The Effect of Serum Mannose-Binding Lectin Levels on Dialysis-Related Peritonitis and Catheter-Related Bacteremia

Periton Diyalizi ve Hemodiyaliz Hastalarında Mannoz Bağlayıcı Lektin Serum Düzeyinin Peritonit ve Kateter Enfeksiyonuna Etkisi

Ertuğrul ERKEN[1]
Dilek TORUN[2]
Nurzen SEZGİN[3]
Hasan MİCOZKADIOĞLU[2]
Ayşegül ZÜMRÜTDAL[2]
Rüya ÖZELSANCAK[2]
İsmail YILDIZ[2]

1 Gaziosmanpaşa University, Faculty of Medicine, Department of Nephrology, Tokat, Turkey
2 Başkent University, Adana Research and Training Hospital, Department of Nephrology, Adana, Turkey
3 Başkent University, Adana Research and Training Hospital, Department of Biochemistry, Adana, Turkey

ABSTRACT

OBJECTIVE: Mannose-binding lectin (MBL) takes part in innate immunity through opsonisation and complement activation. Deficiency of MBL is associated with some infections and autoimmune disorders. This study focused on functional MBL deficiency and its effects on dialysis-related peritonitis and catheter-related bacteremia in patients with end stage renal disease.

MATERIAL and METHODS: The study included 51 patients on chronic peritoneal dialysis (PD) program and 31 under maintenance hemodialysis (HD) who had tunneled/cuffed hemodialysis catheters (total 82). Serum MBL level measurements were performed by ELISA technique.

RESULTS: The mean value for serum MBL in patient groups of PD, HD, and healthy controls were 2536.5 ng/ml, 2088.7 ng/ml, 1924 ng/ml respectively. Difference of MBL level was not significant among groups. Serum MBL value was negatively correlated to the number of peritonitis episodes in PD group (p=0.019). Deficiency of MBL was not associated with high incidence of peritonitis. Surveillance of catheter associated blood stream infection for tunneled/cuffed hemodialysis catheters was 2.07 episodes/1000 catheter days. An association with MBL deficiency and incidence of catheter-related bacteremia was not observed.

CONCLUSION: Serum MBL value was negatively correlated to the number of peritonitis episodes but an expected association of MBL deficiency with high incidence of dialysis-related peritonitis and catheter-related bacteremia was not found. New studies with greater sample size might probably indicate the potential effect of MBL deficiency on dialysis-related peritonitis.

KEY WORDS: Mannose-binding lectin, Peritoneal dialysis, Peritonitis, Hemodialysis, Catheter-related bacteremia

ÖZ

AMAÇ: Mannoz bağlayıcı lektin (MBL), opsonizasyon ve kompleman aktivasyonu aracılığı ile doğal immüniteye katkıda bulunmaktadır. MBL eksikliği bazı enfeksiyöz ve otoimmün hastalıklarla ilişkilidir. Çalışmamızda, kronik periton diyalizi (PD) hastaları ve vasküler giriş yolu olarak tünelli kateter kullanılan hemodiyaliz hastalarında fonksiyonel MBL eksikliğinin enfeksiyon gelişimi ile ilişkisini incelemeyi amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya kronik PD programındaki 51 hasta ve tünelli/kaflı kateter kullanılarak kronik hemodiyaliz (HD) programına devam eden 31 hasta olmak üzere toplam 82 hasta dahil edildi. Bu gruplara 35 sağlıklı kontrol ilave edildi. Hasta ve kontrollerin serum örneklerinde ELİSA yöntemi uygulanarak MBL seviyesi ölçüldü. Serum MBL düzeyi ve fonksiyonel MBL eksikliği ile peritonit ve tünelli kateter enfeksiyonu arasındaki ilişki araştırıldı.

BULGULAR: Serum MBL düzeyi ortalama değeri PD grubunda 2536,5 ng/ml, HD grubunda 2088,7 ng/ml ve sağlıklı kontrol grubunda 1924 ng/ml olarak bulundu. Gruplar arasında; serum MBL düzeyi yönünden farklılık yoktu. PD grubunda serum MBL düzeyi ile peritonit sayısı arasında negatif korelasyon mevcuttu (p=0,019). PD grubunda yıllık peritonit insidansı yüksek olan (>0,67 episod/yıl) olguların ortalama MBL değeri, diğer olgulardan daha düşük olsa da, fonksiyonel MBL eksikliği açısından anlamlı fark bulunmadı. Merkezimizin tünelli kateter ilişkili bakteriyemi sürveyansı; 1000 kateter günü başına 2,07 episod olarak saptandı. HD grubunda kateter enfeksiyonuyla MBL serum düzeyi ve MBL eksikliği arasında ilişki yoktu.

Received : 17.12.2014
Accepted : 07.01.2015

Correspondence Address:
Ertuğrul ERKEN
Gaziosmanpaşa Üniverstesi Tıp Fakültesi, Nefroloji Bilim Dalı, Tokat, Turkey
Phone : + 90 356 212 95 00
E-mail : ertugrulerken@hotmail.com

SONUÇ: Kliniğimizde PD ve HD gruplarında MBL eksikliği ile enfeksiyon sıklığı arasında anlamlı bir ilişki saptamadık. Ancak kronik PD olgularında serum MBL düzeyi ile peritonit sayısı arasında negatif korelasyon mevcuttu. Çalışmaya dahil edilen hasta sayısının artırılması, MBL eksikliğinin diyaliz ilişkili peritonit üzerindeki potansiyel etkisini ortaya çıkarabilir.

ANAHTAR SÖZCÜKLER: Mannoz bağlayıcı lektin, Periton diyalizi, Peritonit, Hemodiyaliz, Kateter enfeksiyonu

INTRODUCTION

Mannose-binding lectin (MBL) is a protein that is found in the lectin pathway of complement activation. It enhances the first line defense mechanisms against infectious organisms (1). Patients with end stage renal disease (ESRD) are susceptible to bacterial infections. Application of renal replacement therapies brings out new colonization sites for pyogenic bacteria. Peritonitis is the most important and frequent complication for patients on chronic peritoneal dialysis (PD). Even with optimal follow up conditions patients have the risk of experiencing peritoneal infection (2). Central venous catheters used for hemodialysis (HD) are important sources of infection. Tunneled/cuffed central venous catheters provide the protection of a fibrous reaction by using a subcutaneous tunnel, and a cuff at the exit site. Using these catheters as vascular access may decrease the risk of catheter-related bacteremia but still there is a probability of septic complications (3).

Specific defects in innate immunity could lead to an increase in infection frequency. MBL is a part of innate immunity without which susceptibility to infections may increase. Gene mutations of MBL have been shown to be associated with MBL deficiency (4). MBL gene (MBL2) has three identified point mutations in exon 1 (5). It has been observed that functional MBL levels drop substantially in individuals with homozygous or heterozygous MBL gene mutations (4,5). Normal serum MBL range in adults is 500-10,000 ng/ml. Still there is no consensus over the serum cut-off value for MBL deficiency. However, MBL deficiency has been defined as less than 500 ng/ml in many reports (6,7). There are studies pointing that higher MBL levels confer protection against infections, while lower levels increase vulnerability to infections in immune suppressed cases (8-10). The aim of the study was to investigate a possible relation between functional MBL deficiency and development of infections in chronic PD and HD patients for whom tunneled/cuffed catheters are used as vascular accesses.

MATERIALS and METHODS

Eighty-two ESRD patients within the renal replacement therapy (RRT) program at the Nephrology Department of Baskent University, Faculty of Medicine, Adana Teaching and Medical Research Center were included to the study. Fifty-one of these patients were in chronic PD program (Male/Female: 24/27, mean age ± SD: 49.1±15.8 years, mean PD duration: 56.1±32.7 months), while 31 were on maintenance HD program (Male/Female: 11/20, mean age ± SD: 56.6±19.5 years, mean HD duration with tunneled/cuffed catheter: 528±286.3 days).

All patients in PD group (n=51) were at least 18 years of age and existed in chronic PD program for at least two years. Because frequency of peritonitis episodes were evaluated in the past, the patients just enrolled in chronic PD program (<2 years) were excluded from the study. Therefore any patient who had technique failure or died of severe peritonitis within two years after the start of peritoneal dialysis was not included. Data used in this retrospective study were taken from database of patients in chronic PD program in January 1998 and February 2012 period. Of 51 patients, 36 were receiving continuous ambulatory peritoneal dialysis (CAPD) treatment and 15 were receiving RRT with automated peritoneal dialysis (APD). Patients that have changed the dialysis modality from PD to HD are not selected for this study. Etiology for chronic kidney disease (CKD) and other underlying comorbid conditions, medications used, past peritonitis episodes and culture growth were recorded.

Patients treated with PD were divided into two groups according to the frequency of peritonitis indicated in 2010 International Society for Peritoneal Dialysis (ISPD) guideline (11). Therefore, 15 patients whose peritonitis frequency is higher than 0.67 episodes a year were placed in group 1 and the remaining 36 PD patients were placed in Group 2. Peritoneal dialysis patients with a characteristic clinical presentation and concurrently peritoneal fluid white cell count higher than 100 cells/mm3 and the percentage of neutrophils higher than 50 percent were considered having peritonitis and dialysate culture sampling was made. The same empirical treatment (intraperitoneal cefazolin and ceftazidime) was applied to all peritonitis episodes, and antibiotherapy was carried out based on peritoneal fluid culture growth in clinical follow-ups.

Culture specimens were taken from all 51 patients in PD group for the presence of nasal bacteria. Tenckhoff Catheters used by patients in PD group were Quinton Curl Cath two cuffs, curled, silicon 24.4 inch peritoneal dialysis catheters. Tenckhoff Catheters were implanted in sterile operating room conditions.

Patients in HD group were selected among the patients who were having HD three times a week with cuffed tunneled catheters. These patients were as a control group for the PD group, which was the primary target of the study. The following data were recorded for each patient in HD group: comorbid conditions, catheter-related infections and involved microorganism strains. All of the tunneled/cuffed HD catheters involved in our study and used in our hospital were implanted in internal jugular vein under sterile conditions with the aid of ultrasound imaging. All catheters used were adjustable tip,

tunneled, cuffed, double lumen, polyurethane Medcomp 14F hemodialysis catheters. For bacterial culture, both catheter and peripheral blood samples were taken from patients in HD group with catheter-related bacteremia (CRB) clinical indications. In addition to septicemia indications, $\geq 10^3$ colony growth in quantitative culture of catheter blood or at least five-fold colony growth in catheter blood compared to simultaneously taken peripheral venous blood were considered CRB.

Thirty-five age and gender matched healthy individuals (Male/Female: 20/15 mean age ± SD: 41.4±13.6 years) without any systemic condition or acute or chronic infection indication constituted healthy control group.

For detection of MBL level, 4 ml peripheral blood samples were taken from all patients and healthy controls in the study. Samples were centrifuged for 10 minutes in 3000 RPM, and obtained serum samples were stored in -20 °C until using. Blood samples of subjects having a major condition or infection were taken at last two weeks after their conditions were treated. MBL levels were determined in serum samples of all patients and controls using ELISA method and a micro ELISA commercial kit (AntibodyShop/BioPorto, Denmark) (12). Measured serum MBL levels by ELISA method were calculated as ng/ml. All of the normal serum MBL levels measured within 4000-10000 ng/ml interval were recorded as 4000 ng/ml. The exact value of these records through a second dilution was not made. Relationship between serum MBL levels and infection frequency in PD and HD groups were investigated. The study was approved by ethics committee of Baskent University, Faculty of Medicine. All participants gave written informed consent.

Statistical Analysis

Data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 15.0, SSPS Inc, Chicago, IL, USA). All values are expressed as mean ± SD. Differences between group results were evaluated using the Student's t test for mean data, chi-square and Fischer's exact analysis was used to analyze results for categorical variables. Pearson's correlation test was used for correlation analysis. P values less than 0.05 were accepted as statistically significant.

RESULTS

The leading etiological factor in PD group was hypertension (37%), followed by diabetes mellitus (27%), glomerulonephritis (11%) and polycystic kidney disease (8%). In HD patient group, the leading etiological factor was diabetes mellitus (32%) followed by hypertension (29%), glomerulonephritis (13%) and reflux nephropathy (9%).

Mean age in HD group was significantly higher than other two groups (P=0.001). There was no difference for gender among the groups (P=0.213). Demographic features of all groups are given in Table I.

Mean serum MBL levels were 2536.5 ng/ml in PD group, 2088.7 ng/ml in HD group and 1924 ng/ml in healthy control group. Mean and range values of all these three groups were given in Table II. There was no difference among the groups for serum MBL levels (Kruskal-Wallis variance analysis, p=0.099).

Nineteen of the 117 cases (16.2%) in the present study had functional MBL deficiency. MBL deficiency was 5/51 in PD group (9.8%), 9/31 in HD group (29.0%) and 5/35 in the healthy control group (14.3%) (Figure 1).

Table I: Demographic features of groups.

	PD	HD	Healthy control
n	51	31	35
Age (year) (mean ± SD)	49.1±15.8	56.6±19.5	41.4±13.6
Age (year) (Min/Max)	20/73	21/83	21/81
Gender (M/F)	24/27	11/20	20/15

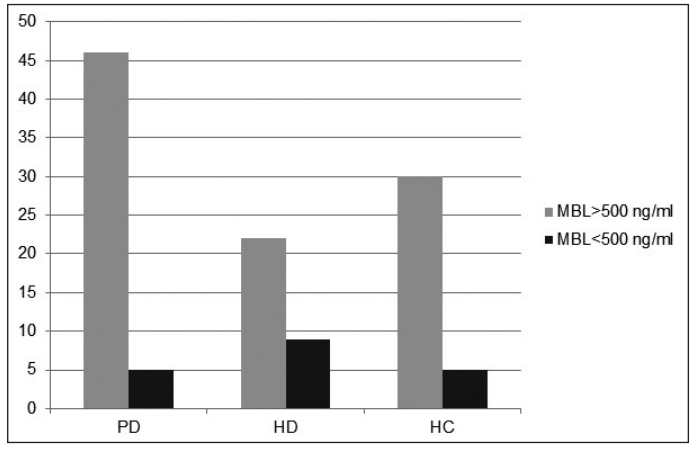

Figure 1: *Comparison of healthy controls (HC) and patient groups (PD and HD) for serum MBL deficiency: Bar graphics. X axis=groups, Y axis=case number.*

Table II: Serum MBL levels of patient and healthy control groups.

MBL value	PD (n=51)	HD (n=31)	Healthy control (n=35)
(ng/ml) (mean ± SD)	2536.5±1529.5	2088.7±1610.4	1924.0±1319.7
(ng/ml) (Min/Max)	17/4000	3/4000	11/4000

Although MBL deficiency in HD group was higher than other two groups, the differences among the groups were not significant (P=0.068).

Mean MBL level of male patients (3416.4 ng/ml) in HD group was higher than that of female patients (1358.5 ng/ml) (P=0.001). Similarly, frequency of MBL deficiency (<500 ng/ml) was higher in females in HD group (P=0.033). There was no difference for the frequency of MBL deficiency between males and females in PD patient and healthy control groups. No association was found between serum MBL levels and presence of diabetes mellitus in PD and HD patient groups (P=0.506 and P=0.167, respectively).

Number of peritonitis episodes did not differ between CAPD and APD sub-groups (P=0.910). No nasal carriage of S aureus was detected in nasal swab culture sample in all PD patients. Dialysis-related peritonitis incidence was 0.37 per year in PD patients monitored in our center and included in the present study. In cultures after peritonitis episodes, 71.6% of the growing microorganisms were gram positives followed by gram negatives (25.9%) and fungi (2.5%).

Serum MBL value was negatively correlated to the number of peritonitis episodes in PD group (p=0.019). No difference was observed for serum MBL level between PD patients with or without history of peritonitis (P=0.249). A comparison of the cases with and without MBL deficiency (MBL< 500 ng/ml) for number of peritonitis episodes revealed a higher number of peritonitis in patients with MBL deficiency (2.61 vs. 1.46, respectively) but the difference was not significant (P=0.19).

As expected, average MBL value of group 1 PD patients (2171.2 ng/ml) which had more than 0.67 peritonitis episode per year was less than PD group 2 (2688.7 ng/ml), but the difference between the two PD groups for serum MBL level and the frequency of MBL deficiency was not significant (P=0.31, P=0.46) (Table III.)

Total number of days for which all 31 patients in HD group had tunneled catheter was 16.368 days. During this time, thirty-two patients had a total of 34 catheter-related bacteremia episodes. Thus, average tunneled CRB in our center was 2.07 episodes per 1000 catheter days. Yearly incidence of tunneled CRB in these patients was 0.92 episodes. In patients who used tunneled catheter for longer term, more bacteremia were observed, but there was no association between duration of catheter use and infection frequency (P=0.239). Coagulase negative staphylococcus grew in culture of 50% of catheter-related bacteremia episodes, followed by coagulase positive staphylococcus (26.5%) and gram negative bacteria (23.5%). Tunneled catheter-related bacteremia was not associated with MBL deficiency.

Table III: MBL deficiency in group 1 and group 2 PD patients.

MBL deficiency	Group 1	Group 2
MBL<500 ng/ml	2/15 (13.3%)	3/36 (8.3%)

DISCUSSION

Increased susceptibility to infection in chronic kidney disease is attributed to uremia dependent immune system compromise and association with comorbid factors such as DM (13). MBL functions as a part of innate immunity. It accelerates phagocytosis and activates complement system (1,13). There is no consensus over the cut-off value for MBL deficiency but MBL deficiency has been defined as less than 500 ng/ml in many reports (6,7,13). In this study, serum MBL levels were measured in 117 cases and the results varied from 11 to 4000 ng/ml. High MBL values that are greater than 4000 ng/ml were recorded as 4000 ng/ml. It was not possible to detect the exact value through a second dilution. After all, even in studies with high number of cases, the highest value of serum MBL levels were up to 6000 ng/ml (14,15).

In a study by Yuen et al., an association was revealed between MBL deficiency and spontaneous bacterial peritonitis in cases with chronic viral hepatitis dependent liver disease (16). In a recent study, MBL has been shown to function in primary defense line against Candida albicans (17). Van Till et al. found that there was an association between MBL deficiency and fungal peritonitis in patients with secondary peritonitis whom required emergency laparotomy. Additionally, abdominal yeast infection risk was found about 4.5 times higher when the serum MBL level was less than 500 ng/ml (18). Man Fai et al. studied the association between MBL2 gene mutations and serum MBL levels in PD patients, assuming that MBL deficiency could increase susceptibility to infection in ESRD cases (2). In this study, no association was found between functional MBL level and dialysis-related peritonitis, and lack of this association was attributed to additional risk factors involved in peritonitis development.

In the present study, average number of peritonitis episodes in PD patients with MBL deficiency was remarkably higher than those with normal MBL levels, but the difference was not statistically significant. Possible explanation for this result could be related with small sample size and no genotyping detection was done in our PD patient group.

Man Fai et al. observed lower serum MBL levels in chronic PD cases than in HD cases. They speculated that a MBL loss might occur through peritoneal membrane (2). In the present study, no difference was observed for MBL levels between PD and HD patient groups. Our conclusion was that MBL loss through peritoneal membrane did not affect serum MBL levels, since MBL synthesis went on continuously in liver.

There are factors interfering serum MBL levels. Among the most important ones are immune activation and hormonal statue (5). MBL is considered an acute phase reactant, and

MBL levels can increase two-fold depending on infection or inflammatory response. None of our cases was receiving any hormone replacement therapy. Blood samples of the cases in HD program were taken on the day of HD session, just before the HD treatment. However, we assume that the day on which blood sample is taken will not affect the results, since MBL levels, having a quite stable course, show no circadian change and are not affected by dialysis practice and residual renal functions (13,19).

No association was found between the tunneled catheter-related infection frequency and MBL deficiency. Studies in the literature were generally survey studies aiming to determine the infection risk rather than the ones aiming to determine infection frequency of CRB (20,21). Therefore, the HD group was used both as a separate patient group and as a patient control group for PD group.

CONCLUSION

There is no consensus in studies investigating the possible associations between serum MBL levels and various infections and autoimmune diseases. Recurrent infections and infections with poor prognosis were observed in some MBL deficient individuals. On the other hand, MBL deficiency disclosed no clinical manifestations in many individuals. The reason for different results could be that normal MBL levels were much more than the level needed by immune system.

A negative correlation was detected between serum MBL levels and number of peritonitis in chronic PD cases. Small sampling size seemed to be the major potential limitation of the present study. Larger patient populations might reveal a significant effect of MBL deficiency on infection frequency. Based on available data, both basic and clinical studies should continue to elucidate the exact role of MBL in immune system.

Authors' Contributions

EE (corresponding author) made the conception and design of the study, collected the data, performed the statistical analysis and wrote the study. DT conceived of the study and participated in its design and coordination. NS made the biochemical assays. HM, AZ, RO and IY contributed in study design, interpretation of data and revision of the study. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Prof. Z. Nazan Alparslan for her contribution in statistical analysis.

REFERENCES

1. Degn SE, Thiel S, Jensenius JC: New perspectives on mannan-binding lectin-mediated complement activation. Immunobiology 2007;212:301-311
2. Lam MF, Leung JC, Tang CC, Lo WK, Tse KC, Yip TP, Lui SL, Chan TM, Lai KN: Mannose binding lectin level and polymorphism in patients on long-term peritoneal dialysis. Nephrol Dial Transplant 2005;20(11):2489-2496
3. Inrig JK, Reed SD, Szczech LA, Engemann JJ, Friedman JY, Corey GR, Schulman KA, Reller LB, Fowler VG Jr: Relationship between clinical outcomes and vascular access type among hemodialysis patients with Staphylococcus aureus bacteremia. Clin J Am Soc Nephrol 2006;1:518-524
4. Larsen F, Madsen HO, Sim RB, Koch C, Garred P: Disease-associated mutations in human mannose-binding lectin compromise oligomerization and activity of the final protein. J Biol Chem 2004;279:21302-21311
5. Garred P: Mannose-binding lectin genetics: From A to Z. Biochem Soc Trans 2008;36:1461-1466
6. Lipscombe RJ, Sumiya M, Hill AV, Lau YL, Levinsky RJ, Summerfield JA, Turner MW: High frequencies in African and non-African populations of independent mutations in the mannose binding protein gene. Hum Mol Genet 1992;1:709-715
7. Thiel S, Frederiksen PD, Jensenius JC: Clinical manifestations of mannan-binding lectin deficiency. Mol Immunol 2006;43:86-96
8. Naito H, Ma Y, Uemura K, Arano Y, Kawasaki T: Metabolic properties of normal and mutant mannan-binding proteins in mouse plasma. Biochem Biophys Res Commun 1999;256:231-234
9. Verschuren JJ, Roos A, Schaapherder AF, Mallat MJ, Daha MR, de Fijter JW, Berger SP: Infectious complications after simultaneous pancreas-kidney transplantation: A role for the lectin pathway of complement activation. Transplantation 2008; 85:75-80
10. Worthley DL, Johnson DF, Eisen DP, Dean MM, Heatley SL, Tung JP, Scott J, Padbury RT, Harley HA, Bardy PG, Angus PW, Mullighan CG: Donor mannose-binding lectin deficiency increases the likelihood of clinically significant infection after liver transplantation. Clin Infect Dis 2009;48(4):410-417
11. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, Johnson DW, Kuijper EJ, Lye WC, Salzer W, Schaefer F, Struijk DG; International Society for Peritoneal Dialysis: Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int 2010;30:393-423
12. MBL Oligomer ELISA Kit CE IVD Cat.No. KIT 029CE. Bioporto Diagnostics (AntibodyShop) A/S Grusbakken 8 DK-2820 Gentofte Denmark
13. Turner MW: The role of mannose-binding lectin in health and disease. Mol Immunol 2003;40(7):423-429
14. Eisen DP, Dean MM, Boermeester MA, Fidler KJ, Gordon AC, Kronborg G, Kun JF, Lau YL, Payeras A, Valdimarsson H, Brett SJ, Ip WK, Mila J, Peters MJ, Saevarsdottir S, van Till JW, Hinds CJ, McBryde ES: Low serum mannose-binding lectin level increases the risk of death due to pneumococcal infection. Clin Infect Dis 2008;47:510-516
15. Heitzeneder S, Seidel M, Förster-Waldl E, Heitger A: Mannan-binding lectin deficiency - Good news, bad news, doesn't matter? Clin Immunol 2012;143(1):22-38

16. Yuen MF, Lau CS, Lau YL, Wong WM, Cheng CC, Lai CL: Mannose binding lectin gene mutations are associated with progression of liver disease in chronic hepatitis B infection. Hepatology 1999;29(4):1248-1251

17. Lillegard JB, Sim RB, Thorkildson P, Gates MA, Kozel TR: Recognition of Candida albicans by mannan-binding lectin in vitro and in vivo. J Infect Dis 2006;193:1589-1597

18. van Till JW, Modderman PW, de Boer M, Hart MH, Beld MG, Boermeester MA: Mannose-binding lectin deficiency facilitates abdominal Candida infections in patients with secondary peritonitis. Clin Vaccine Immunol 2008;15(1):65-70

19. Terai I, Kobayashi K, Fujita T, Hagiwara K: Human serum mannose binding protein (MBP): Development of an enzyme-linked immunosorbent assay (ELISA) and determination of levels in serum from 1085 normal Japanese and in some body fluids. Biochem Med Metab Biol 1993;50:111-119

20. Seifert H, Jansen B, Widmer AF, Farr BM: Central venous catheters. In: Seifert H, Jansen B, Farr BM (eds), Catheter-Related Infections. 2th ed. New York: Marcel Dekker, 2005; 293-326

21. Siegman-Igra Y, Golan H, Schwartz D, Cahaner Y, De-Mayo G, Orni-Wasserlauf R: Epidemiology of vascular catheter-related bloodstream infections in a large university hospital in Israel. Scand J Infect Dis 2000;32:411-415