REVIEW ARTICLE

A brief review of septic cardiomyopathy and possible preventive strategies

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ABSTRACT

Sepsis induced cardiomyopathy leads to significant morbidity and mortality if not identified early and treated judiciously. A lot is written and discussed about it but till date, the syndrome remains a dilemma. Clinicians have used various modalities like beta- blockers to reduce heart rate , polymyxin B hemofiltration to neutralize the endotoxinemia thereby interfering with the progression of myocardial dysfunction, statins for its anti - inflammatory, antithrombotic and antioxidative properties thereby causing myocardial protection in the same way as it does in coronary artery disease. Ivabradine is a novel drug which is the first I*f* current inhibitor that causes selective heart rate reduction without any antihypertensive effect like beta blockers and doesn't affect hemodynamics. Its still in the trial stage. At present the only effective measure seems to be intensive fluid therapy, aggressive source control and use of broad spectrum antibiotics and maintenance of optimum hemodynamics with vasoactive agents.

Key words: Sepsis; Beta- adrenergic blockers; Polymyxin B; Ivabradine; Statins.

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INTRODUCTION

Septic cardiomyopathy is a syndrome in which there is acute and reversible myocardial depression due to sepsis, which is associated with normal or low left ventricular filling pressures.[1] Sepsis induced cardiac dysfunction can turn out to be a catastrophic situation which increases the ICU stay and increases the cost of treatment. It is responsible for a significant mortality and morbidity if not treated aggressively and in time. The morbidity and hospital stay is more if there is a delay between onset of sepsis and initiation of proper care in an intensive care unit.[2]

The magnitude of problem:

The incidence of left ventricular systolic dysfunction is variable which ranges from 18-29% in first 6 hours, up to 46% at 12 hours and an alarming 65% at the end of day one.[3] Even if the syndrome is recognized on time, it is difficult to predict the outcome in different patients.[4] The duration of vasoplegia determines the outcome rather than the extent of myocardial dysfunction. Factors like intrinsic immunity, presence of systemic co-morbidities, age, duration of illness etc could be responsible for the type of outcome. The progression can be stopped by timely intervention using broad spectrum antibiotics, source control, fluid resuscitation, judicious use of vasoactive drugs, and by preventing end organ damage. This dysfunction may be reversible if sepsis and septic shock is treated aggressively. Zanotti- Cavazzoni et al reviewed the existing concepts of sepsis- induced cardiac dysfunction and its clinical presentation, mechanism and available therapy.[5] Pulido et al described that the myocardial dysfunction can manifest as LV systolic dysfunction, LV diastolic dysfunction, RV dysfunction or biventricular dilatation / dysfunction alone or together.[6] Screening two dimensional echocardiogram on arrival of a patient with sepsis is very important as it helps in quantifying left ventricular function and can also guide in fluid resuscitation. Basu et al suggested two dimensional speckle tracking imaging that can assess deformation and strain by tracking displacement of acoustic markers in myocardium which can help in detecting ventricular dysfunction in sepsis that is not appreciated by routine echocardiogram. [7]

A patient with septic shock always has a central venous catheter (CVC) placed which is used for administering vasoactive agents, medications and for monitoring central venous pressure (CVP). A low CVP implies hypovolemia but a high CVP may not always suggest an adequately filled vasculature. Hence reliability of CVP monitoring is of very

little use in the background of septic cardiomyopathy.[8] Important hemodynamic parameters like extravascular lung water, extravascular lung water index and intrathoracic blood volume can be determined by transpulmonary thermodilution method . Serious cardiac issues like heart failure and pulmonary edema can be avoided by knowing these parameters. Pulmonary artery catheterization is not considered feasible in septic shock due to the invasive nature of the procedure, the expertise required and the serious problems posed by its placement in a sick patient. As described earlier, left ventricular filling pressures can be normal or low in septic shock hence pulmonary capillary wedge pressure guided fliud resuscitation may not be helpful as the heart is already failing with

a normal or low wedge pressure. Yu DT et al felt that placing a pulmonary artery catheter was not associated with a change in mortality rate.[9]

The FloTrac / Vigileo assembly estimates aortic impedance by the analysis blood pressure curve. The system requires no calibration, only demographic data with values like heart rate, mean arterial pressure and CVP has to be entered. However this system has been found to be less reliable in patients with severe sepsis. In a recent study by Monnet at al with 80 patients in a state of septic shock in which cardiac output was compared measured by PiCCO and Vigileo systems, the PiCCO system was found to detect more accurately changes in cardiac output produced by volume expansion as those induced by norepinephrine. The inaccuracy with Vigileo system was higher with increasing change in systemic vascular resistance.[10]

The impedance cardiography is a non-invasive method which makes continuously measures stroke volume, cardiac output, systemic vascular resistance, left cardiac work, acceleration of contractility index and left ventricular ejection time by converting changes in thoracic impedance in volume over time. Napoli et al did impedance cardiography in 56 patients admitted in emergency room and measured cardiac index. They found that a low cardiac index was associated with more mortality in the hospital.[11]

FJ Romero- Bermejo et al reviewed relevant aspects of sepsis induced myocardial dysfunction like clinical presentation, pathophysiology, etiopathogenesis, diagnostic tools and strategies available.[12] Constantino Jose Fernandes Jr et al mentioned in their review that till date myocardial dysfunction in sepsis remains a dilemma and only supportive treatment has been shown to be helpful as there are no proven specific drugs to reverse this.[13]

Etiopathology of septic cardiomyopathy and coronary vasculature in sepsis:

It's unusual how the coronary arteries are absolutely normal in cardiac dysfunction due to sepsis. In fact, studies in animals have shown that that there is an increased coronary blood flow in sepsis. There is actually no ischemia or lesion in the coronaries. Paradoxically, the myocardial dysfunction is not because of myocardial hypoperfusion or ischemia as seen in acute coronary syndrome. Giantomasso et al induced hyperdynamic non lethal sepsis in sheeps by injection of *E. coli* and observed that blood flow to the heart, gut and kidney increased markedly but still organ dysfunction developed. They postulated that global ischemia is not the principal mechanism of organ dysfunction in sepsis.[14] The factors responsible for myocardial dysfunction are inflammatory mediators like tumor necrosis factor α (TNFα), cytokines, lysozyme c, endothelin–1. Also nitric oxide (NO) dependent and independent alteration of basal and catecholamine stimulated cardiac myocytes contractility is also responsible for cardiomyopathy. Mitochondrial dysfunction which is characteristic of sepsis syndrome also occurs in cardiac myocytes which leads to ATP depletion that progressively contributes to dysfunction. There is apoptosis of cardiac myocytes if the progression of myocardial dysfunction is not interrupted by appropriate measures. Further, there is down regulation of ß- adrenoreceptors, depressed post receptor signaling pathways, impaired calcium liberation for sarcoplasmic reticulum and impaired electromechanical coupling at myofibrillar level.

Court et al described in their review described how myocardial dysfunction in sepsis is not associated with hypoperfusion or ischemia. They postulated that it is the interplay of inflammatory mediators that leads to cardiomyopathy.[15]

Cardiac markers in sepsis:

Surprisingly, cardiac troponins increase even though there are no myocardial ischemic events. Routine biomarkers done after acute coronary events like troponin T and I are usually elevated in septic myocardial involvement. Maeder et al postulated that it could be due to transient loss of membrane integrity due to myocardial dysfunction due to inflammatory mediators or due to microvascular thrombotic injury.[16] Post et al investigated the relationship of plasma BNP concentration in septic patients with myocardial dysfunction. They did a prospective study on 93 patients with septic shock and divided into 2 groups: one with normal ventricular function and other with impaired function. They found that plasma BNP levels provided as a reliable marker for identification of patients developing sepsis induced myocardial dysfunction. They suggested that 5th day BNP concentration may be used as a prognostic marker to identify patients with adverse outcomes.[17] Pulido et al did a prospective study on 106 patients with severe sepsis and septic shock who underwent transthoracic echocardiography (TTE) with 24 hrs of admission to ICU. They classified myocardial dysfunction as LV systolic dysfunction, LV diastolic dysfunction and RV dysfunction.

They found no difference in mortality between patients with normal and in patients with myocardial dysfunction. Frequency of myocardial dysfunction was 64%. This could be because the dysfunction was identified early and treated aggressively. Similarly, Nasir Hussain described that patients with SIRS, sepsis and SRTE (septic shock related troponin elevation) who on investigation were found to have high troponin levels had no prior history of CAD.[18] Recently, Wang et al published a systematic review and meta analysis to evaluate prognostic role of BNP/ NT-pro BNP IN sepsis. They included 1865 patients from 12 studies. They suggested that it may be used as a powerful predictor of mortality in septic patients but further large and adequately powered studies are required to come to a definitive conclusion.[19]

Beta blockers in sepsis:

Many articles have been published suggesting beneficial effects of β-blockers in sepsis syndrome to reduce heart rate in addition to other line of treatment. This has been fairly successful in animals. But using a drug with antihypertensive effect in presence of hypotensive, vasodilated state with probable myocardial dysfunction can be disastrous. We reviewed recent articles describing use of β -blockers for rate reduction in sepsis.

Novotny et al described how β -blockers in sepsis decreases cytokine effects, decreases cardiac dysfunction, normalizes cellular metabolism and improved glucose homeostasis. However they suggested that institution review board approval must be sought for using β-blockers in septic patients.[20] Shakar et al warned about potential hemodynamic compromise and risks associated with acute use of β-blockers in patients with sepsis induced myocardial dysfunction as possibility of hypotension and decrease in cardiac output in very high in septic patients.[21] They mentioned about an article by Schmittinger et al who used milrinone and enteral metoprolol to treat septic cardiac dysfunction. Requirement of noradrenaline was more in these patients, at times vasopressin was also used to support hemodynamics.[22] Shakar et al felt efficacy of this couldn't be established without a control group. Rudiger mentioned about encouraging results with ß1 receptor blockers during sepsis in preclinical and clinical studies but suggested further studies to formulate optimal dose and timing of medication.[23] Suzuki et al did a randomized animal study to investigate the efficacy of esmolol on myocardial function in peritonitis induced septic rats. They concluded that esmolol infusion improved oxygen utilization of myocardium and preserved myocardial function as well.[24] Werdan et al described how endotoxin makes alteration in cardiac pacemaker cells and how endotoxinemia modulates autonomic nerves regulation of heart function. They also described the preliminary data of offered therapeutic benefits of statins, β-blockers and ACE inhibitors in patients with MODS at that time.[25] Ackland et al conducted a prospective , randomized, controlled study in rats to investigate beneficial effects and survival benefits of β_1 adrenoceptor blockade in septic rats. They concluded that although anti-inflammatory and cardioprotective effects with mortality reduction was seen when β-blockers were used before septic insult, they suggested this hypothesis needs further exploration.[26] In clinical practice, to start β-blockers before septic insult is not possible. Only patients with coronary artery disease are usually on β-blockers. We haven't come across data in patients with CAD who had survival benefit in septic shock because of existing β-blockers therapy.

In the early stage of sepsis, there is a catecholamine surge which increases cardiac contractility and heart rate usually by stimulating β adrenoreceptors in the heart. Later in the course, due to excessive and continuous stimulation of β receptors, its density on myocardium will get reduced. There will be ongoing systolic and diastolic dysfunction already going on due to interplay of cytokines IL-6. To use β-blockers in such situation may really turn out to be counterproductive. [27] Klaus Zorn- Pauly et al did a study by incubating human myocytes from right atrial appendage for 6-10 hrs with lipopolysaccharide (LPS) 1 & 10 μg/ml and investigated the effect on cardiac pacemaker current I*f* (*f* stands for *funny*). They hypothesized that LPS induced I*f* impairment could lead to reduction in heart rate variability in sepsis and could be the reason behind cardiomyopathy and heart failure.[28]

Other therapies/ modalities:

Cruz et al used Polymyxin B (Pmx B) hemoperfusion along with conventional therapy in a targeted population of 64 patients in EUPHAS trial with severe sepsis or septic shock due to intra- abdominal gram negative sepsis and concluded that it significantly improved hemodynamics and organ dysfunction and a 28 day mortality.[29] However till date , Pmx B cartridge is an extremely costly affair and it also requires a hemodialysis sheath and dialysis unit, which further increases the cost. Mitaka et al published a meta analysis in which they described beneficial effects of Pmx B hemofiltration in septic shock patients. The meta analysis showed that there was improvement in hemodynamics, pulmonary oxygenation and mortality which could be due to adsorption of endotoxins, monocytes, activated neutrophils and a reduction in circulatory levels of cytotoxins and other mediators. It is also known to reduce endothelial damage, proapoptotic activity and immunosuppresion.[30]

Role of Ivabradine:

Ivabradine is the first heart rate lowering agent that acts on I*f* current at the sinus node. This is the same I*f* current described by Klaus Zorn- Pauly et al. The drug has no negative inotropic or lusiotropic effects, doesn't

cause any hemodynamic compromise even in presence of biventricular dysfunction.[31,32] MODIfY is a prospective, single centre, open label, randomized, controlled two arms, Phase II trial to evaluate the ability of Ivabradine to reduce an elevated heart rate in MODS patients, registered with clinicaltrials.gov. [33] The primary end point is the proportion of patients with a reduction of heart rate by at least 10 beats per minute (bpm) within 4 days. Treatment period will last 4 days and the follow up will be upto 6 months. The results are not out as of now. We will have to wait for the results to know if ivabradine will be really of any use in septic tachycardia. In theory, ivabradine may be a useful drug in patients with sepsis because it reduces heart rate purely without interfering with ß- adrenoreceptor thus not causing any hemodynamic compromise.

Role of NO inhibition:

A lot is described about the role of NO (nitric oxide) as an inflammatory mediator causing organ damage in sepsis. NO leads to hypotension, resistance to cathecholamines in septic shock and thus leads to cardiac dysfunction. In their study conducted on mice rendered septic by cecal ligation and puncture, van de Sandt et al proved that endothelial nitric oxide synthase (NOS3) which produces NO, if made inactive may lead to less hemodynamic compromise and can contribute to survival benefit and less stay in ICU.[34] To achieve NOS inhibition, they injected S- ethylisothiourea (ETU) into the peritoneal cavity after sepsis induction. They found that there was slight improvement in survival time in mice who received ETU. Also they found out that NOS3 induces a hyperdynamic state inspite of impaired cardiac function, impaired coronary reserve and leads to myocardial inflammatory response. However, similar positive results are not found in humans. Pathan et al investigated the role of IL-6 in myocardial dysfunction in patients with meningococcal septic shock. They identified 174 significant upregulated genes in meningococcus infected blood . They showed that removal of IL-6 from serum and from supernatant inflammatory cells stimulated by meningococci in vitro abolished negative inotropic activity. They described the stress activated p38 mitogen activated protein kinase (p38MAPK) pathway which controls IL-6 induced myocardial depression. They also suggested that myocardial dysfunction can be reversed by using an inhibitor of this enzyme.[35] Cannell et al also suggested that IL-6 blocking monoclonal antibodies may have a promising role in blocking this enzyme.[36] However, studies till date have been done on animals and the antibodies are mostly used in humans to down regulate genes responsible for tumors (especially prostate and ovary).[37,38] More studies will be requires to really prove the efficacy of monoclonal antibodies in humans with sepsis.

Statins in sepsis:

A lot has been written , discussed and published about use of statins in sepsis. It has been proven that statins are anti-inflammatory, antithrombotic , antioxidant agents, which also help by causing immunomodulation and improve endothelial function. As sepsis syndrome involves systemic inflammation, lots of inflammatory mediators and oxidants in circulation, endothelial dysfunction and an immune-compromised status; statins were considered useful in sepsis.[39] Gao et al did a review of available literature and thought that due to its pleotropic effects, statins may be a useful adjuvant therapy in sepsis by decreasing inflammation, by restoring endothelial function and by increasing immunity.[40] Loecker et al felt that patient should be individualized for statins as they found a paucity of a well- designed prospective studies and inconclusive evidence to support its use in sepsis.[41] The available retrospective publications are not enough for a conclusive evidence. Which generic statin and what strength is also not clear. They felt that the anti- inflammatory effects may harmful in patients with sepsis. Falagus et al did a systematic review of literature comprising 20 studies and felt that statins may have a positive role in patients with sepsis, although the studies had methodological limitations.[42]

Even Tleyjeh et al felt that there is a need for randomized trials to confirm the benefits of statins in sepsis.[43] The available literature doesn't make it clear which statin to start, when to start, what dose should be started, how long to continue. There are further limitations like it is not available for intravenous use and it can't be used in presence of liver dysfunction. One should be careful in presence of renal dysfunction.

CONCLUSION

Septic cardiomyopathy continues to be a mysterious entity even after so many years of research. Many modalities have been tried till date to interfere with the onset or progression of myocardial dysfunction, some strategies have been successful. But the fact remains that no modality is single handedly beneficial. Every patient has to be individualized for a preventive strategy. A screening 2D echocardiography on arrival to ICU can help in quantifying baseline myocardial function. Progressive myocardial dysfunction in a septic patient should raise the suspicion that the ongoing antibiotics are not appropriate provided other hemodynamic goals are achieved with fluids and inotrpoes. β -blockers, polymyxin B hemofiltration, statins etc have been used with considerable success rate. But we don't have definitive guidelines for their use. Ivabradine is still under trial. We conclude by mentioning that cardioprotective strategies like heart rate control, maintaining MAP (mean arterial pressure) with vasopressor/ inotropic support and aggressive supportive measures like source control, broad spectrum antibiotics and goal directed therapies should be used in order to have a better outcome in septic patients.

REFERENCES

1. Flynn A, Chokkalingam Mani B, Mather PJ. Sepsis-induced cardiomyopathy: a review of pathophysiologic mechanisms. Heart Fail Rev. 2010;15:605-11. [PubMed]
2. Funk D, Sebat F, Kumar A. A systems approach to the early recognition and rapid administration of best practice therapy in sepsis and septic shock. Curr Opin Crit Care. 2009;15:301-7. [PubMed]
3. Antoine VieillardBaron. Septic cardiomyopathy. Ann Intensive Care.2011;1:6. [PubMed] [Free Full Text]
4. Fry DE. Sepsis, systemic inflammatory response, and multiple organ dysfunction: the mystery continues. Am Surg. 2012;78:1-8. [PubMed]
5. Zanotti-Cavazzoni SL, Hollenberg SM. Cardiac dysfunction in severe sepsis and septic shock. Curr Opin Crit Care. 2009;15:392-7. [PubMed]
6. Pulido JN, Afessa B, Masaki M, Yuasa T, Gillespie S, Herasevich V et al. Clinical Spectrum, Frequency, and Significance of Myocardial Dysfunction in Severe Sepsis and Septic Shock. Mayo Clin Proc. 2012;87: 620–628. [PubMed] [Free Full Text]
7. Basu S, Frank LH, Fenton KE, Sable CA, Levy RJ, Berger JT. Two-dimensional speckle tracking imaging detects impaired myocardial performance in children with septic shock, not recognized by conventional echocardiography. Pediatr Crit Care Med. 2012;13:259-64. [PubMed]
8. Zanotti Cavazzoni SL, Dellinger RP. Hemodynamic optimization of sepsis-induced tissue hypoperfusion. Cri t Care. 2006;10 Suppl 3:S2. [PubMed] [Free Full Text]
9. Yu DT, Platt R, Lanken PN, Black E, Sands KE, Schwartz JS et al. Relationship of pulmonary artery catheter use to mortality and resource utilization in patients with severe. Crit Care Med.2003;31:2734-41. [PubMed]
10. Monnet X, Anguel N, Naudin B, Jabot J, Richard C, Teboul JL. Arterial pressure-based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. Crit Care 2010; 14: R109. [PubMed] [Free Full Text]
11. Napoli AM, Machan JT, Corl K, Forcada A. The use of impedance cardiography in predicting mortality in emergency department patients with severe sepsis and septic shock. Acad Emerg Med. 2010;17:452-5. [PubMed]
12. Romero-Bermejo FJ, Ruiz-Bailen M , Gil-Cebrian J , Huertos-Ranchal MJ. Sepsis-induced Cardiomyopathy. Curr Cardiol Rev. 2011;7:163–83. [PubMed] [Free Full Text]
13. Constantino Jose Fernandes Jr., Murillo Santucci Cesar de Assuncao. Myocardial Dysfunction in Sepsis: A Large, Unsolved Puzzle. Crit Care Res Pract. 2012; 2012: 896430. [PubMed] [Free Full Text]
14. Di Giantomasso D, May CN, Bellomo R. Vital organ blood flow during hyperdynamic sepsis. Chest. 2003;124:1053-9. [PubMed] [Free Full Text]
15. Olivier Court, Aseem Kumar, Joseph E Parrillo, Anand Kumar. Clinical review: Myocardial depression in sepsis and septic shock. Crit Care. 2002;6:500–508. [PubMed] [Free Full Text]
16. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. Chest. 2006;129:1349-66. [PubMed] [Free Full Text]
17. Post F, Weilemann LS, Messow CM, Sinning C, Münzel T. B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. Crit Care Med. 2008;36:3030-7. [PubMed]
18. Nasir Hussain. Elevated Cardiac Troponins in Setting of Systemic Inflammatory Response Syndrome, Sepsis, and Septic Shock. ISRN Cardiol. 2013; 2013: 723435. [PubMed] [Free Full Text]
19. Wang F, Wu Y, Tang L, Zhu W, Chen F, Xu T et al. Brain natriuretic peptide for prediction of mortality in patients with sepsis: a systematic review and meta-analysis. Crit Care. 2012; 16:R74. [PubMed] [Free Full Text]
20. Novotny NM, Lahm T, Markel TA, Crisostomo PR, Wang M, Wang Y, et al. beta- Blockers in sepsis: reexamining the evidence. Shock. 2009;31:113-9. [PubMed]
21. Shakar S, Lowes BD. Myocardial protection in sepsis. Crit Care. 2008;12:177. [PubMed] [Free Full Text]
22. Schmittinger CA, Dünser MW, Haller M, Ulmer H, Luckner G, Torgersen C, et al . Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. Crit Care. 2008;12:R99. [PubMed] [Free Full Text]
23. Rudiger A. Beta-block the septic heart. Crit Care Med. 2010 Oct;38(10 Suppl):S608-12. [PubMed]
24. Suzuki T, Morisaki H, Serita R, Yamamoto M, Kotake Y, Ishizaka A et al. Infusion of the beta-adrenergic blocker esmolol attenuates myocardial dysfunction in septic rats. Crit Care Med. 2005;33:2294-301. [PubMed]
25. Werdan K, Schmidt H, Ebelt H, Zorn-Pauly K, Koidl B, Hoke RS et al. Impaired regulation of cardiac function in sepsis, SIRS, and MODS. Can J Physiol Pharmacol. 2009;87:266-74. [PubMed]
26. Ackland GL, Yao ST, Rudiger A, Dyson A, Stidwill R, Poputnikov D et al. Cardioprotection, attenuated systemic inflammation, and survival benefit of beta1-adrenoceptor blockade in severe sepsis in rats. Crit Care Med. 2010;38:388-94. [PubMed]
27. Flierl MA, Rittirsch D, Huber-Lang MS, Sarma JV, Ward PA. Molecular Events in the Cardiomyopathy of Sepsis. Mol Med. 2008;14:327–336. [PubMed] [Free Full Text]
28. Zorn-Pauly K, Pelzmann B, Lang P, Mächler H, Schmidt H, Ebelt H, et al. Endotoxin impairs the human pacemaker current If. Shock. 2007;28:655-661. [PubMed]
29. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA. 2009;301:2445-52. [PubMed] [Free Full Text]
30. Mitaka C, Tomita M. Polymyxin B-immobilized fiber column hemoperfusion therapy for septic shock. Shock. 2011;36:332-8. [PubMed]
31. Borer JS, Tardif JC. Efficacy of ivabradine, a selective I(f) inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. Am J Cardiol. 2010;105:29-35. [PubMed]
32. S Sulfi , AD Timmis. Ivabradine – the first selective sinus node I channel inhibitor in the treatment of stable angina. Int J Clin Pract. 2006;60:222–228. [PubMed] [Free Full Text]
33. Reducing Elevated Heart Rate in Patients With Multiple Organ Dysfunction Syndrome (MODS) by Ivabradine (MODIfY). [Access Online] http://clinicaltrials.gov/ct2/show/record/NCT01186783]
34. van de Sandt AM, Windler R, Gödecke A, Ohlig J, Zander S, Reinartz M et al. Endothelial NOS (NOS3) impairs myocardial function in developing sepsis. Basic Res Cardiol. 2013;108:330. [PubMed] [Free Full Text]
35. Pathan N, Hemingway CA, Alizadeh AA, Stephens AC, Boldrick JC, Oragui EE, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet. 2004;363:203–209. [PubMed]
36. Cannell IG, Yaffe MB. Salvaging the septic heart through targeting the IL-6/p38 MAPK signaling network. Crit Care Med. 2011;39:1836–1837. [PubMed] [Free Full Text]
37. Karkera J, Steiner H, Li W, Skradski V, Moser PL, Reithdorf S, et al. The anti-inerleukin – 6 antibody siltuximab down regulates genes implicated in tumorigenesis in prostate cancer patients from a phase I study. Prostate 2011;71:1455-65. [PubMed]
38. Guo Y, Nemeth J, O'Brien C, Susa M, Liu X, Zhang Z, et al. Effects of siltuximab on the IL-6-induced signaling pathway in ovarian cancer. Clin Cancer Res. 2010;16:5759-69. [PubMed] [Free Full Text]
39. Novack V, Terblanche M, Almog Y. Do statins have a role in preventing or treating sepsis? Crit Care. 2006;10:113. [PubMed] [Free Full Text]
40. Gao F, Linhartova L, Johnston AM, Thickett DR. Statins and sepsis. Br J Anaesth. 2008;100:288-98. [PubMed] [Free Full Text]
41. I De Loecker, J-C Preiser. Statins in the critically ill. Ann Intensive Care. 2012;2:19. [PubMed] [Free Full Text]
42. Falagas ME, Makris GC, Matthaiou DK, Rafailidis PI. Statins for infection and sepsis: a systematic review of the clinical evidence. J Antimicrob Chemother. 2008;61:774-85. [PubMed] [Free Full Text]
43. Tleyjeh IM, Kashour T, Hakim FA, Zimmerman VA, Erwin PJ, Sutton AJ, et al. Statins
for the prevention and treatment of infections: a systematic review and meta-analysis. Intern Med. 2009;169:1658-67. [PubMed] [Free Full Text]