Pericarditis caused by Enterococcus faecium with acute liver failure treated by a multifaceted approach including antimicrobials and hemoadsorption

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Case Report

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Abstract

Background

Sepsis and septic shock are still life-threatening diseases with a high mortality rate. We report a complex case of peritonitis with pericarditis and acute liver failure caused by septic shock. Potentially hepato-toxic antibiotic therapy levels were monitored using the liver maximum capacity (LiMAx®) test and standard treatment was supplemented by adjunctive hemoadsorption with CytoSorb®.

Case presentation

The case features a 29-year-old woman with a history of Crohn's disease and cachexia. Peritonitis caused by *Enterococcus faecium* was diagnosed later due to an ileum perforation. The hematogenic spread led to the pericarditis. In addition, sepsis-related acute-liver-failure complicated antimicrobial therapy further. The combination of standard therapy, anti-infective medication and blood purification was associated with inflammation control, hemodynamic stabilization and a concomitant decrease in vasopressor support. An efficient, sustained reduction in plasma bilirubin levels was achieved while maintaining liver function.

Conclusions

This case shows how complex infectious diseases with an atypical infectious focus resulting in septic shock can be successfully treated. A combination of antimicrobial (tigecycline and caspofungin) and long-term adjunctive hemoadsorption therapy was administered while hepato-toxic antibiotic medication was monitored by liver function testing.

Background

In 2016, out of a total of 2.94 million German patients with a "cardiac diagnosis," only 2531 cases were hospitalized due to acute pericarditis (an estimated 0.086% of all cardiac diagnoses) (1). The most common form of acute pericarditis is viral in origin, self-limiting, and minimally life-threatening (2). However, bacterial pericarditis differs markedly from that of viral origin and reaches 100% lethality if untreated (2).

Pericarditis represents an inflammatory cardiac disease and can potentially induce systemic hyperinflammation mediated by inflammatory mediators such as IL-1 (3). In this context, multiorgan failure may occur, further worsening the prognosis. The liver, as an accelerator but also as a victim of the systemic inflammatory process, plays a key role (4). This must be taken into account particularly when a potentially liver toxic drug (e.g. antibiotics/antifungals) is used.
These rare cases require individual and patient-centered treatment plans. In the present case, we have combined established standard care, including antimicrobial therapy, with new therapeutic modalities such as hemoadsorption with CytoSorb® and LiMAx. CytoSorb® therapy is used for elevated cytokine and bilirubin levels. When combined with the liver maximum capacity test (LiMAx), an equally innovative diagnostic tool to adjust for anti-infective medication in the setting of sepsis-associated liver failure the effects are additive. These concepts are therefore of great value for our daily clinical work and management of complex diseases.

We report here the case of a 29-year-old woman with known Crohn's disease and cachexia who developed bacterial pericarditis caused by Enterococcus faecium, most likely based on peritonitis followed by acute liver failure. Our approach included a personalized treatment plan consisting of antimicrobials, hemoadsorption and liver function tests which lead to a full recovery of the patient (within 13 weeks).

**Case Presentation**

A 29-year-old woman with a history of Crohn's disease and cachexia presented with painful diarrhea, unintentional weight loss of 13 kilograms over the past three weeks caused by a mechanical ileus. Transfer to the intensive care unit (ICU) occurred 2 weeks later because of increasing somnolence, impaired gas exchange (PaO2 48 mmHg), and high norepinephrine requirements (1.56 µg/kg/min). Laboratory chemistry revealed significantly altered hepatic and inflammatory parameters (albumin 23.8 g/l, gamma-GT 118 U/l, alkaline phosphatase 142 U/l, cholinesterase 1814 U/l, CRP 194.8 mg/l, procalcitonin 59.80 µg/l). This corresponded to a SOFA score (Sequential Organ Failure Assessment) of 6.

The severity of the clinical picture demanded exploratory laparotomy for source control. Intraoperatively, a perforation with local peritonitis was found in the lower abdomen. A right hemicolectomy, partial resection of the small bowel, and side-to-side anastomosis were performed. Histology revealed massive chronic inflammation of the terminal ileum, typical of Crohn's disease.

Preoperatively started antibiotic therapy with piperacillin/tazobactam was continued for four days according to the resistogram (*Providencia stuartii*, *Escherichia coli* and *anaerobic bacteria*). Blood cultures taken on ICU admission were negative. The patient was treated with differentiated volume and catecholamine therapy. As she still required high doses of norepinephrine, a combination of citrate-anticoagulated continuous renal replacement therapy (CRRT) and a total of 3 adjunctive CytoSorb® hemoadsorption therapy sessions (for a total of 73 h) were applied, resulting in a rapid stabilization of her hemodynamic situation (norepinephrine to 8.3% of the maximum initial dose) and extubation on the day of CytoSorb cessation.

Four days after the operation, the patient's condition started to worsen rapidly with tachycardia, hypotension, and fever up to 39.0°C, as well as diminishing oxygen saturation levels. The patient had to be re-intubated and norepinephrine administration had to be initiated for hemodynamic stabilization.
(1.09 µg/kg/min). Over time, hemodynamics stabilized while diuresis resumed spontaneously and renal replacement therapy could be stopped shortly after.

A chest X-ray performed the same day revealed a pleural effusion. In search for an infectious source, samples (pleural fluid, two sets of blood cultures, bronchoalveolar fluid) were sent to microbiology, but proved negative. Abdominal and chest CT scan revealed an intact anastomosis but showed multiple dense foci inside the lungs. Despite the negative microbiology, the decision was made to intensify antibiotic therapy by escalation to meropenem. The dynamic maximum liver function capacity test (LiMAx®) showed a value of 57 µg/kg/h, indicating severe liver insufficiency (Figure 1). In addition, a subsequent CT scan confirmed severe, previously unknown, emphysematic changes (bullae) in the lungs which further compromised gas exchange. Over the next 9 days, both chest X-ray and CT scans indicated morphological improvement. However, the patient's condition rapidly deteriorated again now presenting a multiple organ-dysfunction syndrome (SOFA score 12). Inflammatory marker levels were clearly increased, the patient became anuric, while FiO₂ levels required an increase to 100%. Liver function was still severely impaired. The hypothesis was septic shock syndrome and blood culture samples were taken, however, neither showed bacterial nor fungal growth.

As the patient required continuous veno-venous hemodialysis (CVVHD) at that point, the decision was made to apply the CytoSorb® system for the second time in order to attenuate the hyperinflammatory response. This was also done to eliminate liver metabolites, such as bilirubin, ammonia and bile acids in the context of sepsis-associated acute liver failure (Figure 2). Consequently, another 13 CytoSorb adsorber cartridges were applied consecutively for a total duration of 346 hours. With maximum interdisciplinary care (laparotomy, CRRT, liver-and ventilation-support, pericardial drainage, antimicrobial therapy, etc.), the hyperinflammatory response was declining which resulted in a marked decrease in vasopressor requirements (reduction of vasopressor support to 16.9% of the maximum initial dose, respectively) and a normalization in bilirubin levels (Figure 2) accompanied by the onset of diuresis.

An emergency re-laparotomy was performed that excluded any intraabdominal source of sepsis. However, echocardiography revealed a significant increase in pericardial effusion and pericardial tamponade was diagnosed. The patient underwent a pericardial tap and a drain was inserted.

One day later, Enterococcus faecium was identified in the pericardial fluid but also in all blood cultures, intraabdominal swab as well as urine and tracheal fluids. All strains proved to have equal resistance patterns suggesting a common origin that was most likely the ruptured ileum. Pathohistologically, a granulocyte-rich pericardial effusion was found to be an expression of a florid inflammation. Based on these findings, an immediate change in the antibiotic regimen was necessary. An antimicrobial chemotherapy supplemented by tigecycline and the antifungal caspofungin was considered appropriate, given the risk profile (parenteral nutrition, intraabdominal perforation, immunosuppression).

Antimicrobial chemotherapy was supplemented by caspofungin is potentially hepatotoxic (likelihood score: D (possible cause of clinically detectable liver damage)) (5) and was closely monitored using the LiMAx® test (8 measurements in total). The dose was reduced accordingly (Figure 3) (6). As for
tigecycline, it is not proven to have a negative impact on liver function (likelihood score: E* (unproven but suspected cause of clinically apparent liver injury)) (7), standard dosing of 50 mg twice daily was applied.

Inflammatory parameters improved consistently over the course of the next week (Figure 2). The catecholamine dose was reduced and invasive ventilation was changed to assisted ventilation. Gradually, the sedation rate was reduced and the patient regained consciousness. Her mental state improved continually. To facilitate weaning, a tracheotomy was performed. In the meantime, the patient’s overall clinical condition improved accompanied by a reduction in SOFA score to 6. As norepinephrine requirements were minimal, CytoSorb® therapy was discontinued. Five days later, *E. faecium* was cultivated from the tip of the central venous catheter under continued antimicrobial therapy with tigecycline. The catheter was removed and tigecyclin was changed to linezolid (600 mg twice daily). The LiMAx® measurement another 8 days later showed a stable, but still medium-gross restricted hepatic function (136 µg/kg/h) (Figure 1). After further improvement the patient was discharged in a stable clinical condition from the ICU to the normal ward 53 days after initial admission.

**Discussion**

To the best of our knowledge, this is the first detailed description of an *E. faecium* pericarditis in a patient with complex pathophysiological changes caused by a multitude of different chronic (Crohn's disease, cachexia) and acute diseases (septic shock with multi-organ failure in bacterial pericarditis). The successful treatment was based on a multi-disciplinary and multi-layered interdisciplinary intervention including anti-infective therapy, hemoadsorption with the CytoSorb®-cartridge and dynamic liver function testing.

Bacterial, non-cardiosurgical pericarditis is very rare (1, 2) and is mainly caused by *Staphylococcus spp.* while *Streptococci*, including *Enterococci*, are much less frequently detected. Apart from an increasing pericardial effusion with life-threatening hemodynamic effects, no clinical symptoms such as chest pain or pericardial rubbing nor ECG alterations or paraclinical findings were detectable in our sedated patient. Echocardiography was the only procedure that quickly led to diagnosis and therapy.

*E. faecium* is a rare pathogen of a very rare acute bacterial pericarditis. It is more likely to occur with immunosuppression (8), seen in our patient who had a high risk of infection due to long-term steroid therapy in combination with an intra-abdominal perforation due to the known Crohn's disease. The most likely cause was a hematogenic scattered infection of the pericardium from the initial intraabdominal focus. Microbiological diagnostics confirmed *Enterococcus faecium* which had caused pericarditis in our patient. We decided to use intravenous therapy with tigecycline in combination with caspofungin, which was dose adapted to the severely impaired liver function. Since there was a risk of insufficient fungicidal caspofungin dosage, monitoring of dynamic liver function with the LiMAx® test was performed in correlation with static liver function values and the clinical presentation with good clinical success.
Patients with septic shock develop liver dysfunction or liver failure (9) and a variety of different drugs commonly used in intensive care medicine (antirheumatics, neuroleptics, antiepileptics, antibiotics, antifungals) can cause hepatotoxic effects, aggravate a pre-existing liver dysfunction or cause a so-called drug-induced liver failure (DILI) (10-12). While static liver tests (i.e. bilirubin, transaminases) only provide a snapshot of liver function, the LiMAX® test allows for a quantitative, dynamic measurement of the maximum liver function capacity (13). To exclude any influence on methacetin metabolism, CVVHD was paused for the duration of each LiMAX® measurement. The LiMAX® results are shown in Figure 1. Note, a result of 315 µg/kg/h or more is physiological (14) and lower values represent a liver function that may be impaired. Any value below 140 µg/kg/h strongly indicates severe liver insufficiency. A test result of less than 100 µg/kg/h in combination with respiratory dysfunction is associated with an increasing mortality rate (15) and values < 60 µg/kg/h indicate acute liver failure.

By using the LiMAX® test we were able to determine the actual functional state of the liver, whereas the standard methods showed a delay of several days between loss of function and paraclinical detection of pathological liver values (Figure 1 and 2). This allowed the detection of a drug-induced impairment of liver function, e.g. by caspofungin, at an early stage and simultaneously time to assess hepatic function in the context of septic multiple organ failure. Hence, instead of the recommended caspofungin dose of 50 mg once daily, we decided to reduce the dose to 35 mg daily, thus possibly preventing further toxic damage. During the course of the clinical improvement, the LiMAX® reading increased to 131 µg/kg/h at hospital day 40 parallel with the clinical improvement as an expression of a slow recovery of liver function under this caspofungin dose, so that no further toxic liver damage was assumed.

Under continuous renal replacement therapy (CRRT) the risk of incorrect or underdosage and therapy failure is increased due to altered pharmacokinetics (16; table 1). Dose recommendations for antimicrobial chemotherapy under CRRT are lacking (17). The same holds true for the CytoSorb adsorber.

**Table 1** Drugs for which an absolute or relative drug overdosage/intoxication can be treated with CytoSorb or a relevant decrease of serum concentrations must be expected (in modification of 16, 18, 19, 20, 27).
Drug group | Active pharmaceutical substances adsorbed by CytoSorb
---|---
Anticoagulants | Dabigatran, Rivaroxaban, Ticagrelor
Psychotropic drugs | Quetiapine, Venlafaxine, 3,4-Methylenedioxymethamphetamine (MDMA, “Ecstasy”)
Antiarrhythmics | Flecainide, Digoxin
Calcium channel blockers | Amlodipin, Verapamil
Anticonvulsants | Carbamazepine, Valproic acid, Phenytoin
Hypnotics and sedatives | Phenobarbital
Immunosuppressives | Tacrolimus, Ciclosporin
Antibiotics | Vancomycin, Amikacin, Tobramycin, Gentamicin, Linezolid, Teicoplanin, Meropenem, Imipenem, Ciprofloxacin, Piperacillin, Flucloxacillin
Antimycotics | Voriconazole, Fluconazole
Contrast agents | Iodixanol, Iohexol
Others | Aatoxine

The overall findings in the reported case taking into account the acute threat to life, the microbiological findings, the difficult localisation of the underlying infection, the existing multi-organ failure with severe liver failure, the need for rapid, bactericidal therapy with immediate achievement of relevant tissue levels, led us to intentionally administer an antibiotic therapy with tigecycline in an unchanged standard dose, (i.e. without the weight-adapted required dose reduction) under dynamic monitoring of liver function. In cases of severe liver dysfunction, dose adjustment to 2 x 25 mg daily should be performed.

Due to MW > 55 kDa, an interaction with the CytoSorb® adsorber was not very likely. In this regard, relevant adsorption phenomena with extraction rates between 85 and 100% (16) are described for various antibiotics and antifungals (Table 1). Dose adjustment is difficult to extrapolate because clearance is highest within the first two hours (18). Therefore, the administration of an additional antibiotic/antifungal dose within the first hours should be considered. If possible, an intensive drug monitoring should be carried out. In our case, a relevant adsorption of linezolid by CytoSorb (19, 20) in addition to the described high liver toxicity was a further reason to perform the primary therapy with tigecycline and not with linezolid.

The use of the CytoSorb® adsorber in patients with septic shock is currently the subject of controversial discussion with regard to the right indication, start and duration of therapy and the potential clinical benefit. We have used CytoSorb® for a previously unpublished total treatment time of 419 h in combined conditions (septic shock/liver failure). During treatment, an interdisciplinary intensive care therapy (laparotomy, CRRT, liver- and ventilation-support, pericardial drainage, antimicrobial chemotherapy, etc.) in
combination with CytoSorb® as an individual adjuvant treatment concept in both cycles (hospital day 15 to 18 and hospital day 22 to 38) allowed to control hyperinflammation and to clearly decrease vasopressor requirements (Figure 2).

Importantly, bilirubin serum concentrations were almost normal throughout the entire course of treatment, which can only be explained by the efficient clearance of CytoSorb over 2.5 weeks of treatment in persistent liver failure (Figure 2). In this regard, recent data shows that the CytoSorb adsorber can dissolve the strong bilirubin-albumin binding and adsorb bilirubin without a relevant change in albumin concentrations (21). CytoSorb therefore represents a promising, easy to carry out method for liver support. The combination of the adsorption and elimination of bilirubin and bile acids, the modulation of involved cytokines and the reduction of excess ammonia levels via a parallel renal replacement procedure allows to bridge the time until functional recovery or orthotopic liver transplantation (21). This concept has been described by several authors (22-24).

**Limitations**

In the overall view of the complex treatment process, some aspects remain worth discussing. The antimicrobial treatment with tigecycline and caspofungin for 12 days each followed by linezolid for a total of 41 days (including rehabilitation) led to full recovery of the patient. Whether a shorter treatment period would have been sufficient is unclear. With regard to the "original" intra-abdominal focus, a possible mixed infection and the existing liver failure, we decided to prioritise tigecycline. Daptomycin is not used for the treatment of pericardial *E. faecium* infection due to its limited spectrum and the ongoing discussion about the optimal dose, although it has a better efficacy compared to linezolid. Furthermore, daptomycin, like linezolid, is classified as toxic to the liver and was therefore not considered here as a therapeutic option (likelihood score: C (probable cause of clinically detectable liver damage). The catheter-associated infection by *E. faecium* at day 43 under ongoing tigecycline medication was possibly caused by the high distribution volume (7-12 l/kg) and the resulting (too) low serum levels (30).

We deliberately decided in favor of echocardiographic monitoring in pericarditis as our risk-benefit analysis and refrained from repeated puncture of the pericardial space. Microbiological sanitation was therefore not detectable.

We assume that the dynamic liver function measurement in septic shock using the LiMAx test reflects the liver function in real time during multi-organ failure. For cost reasons, a more frequent e.g. daily determination was not possible and thus therapeutically important information might not have been recorded.

Kogelmann et al. recommend changing the CytoSorb cartridges at intervals of 24 hours. In our case the average changing interval was 30.2 hours. Taking into account the time-dependent saturation kinetics, it must be assumed that the clearance decreases with time. Arguably, a better effectiveness of the hemoadsorption treatment could have been achieved by shortening the lifetime of the CytoSorb® cartridge to 24 hours.
Conclusions

To the best of our knowledge, this is the first case report of a patient with intraabdominal perforation caused by Crohn's disease with a secondary pericardial infection which was most likely hematogenically acquired. The patient required a tailored and unconventional treatment approach. In particular, the management of septic liver failure with dynamic liver function test (LiMAx®), adapted antibiotics/antimycotics medication and the long-term use of the CytoSorb® adsorber was described for the first time. Further studies are needed to clarify to what extent the presented concept can contribute to reducing the high mortality in sepsis, which has remained unchanged for decades.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

The patient gave the informed consent to publish the information from this case.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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TK has received lecture fees from the company Cytosorbent Europe.

Authors’ contribution

TK treated the patient on intensive care unit and analyzed and interpreted data regarding microbiological aspects as well as sepsis treatment and was a major contributor in writing the manuscript.

MWP treated the patient consularly and revised the manuscript from an infectiological point of view.

SA analyzed and interpreted the clinical data and was also involved in the creation of the manuscript.

CK analyzed and interpreted data regarding surgical aspects as well as concerning liver function and LiMAx diagnostic and reworked the manuscript.
ES performed literature research and reviewed the manuscript.

DH analyzed and interpreted data from anesthesiological point of view and reworked the manuscript.

GW analyzed and interpreted data from surgical point of view and reworked the manuscript.

CE was intensively involved in all aspects of clinical treatment and revised the manuscript.

All authors read and approved the final manuscript.

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**Abbreviations**

CRP: C-reactive protein

CRRT: Continuous renal replacement therapy

CVVHD: Continuous veno-venous hemofiltration

DILI: Drug-induced liver insufficiency

ICD-10: International Code of Diseases-10

ICU – Intensive Care Unit

LiMAX: Liver maximum capacity test

MELD: Model for End-Stage Liver Disease

SOFA: Sequential Organ Failure Assessment

**References**

1. Diagnosedaten der Patienten und Patientinnen in Krankenhäusern (einschl. Sterbe- und Stundenfälle). In: Bundesamt S, editor. Wiesbaden2017. 10.

2. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921-64.
3. Tomelleri A, Cavalli G, De Luca G, Campochiaro C, D’Aliberti T, Tresoldi M, Dagna L. Treating Heart Inflammation With Interleukin-1 Blockade in a Case of Erdheim-Chester Disease. Front Immunol. 2018 Jun 1;9:1233.

4. Sheth AA, Lim JK. Liver disease from asymptomatic constrictive pericarditis. J Clin Gastroenterol. 2008 Sep;42(8):956-8.

5. Clinical and Research Information on Drug-Induced Liver Injury - Echinocandins National Institute of Diabetes and Digestive and Kidney Diseases. Accessed 05 Jan 2020

6. Bellmann R, Smuszkiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. Infection. 2017;45(6):737-79.

7. Clinical and Research Information on Drug-Induced Liver Injury - Tigecycline National Institute of Diabetes and Digestive and Kidney Diseases; https://www.ncbi.nlm.nih.gov/books/NBK547888/. Accessed 05 Jan 2020

8. Sotoudeh Anvari M, Kianinejad R, Boroumand MA, Arzhan S, Jalali A. Bacterial pericarditis and antimicrobial resistance at the Tehran Heart Center, Iran. J Infect Dev Ctries. 2015;9(7):780-4.

9. Kirchner C, Sibai J, Schwier E, Henzler D, Eickmeyer C, Winde G, et al. Dosing of Antimycotic Treatment in Sepsis–Induced Liver Dysfunction by Functional Liver Testing with LiMAx®. Case Reports in Critical Care. 2019;2019:6.

10. Sarin SK. Acute-on-chronic liver failure: terminology, mechanisms and management. Nat Rev Gastroenterol Hepatol. 2016

11. Pandit A, Sachdeva T, Bafna P. Drug-Induced Hepatotoxicity: A Review. Journal of Applied Pharmaceutical Science. 2012;2(5):233-43.

12. Spernovasilis N, Kofteridis DP. Pre-Existing Liver Disease and Toxicity of Antifungals. J Fungi (Basel). 2018;4(4).

13. Buechter M, Gerken G, Hoyer DP, Bertram S, Theysohn JM, Thodou V, et al. Liver maximum capacity (LiMAx) test as a helpful prognostic tool in acute liver failure with sepsis: a case report. BMC Anesthesiol. 2018;18(1):71

14. Stockmann M, Vondran FWR, Fahrner R, Tautenhahn HM, Mittler J, Bektas H, et al. Randomized clinical trial comparing liver resection with and without perioperative assessment of liver function. BJS Open. 2018;2(5):301-9

15. Kaffarnik MF, Lock JF, Vetter H, Ahmadi N, Lojewski C, Malinowski M, et al. Early diagnosis of sepsis-related hepatic dysfunction and its prognostic impact on survival: a prospective study with the LiMAx test. Crit Care. 2013;17(5):R259

16. Roberts DM, Liu X, Roberts JA, Nair P, Cole L, Roberts MS, et al. A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics. Crit Care. 2015;19:84

17. Li AM, Gomersall CD, Choi G, Tian Q, Joynt GM, Lipman J. A systematic review of antibiotic dosing regimens for septic patients receiving continuous renal replacement therapy: do current studies supply sufficient data? J Antimicrob Chemother. 2009;64(5):929-37.
18. König C, Röhr AC, Brinkmann A, Roberts JA, Wichmann D, et al. In vitro removal of anti-infective agents by a novel cytokine adsorbent system. Int J Artif Organs. 2019;42(2):57-64
19. Poli EC, Rimmelé T, Schneider AG. Hemoadsorption with CytoSorb. Intensive Care Med. 2019;45(2):236-9
20. Morris C, Gray L, Giovannelli M. Early report: The use of CytoSorb™ haemabsorption column as an adjunct in managing severe sepsis: initial experiences, review and recommendations. J Intensive Care Soc. 2015;16(3):257-64
21. Gemelli C, Cuoghi A, Magnani S, Atti M, Ricci D, Siniscalchi A, et al. Removal of Bilirubin with a New Adsorbent System: In Vitro Kinetics. Blood Purif. 2019;47(1-3):10-5.
22. Piwowarczyk P, Kutnik P, Potręć-Studzińska B, Sysiak-Slawecka J, Rypulak E, Borys M, et al. Hemoadsorption in isolated conjugated hyperbilirubinemia after extracorporeal membrane oxygenation support. Cholestasis of sepsis: A case report and review of the literature on differential causes of jaundice in ICU patient. Int J Artif Organs. 2019;42(5):263-8
23. Guarneri M, Calandra L, Di Bella R, Riccobene R, Vccaro F, Mulé G, et al. Successful Treatment of Bilirubin Nephropathy by CytoSorb Hemodialysis. Blood Purification. 2019;47(3-37)
24. Dhokia VD, Madhavan D, Austin A, Morris CG. Novel use of CytoSorb™ haemadsorption to provide biochemical control in liver impairment. J Intensive Care Soc. 2019;20(2):174-81
25. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017 Jul 10;12:29.
26. Kogelmann K, Jarczak D, Scheller M, Drüner M. Hemoadsorption by CytoSorb in septic patients: a case series. Crit Care. 2017;21(1):74
27. Hassan K, Kannmacher J, Wohlmuth P, Budde U, Schmoeckel M, Geidel S. CytoSorb Adsorption During Emergency Cardiac Operations in Patients at High Risk of Bleeding. Ann Thorac Surg. 2019 Jul;108(1):45-51.