Pharmacological and Non-pharmacological management of Sepsis

Sepsis is a potentially life-threatening condition if left untreated and its mortality and morbidity all over the world is very high. It is caused due to an abnormal inflammatory response to a microbial infection. As its pathogenesis involves the entire body, early and extensive care is required for a patient's recovery from sepsis (Yealy et al, 2015). The current approaches to sepsis management include antimicrobial therapy, fluid resuscitation, glycemic control, steroids and acute blood purification. However, in spite of several advances in this area, mortality rates remain high and clear understanding of its reasons is lacking (Oda et al, 2014). This work is undertaken with the intention of throwing light on the current advances and gaps in our understanding of sepsis management in varied settings such as emergency departments, intensive care units, third world countries and pre-hospital care.

Relevant literature pertaining to the management of sepsis was obtained by examining the database PubMed. The search terms used were 'sepsis', 'treatment', 'pharmacological' and 'non-pharmacological' in different combinations to obtain the most relevant hits in the database. A total of 227 results were obtained. The titles of all publications were scanned and 72 original research articles on sepsis management were chosen for further review. The abstracts of all these articles were read and 10 articles from different settings and management strategies were selected as listed below.

Bloos, F., Thomas-Ruddel, D., Ruddel, H., Engel, C., Schwarzkopf, D., Marshall, J. C., Harbarth, S., Simon, P., Riessen, R., Keh, D., Dey, K., Weib, M., Toussaint, S., Schadler, D., Weyland, A., Ragaller, M., Schwarzkopf, K., Eiche, J., Kuhnle, G., Hoyer, H., Hartog, C., Kaisers, U. &

Reinhart, K. (2014). Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. *Critical Care, 18*, R42.

This article was published in Critical Care, which is a credible peer-reviewed journal. The authors of this article represent the Jena University of Germany, which is famous for its sepsis control center. This article concentrates on antimicrobial therapy for sepsis, including time of delivery and dosage. This is a longitudinal observational multi-center cohort study conducted to understand the delivery of antimicrobial therapy to sepsis patients and its consequences. Tables and graphs are extensive and help in providing a bird's eye view to the methodology. This study identified that if surgery is performed within 6 hours of diagnosis, the prognosis improves considerably. Also, it was found that different types of antimicrobial therapies in the initial stage led to different outcomes in patients. However, this study was unable to rule out other causes for the deterioration of the patient not related to antimicrobial therapy. This is similar to Jacob et al (2012) which also focuses on the use of antimicrobial therapy in patients with sepsis.

Rating 9/10: It considered the administration of antimicrobial therapy to sepsis patients related to the time of diagnosis.

Dunser, M. W., Festic, E., Dondorp, A., Kissoon, N., Ganbat, T., Kwizera, A., Haniffa, R., Baker, T. & Schultz, M. J. (2012). Recommendations for sepsis management in resource-limited settings. *Intensive Care Med, 38*, 557-574.

This article was published in the journal Intensive Care Med and its authors represent institutions in USA, Canada and Thailand. In this article, the authors have tried to understand and

analyze the management of sepsis in resource-limited settings. Physicians and nurses were trained according to the guidelines set by the European Society of Intensive Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. They were then sent to countries with resource-limited settings to provide good intensive care to patients with sepsis. The detailed guidelines and extensive training went a long way in enabling the healthcare workers to effectively care for the patients. As with any extensive care program, this too had its challenges. However, the authors have a number of recommendations in place for continual improvements in the training regimen. This article is similar to Zaidi et al (2011) in that it provides an overview of sepsis management in resource-limited settings.

Rating 10/10: It talks about sepsis management in resource-limited settings.

Girardis, M., Rinaldi, L., Donno, L., Marietta, M., Codeluppi, M., Marchegiano, P. & Venturelli, C. (2009). Effects on management and outcome of severe sepsis and septic shock patients admitted to the intensive care unit after implementation of a sepsis program: a pilot study. *Critical Care, 13*, R143.

This article was published in the journal Critical Care, which is well known for its articles on deathly conditions. The authors represent popular institutions in Italy. The authors of this article sought to examine the situation of sepsis management in Intensive Care Units (ICUs) in hospitals. This was a prospective observational study where the focus was on patients admitted to the ICU for severe sepsis or septic shock. Interventions and management strategies for these patients were monitored keeping in mind a number of other factors as well. This study found that hospitals which had well-formulated strategies and in-house management programs in place also had better recovery rates of patients. Tables and figures summarized these results well. However, the number of hospitals surveyed was not enough to allow coming to conclusions as to which

strategies work best. This article is different from the rest as it surveys patients with severe sepsis in an ICU setting.

Rating 8/10: Data pertains to ICU settings and patients with septic shock.

Glassford, N. J., Eastwood, G. M. & Bellomo, R. (2014). Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. *Critical Care, 18*, 696.

This article was published in the journal Critical Care and represents data from hospitals in Australia. The authors have sought to identify the physiologic outcomes of fluid bolus therapy in patients admitted with septic shock. The authors extensively scanned current available literature relating to sepsis and fluid bolus therapy. Types of articles used included intervention studies, comparison studies and group analyses. Venn diagrams, flow charts, tables and graphs have been used suitably to provide a visual guide to the search strategy and summary of results. This study found that literature pertaining to physiologic changes upon administration of fluid bolus therapy is limited and its comparison to alternative management strategies is nil. Given that this is an important strategy for the management of septic shock, research in this area is still lacking. Like Girardis et al (2009), this study also concentrates on patients with septic shock; however, it focuses on only one management strategy.

Rating 7/10: It increased our understanding of the state of current research in the field of septic shock.

Hodder, R. V., Hall, R., Russell, J. A., Fisher, H. N. & Lee, B. (2009). Early drotrecogin alpha (activated) administration in severe sepsis is associated with lower mortality: a retrospective analysis of the Canadian ENHANCE cohort. *Critical Care, 13*, R78.

This article has been published in the journal Critical Care, which is peer-reviewed and carries numerous articles about life-threatening diseases and conditions. The authors of this article belong to institutions like University of Ottawa and Dalhousie University and are pioneers in this field. In this article, the authors have sought to examine data from the ENHANCE trial which was conducted to test the safety and efficacy of drotrecogin alpha (activated) in patients with sepsis. A retrospective exploratory review of this trial was carried out as follow-up to identify the long-term effects of the use of drotrecogin alpha in sepsis patients. The authors found that administration of drotrecogin alpha at an early stage rather than late proved to be more effective in the prognosis of sepsis. The tables presented were effectively able to summarize the factors and variables involved in the study. This article has concentrated on the use of drotrecogin alpha for patients facing severe organ dysfunction or death. However, most patients examined were defined as 'stable' and hence, a true picture of the contribution of drotrecogin alpha in sepsis patients could not be obtained. As this study concentrates on data obtained from a single trial, it stands out from the rest.

Rating 7/10: Due to small sample size, sufficient emphasis on the therapeutic strategy could not be obtained.

Jacob, S. T., Banura, P., Baeten, J. M., Moore, C. C., Meya, D., Nakiyingi, L., Burke, R., Horton, C. L., Iga, B., Wald, A., Reynolds, S. J., Mayanja-Kizza, H. & Scheld, W. M. (2012). The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study. *Critical Care Medicine, 40*(7), 2050-2058.

This article was published in the journal Critical Care Medicine which is peer-reviewed and credible, and the authors of this article represent a number of popular institutions and universities in USA. This study is based in Uganda where sepsis is a major cause of death and

resources for its management are limited. This is a prospective intervention study where patients with sepsis were treated with antimicrobial therapy, fluid resuscitation and continuous monitoring during the first few hours after diagnosis. This was done for 1 year and mortality rates were calculated. The results showed that the mortality rates were significantly lower for the group who had received intervention and care as compared to the control group. Results were more favorable for patients who received fluid bolus therapy during the initial stages. This study is very similar to Dunser et al (2012) which also focuses on sepsis management in resource-limited settings. It also combines the themes of Glassford et al (2014) and Bloos et al (2014) in throwing light on the importance of fluid bolus therapy and antimicrobial therapy administration during the early stages.

Rating 10/10: It focuses on the use of two important management strategies in resource-constrained settings.

Patel, A., Laffan, M. A., Waheed, U. & Brett, S. J. (2014). Randomized trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ, 349*, g4561.

This article has been published in the journal BMJ, which is a peer-reviewed popular journal that carries numerous articles by established scientists. The authors of this article are either professors or consultants belonging to famous institutions in the UK. The objective of this study was to understand the effects of pooled human albumin in patients with sepsis as part of fluid resuscitation therapy. This study is a meta-analysis focusing on clinical trials where the use of human albumin has been compared to a control colloid fluid. An extensive review of literature found that the use of human albumin as part of fluid resuscitation therapy did not have any

significant effect on the mortality rates in patients with severe sepsis. The use of this therapy does not lead to any particular harm to the patient neither does it lead to improvement in the disease condition. This study is different from Glassford et al (2014) in that it concentrates on only one type of therapy as part of fluid resuscitation for sepsis patients.

Rating 7/10: This study proved that the treatment of sepsis patients with human albumin was pointless.

Seymour, C. W., Rea, T. D., Kahn, J. M., Walkey, A. J., Yealy, D. M. & Angus, D. C. (2012). Severe sepsis in pre-hospital emergency care – analysis of incidence, care and outcome. *American Journal of Respiratory and Critical Care Medicine, 186*(12), 1264-1271.

This article was published in the American Journal of Respiratory and Critical Care Medicine which focuses on conditions that can have life-threatening, and often respiratory, consequences. The authors of this article represent highly credited institutions in USA. This study focuses on management of sepsis in pre-hospital emergency care settings. This was a retrospective cohort study where reports of emergency medical service (EMS) encounters were obtained from a database and pre-hospital outcomes of these encounters were analyzed. It was found that at least 40% of all encounters resulted in hospital admissions for sepsis. In most of the cases, diagnosis of sepsis was done upon admission in the emergency care department and hence, pre-hospital care given to these patients was minimal. Tables and graphs have summarized the results well. One limitation of this study is that it was limited by location and time and hence, failed to provide an extensive view of the situation. This study is different from all the other studies in that it focuses on care given to sepsis patients before admission into the hospital.

Rating 8/10: It focuses on pre-hospital care in emergency situations.

Volbeda, M., Wetterslev, J., Gluud, C., Zijlstra, J. G., van der Horst, I. C. C. & Keus, F. (2015). Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med, 41*, 1220-1234.

This study has been published in a peer-reviewed and widely accredited journal Intensive Care Med and the authors belong to famous institutions in Denmark and Netherlands. This study was done to establish the safety and potential risks of using glucocorticosteroids at different doses in patients with sepsis. This was a meta-analysis and trial sequential analysis of clinical trials focusing on the use of high and low doses of steroids for sepsis management. Tables and graphs have been used to summarize the results, including statistical analyses, of this study. No potentially beneficial effects were noticed with the use of steroids in patients with severe sepsis with either high or low doses. However, this study lacks sufficient number of sources to draw any definitive conclusion regarding the use of glucocorticosteroids in patients with septic shock. This study is similar to Patel et al (2014) which is also a meta-analysis and trial sequential analysis. The difference lies in the fact that Patel et al (2014) performed the study on use of human albumin whereas the focus of this study was glucocorticosteroids.

Rating 7/10: This study negates the use of glucocorticosteroids in patients with sepsis.

Zaidi, A. K. M., Ganatra, H. A., Syed, S., Cousens, S., Lee, A. C. C., Black, R., Bhutta, Z. A. & Lawn, J. E. (2011). Effect of case management on neonatal mortality due to sepsis and pneumonia. *BMC Public Health, 11*(Suppl 3), S13.

This article was published in the journal BMC Public Health which is well-known for its publications on diseases with severe consequences. The authors belong to the Aga Khan University in Karachi, Pakistan, which is widely known for the quality of its research. This

article concentrates on the mortality rates of neonates who are diagnosed with sepsis in the third world countries. This is a systematic analysis of articles with data on the mortality of newborns with sepsis. Detailed flowcharts and tables reveal the search strategy and results of the study. This study found that sepsis is one of the three causes of high mortality rates of newborns in low-income countries, the other two being meningitis and pneumonia. Especially in resource-constrained settings, sepsis remains untreated in mothers, which also gets transmitted to the fetus. Antimicrobial therapy is strongly recommended in such scenarios. This study is similar to Dunser et al (2012) and Jacob et al (2012) in focusing on resource-limited settings and it is also similar to Bloos et al (2014) in concentrating on use of antimicrobial therapy. However, this study stands out from the rest in being focused on mortality due to sepsis in newborns.

Rating 9/10: It focuses on sepsis in newborns in resource-limited settings.

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