causation and treatments of sepsis have been shrouded with superstition since the earliest times (3). The Chinese utilized moldy soybean curd to treat infections some 2,500 years ago (3). Hippocrates (460–370 BC) the "father of medicine" popularized the concept of "dysregulated body humors" as a cause of disease and used myrrh, wine, and inorganic salts to treat infected wounds. Galen (129–199 AD) a prominent Roman physician, devoted much of his practice to bloodletting and the use of "medicinals" including theriac, a mixture of over 70 substances (4). Bloodletting remained a popular treatment for sepsis and was the treatment of choice for cholera in the European epidemic of 1832 (5). The most important advance in our understanding of sepsis came in 1878 when Louis Pasteur [1822–1895] proposed the "germ theory". This was followed by the discovery of penicillin by Sir Alexander Fleming [1881–1955] in 1929. Following the discovery of penicillin numerous other antibiotics followed and the understanding and treatment of infectious diseases advanced significantly. However, there were also a number of setbacks, most notably the formation of the Surviving Sepsis Campaign in 2004 (6). Ostensibly to improve the outcome of patients with sepsis, this endeavor was conceived by Eli Lilly and Company to promote the sales of their drug (Xigris) (7). More recent iterations of this guideline have dominated the approach to patients with sepsis (8,9), however, unfortunately, much like the approaches of Hippocrates and Galen many of the recommendations of these guidelines are based on myths and personal beliefs (Grade level of evidence: expert opinion) (10). Indeed, many of these recommendations may be harmful (see *Table 1*) (11-13). These concepts are highlighted in the reviews by Spiegel *et al.*, Marik *et al.*, and Wang *et al.* (14-16). While we believe that the approach to patients with sepsis should be personalized rather than based on rigid protocols (17), a number of basic principles are critical, these include:

(I) Early diagnosis. The early diagnosis of sepsis is critical to achieve a good outcome. This requires a high index of suspicion and the realization that up to 40% of patients with septic shock may present with vague non-specific symptoms (18). In addition, readily available tests including the complete blood count and differential and procalcitonin may aid in the early diagnosis of sepsis. These tests are reviewed in the papers of Farkas and Gregoriano *et al.* respectively (19,20).

(II) Early and appropriate antibiotics. Antibiotics should be administered as soon as feasible; however, artificial time constraints lack scientific validity. This topic is reviewed Schinkel *et al.* (21).

(III) Early source control. The septic episode will not resolve until source control is achieved.

(IV) An individualized, physiologically guided, conservative approach to fluid management. This topic is reviewed by Marik *et al.* (15).

(V) The early use of norepinephrine in patients with septic shock. This approach is reviewed by Hamzaoui and Shi (22).

(VI) The early use of adjunctive supportive therapy including thiamine and vitamin C. This topic is summarized by Moskovitz *et al.* and Marik (23). In addition, the scientific rationale for using melatonin as adjunctive therapy for sepsis is reviewed by Colunga Biancatelli *et al.* (24).

The evidence based "revised" approach to the management of patients with sepsis is summarized in *Figure 1* (25). Recent publications suggest that the incidence of sepsis has increased substantially while the mortality has decreased. This may, however, be an artifactual observation due to changes in the definitions of sepsis. This is an important concept as the changing definitions of sepsis may account for claims of improved outcomes in observational cohort studies that span a number of years (26). This is illustrated by a study which claimed a dramatic (>50%) decline in sepsis mortality with the introduction of early goal-directed therapy (EGDT) (27), whereas in reality the mortality likely increased (28). This topic will be reviewed by Rhee and Klompass (29). Finally, over the last two decades countless dozens of randomized controlled trials (RCTs) have been performed testing novel approaches to sepsis. Twenty-eight- or 90-day mortality were the primary end-points in almost all of these studies. While RCTs are considered the "Golden Standard" by which to judge the efficacy of an intervention, in the

Table 1 The myths and the facts: Surviving Sepsis Campaign recommendations that lack scientific evidence and may be harmful

Myths	Facts
All patients with sepsis should receive antibiotics within an hour of presentation	Not supported by data: such an approach has a number of negative effects
Patients with refractory hypotension and/or an elevated lactate (>4 mmol/L) should receive a 30 mL/kg fluid bolus	Not supported by data. Likely to be harmful
Fluid administration should be titrated to achieve a central venous pressure >8 mmHg. This directive first appeared in the 2004 guideline and continues to be propagated	This endorsement has clearly been demonstrated to increase the risk of acute kidney injury and death
Lactate should be measured frequently and therapy titrated (with fluids) to the lactate clearance	Not supported by data. Likely to be harmful
Apply vasopressors "after" fluid resuscitation	Not supported by data. Vasopressors should be started early. Patients with sepsis are poorly fluid responsive
A protocolized approach to blood glucose management in ICU patients with sepsis improves outcome	Not supported by data. No study exists in critically ill patients which demonstrates improved outcomes with glycemic control

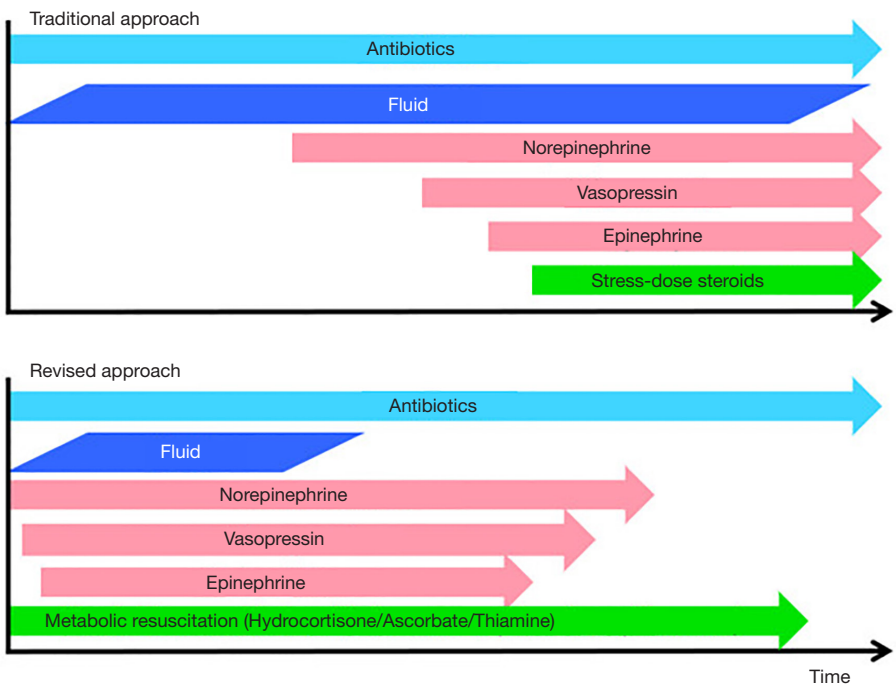

Figure 1 Paradigm change in the management of sepsis and septic shock. Reproduced with permission from Wolters Kluwer Health, Inc.

critically ill patients RCT's have many limitations. These include patient heterogeneity, non-standardized co-interventions, numerous exclusion criteria and delays in instituting therapy, to name but a few. Girbes and de Grooth make a plea that it is time to stop randomized and large pragmatic trials for intensive care unit (ICU) syndromes (30).

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Footnote

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