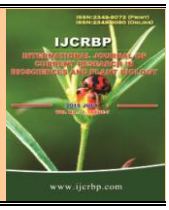
*Int. J. Curr. Res. Biosci. Plant Biol.* 2015, 2(7): 92-100

EXCELLENT PUBLISHERS

*International Journal of Current Research in Biosciences and Plant Biology*

**ISSN: 2349-8080 Volume 2 Number 7 (July-2015) pp. 92-100**

www.ijcrbp.com



**Review Article**

# Role of Biochemistry in Bacteremia

**S. Rajeswari[1] and S. Swaminathan[2]***

[1]Junior Technical Officer, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai 600 095, Tamil Nadu, India and Research Scholar, Department of Biochemistry, Vels University, Chennai 600 117
[2]Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Ayanambakkam, Chennai 600 095, Tamil Nadu, India

**Corresponding author.*

**A b s t r a c t**

Bacterial infections are very common and each type of bacteria affects the functional levels of vital organs and the three organs mostly affected by bacteraemia are liver, kidney and cardiac muscles. The review articles is an attempt to link the role of biochemistry in bacteraemia and the various organs affected and the specific tests used and its clinical significance in depicting the severity of such organs affected and to recommend routine biochemical tests as additional diagnostically useful tools for infectious diseases. Biochemical tests such as alanine aminotransferase (ALT), Aspartate aminotransferase (AST), blood urea nitrogen, creatinine, creatine kinase, lactate dehydrogenase, procalcitonin and C-reactive protein have been found to be useful for assessing the alteration in the functional activities of the above mentioned three organs.

**K e y w o r d s**

Alanine aminotransferase
Aspartate aminotransferase
Bacteraemia
Blood urea nitrogen
C-reactive protein
Creatinine
Procalcitonin

## Introduction

Laboratory diagnosis comprises of tests done in clinical pathology, haematology, biochemistry, microbiology, histopathology, immunohistochemistry and immunology. Although each branch of laboratory science is distinct, there is always some clinical correlation exists mostly between biochemistry and the various branches of laboratory sciences. The latest trend in laboratory sciences research are focussed on the link between biochemistry and clinical microbiology as every infectious disease identified by microbiologists are linked to alterations in biochemical analytes depicting the severity of infection.

## *Escherichia coli* and renal function

It seems likely that montelukast protects kidney tissue by inhibiting neutrophil infiltration, balancing oxidant-antioxidant status, and regulating the generation of inflammatory mediators suggesting a future role for leukotriene CysLT1 receptor antagonists in the treatment of pyelonephritis (Tugtepe et al., 2007) Co-administration of Gentamicin (GEN) with Mycophenlate Mofetil (MMF) in Acute pyelonephritis (APN) may enhance kidney damage and the adverse effects of combination therapeutic regimen could be related partly to incompatibility of these compounds (Malekinejad et al., 2012). *E. coli* bacteraemia rates have risen due to

rising rates of resistant organisms; little change occurred in susceptible *E. coli*. Although the severity of resistant infections, and their outcome, appear similar to susceptible *E. coli* in the setting studied, the increasing burden of highly resistant organisms is alarming and merits on-going surveillance (Schlakow et al., 2012) Several biochemical urine tests and derived indices are reported as useful in the diagnosis of acute renal failure (ARF) and its classification in prerenal (hypoperfusion) or intrarenal (acute tubular) necrosis. However, they have not been adequately studied in sepsis, the most frequent cause of ARF in Intensive Care Unit (ICU).Infusion of live *E. coli* induced systemic hyper dynamic sepsis with renal vasodilatation and increased renal blood flow (RBF). The urine protein (u/p) creatinine ratio did not change. Sustained Gram-negative sepsis induced a hyper dynamic state and hyperaemic ARF. Despite increased renal perfusion, urine sodium concentration (UNa), fractional excretion of sodium (FeNa) and fractional excretion of urine nitrogen (FeUn) decreased significantly. These findings suggest that, in sepsis, these urinary biochemical changes are not reliable markers of renal hypo-perfusion (Langenberg et al., 2012).

## *E. coli* and liver function

Probiotic therapy can reduce plasma endotoxin levels and postpone alcoholic fatty liver disease (ALD) progression by altering the composition of the gut microbiota and up-regulating expression of the occluding protein in intestinal epithelial cells (Zhang et al., 2012) Concurrent treatment with an *E. coli* glycolipoprotein macromolecule that induced rheumatoid factors (RF), protected against carbon tetrachloride (CCL(4))-induced liver damage as measured by a highly significant decrease at 4 weeks in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). RF induced by *E. coli* glycolipoprotein correlated with 'protection' from liver damage, indicating that the RF autoimmune response does not necessarily exacerbate liver disease (Nowak et al., 2007) Transgenic (TG) *E. coli* mice displayed reversed endothelial leakage index; reduced serum levels of AST, ALT, blood urea nitrogen (BUN), and creatinine; and improved survival. These data demonstrate that endothelial NF-kappa B-driven inflammatory response contributes minimally to systemic inflammation, but plays a pivotal role in septic multiple organ dysfunction and injury (MOD/I), suggesting that endothelium is mainly a target rather than a source of systemic inflammation (Xu H et al., 2010).

TNF-a concentration was lower in cidomycin group than in Non-alcoholicsteatohepatitis (NASH). Treatment with cidomycin showed its effect by significantly lowering serum ALT, AST and Tumor necrosis factors alpha (TNF-a) levels of NASH rats. Small intestinal bacteria overgrowth (SIBO) may decrease small intestinal movement in NASH rats. SIBO may be an important pathogenesis of NASH. And treatment with cidomycin by mouth can alleviate the severity of NASH (Wu et al., 2008). The Community-Acquired Pneumonia (CAP) patients who have higher BUN/Alb ratio are under higher risk of the development of need for ICU treatment. Low albumin level is a more valuable predictor than BUN/Alb ratio for prognosis of CAP (Akpinar et al., 2013). Procalcitonin (PCT), and to a lesser degree high sensitivity c reactive protein (hsCRP), improve the accuracy of currently recommended approaches for the diagnosis of CAP, thereby complementing clinical signs and symptoms. PCT is useful in the severity assessment of CAP (Müller et al., 2007) Patients with biochemical evidence of liver disease generate significantly lower serum CRP concentrations during bacteraemia than patients without liver dysfunction. Serum CRP concentrations should be interpreted with caution in patients with liver disease to diagnose and monitor bacterial sepsis (Mackenzie et al., 2006).

Cases with 42% of monomicrobial necrotizing fasciitis were found to be caused by Gram-negative organisms, mostly *E. coli*. These infections usually appeared in immunocompromised or postoperative patients, often presented with normal Creatine Kinase (CK) levels, and were associated with high mortality rates (Yahav et al., 2014). The model of bacterial multiple organ injury (MOI) in aged rats is reproduced successfully, and it mimics the pathogenesis of multiple organ dysfunction syndrome (MODS) which initiates from infection in the lungs. The model is simple and convenient to replicate with a high success rate. The MOI in the aged rats is characterized by the severity of the organ injury and a high mortality rate (Li et al., 2009)The serum PCT concentration can be used to effectively determine whether the acute asthma patients have bacterial infections in the respiratory tract, and to guide the use of antibiotics in the treatment of acute asthma exacerbations, which may substantially reduce unnecessary antibiotic use without compromising the therapeutic outcomes (Tang et al., 2013)soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), PCT, and CRP levels are of no use in determining new fever caused by bacteraemia in ICU

patients, but sTREM-1 levels reflect the prognosis of bacteraemia (Su et al., 2012).

### *Pseudomonas*

Assessment of the individual effect of each treatment regimen suggests a greater efficacy when colistin is combined with a second antibiotic to which the pseudomonas shows in vitro sensitivity. Changes in renal function should be monitored (Conway et al., 1997) Thrice daily aerosol tobramycin administration for 3 months is not associated with detectable eighth cranial nerve or renal toxicity. Transient emergence of tobramycin resistant *P. aeruginosa* may occur (Smith et al., 1989). Systemic therapy with amikacin plus ceftazidime causes mild hypomagnesaemia secondary to renal magnesium wasting even in the absence of a significant rise in circulating creatinine and urea (Von vigier et al., 2000)The combination of mental retardation, obesity, postaxial polydactyly, and bilateral renal hypoplasia were compatible with the diagnosis Bardet-Biedl syndrome (BBS). The combination of posterior urethral valve (PUV) and BBS is a rare condition that caused this early onset of renal failure and inappropriate obesity may guide us to the diagnosis (Valavai et al., 2009).

Colistin is a good option for treating infections caused by multidrug-resistant (MDR) gram-negative bacillus in patients with severe burn, as no other more effective drug is found (Zhang et al., 2009). No apnea or other evidence of neuromuscular blockade was noted in any of these patients who received prolonged treatment with colistin. No serious toxicity was observed in this group of patients who received prolonged intravenous colistin. Colistin should be considered as a therapeutic option (Falagas et al., 2000)

Congestive heart failure was the most common identifiable cause of a raised plasma urea concentration in about 36% of unselected patients. Among these, plasma creatinine concentration was found to be a more useful discriminant between prerenal uraemia and intrinsic renal failure than was the urea: creatinine ratio or the plasma urea concentration. A plasma creatinine concentration is greater than indicated intrinsic renal failure with a 90% probability (Morgan et al., 1977). Immunization with glycolipoprotein (GLP) protected mice against most biochemical changes were able to be challenged with live cells but did not protect GLP-challenged mice against the biochemical alterations assayed in the sera (Lynn et al., 1984) Zingerone therapy significantly protected liver from endotoxin induced inflammatory damage by down regulating biochemical as well as molecular markers of inflammation, thus providing evidence that zingerone is a potent anti-inflammatory phytomedicine against hepatic inflammation induced by antibiotic mediated endotoxemia, suggesting, that zingerone treatment can be used as a co-therapy with antibiotics to reduced endotoxin induced inflammation during treatment of severe *Pseudomonas aeruginosa* infections (Kumar et al., 2014)

*Pseudomonas* is notorious for causing hospital-associated infections, infection in burn patients, catheter-associated infections, chronic otitis media, eye infection, necrotizing pneumonia, septicaemia in new-borns and old debilitated persons, cystic fibrosis, malignancy and immunosuppression. It rarely causes antibiotic-associated diarrhoea, however, it can cause diarrhoea in immunocompromised patients and is also associated with neutropenic enterocolitis in patients with acute leukaemia, lymphoma and aplastic anaemia (De et al., 2009). Decreased metabolic activity of liver cells was associated with bacteremia leading to impaired bilirubin excretion and patients died despite appropriate antibiotic therapy. Isolated hyperbilirubinemia, thus, seemed to be an ominous prognostic sign in severe infection (Funada et al., 1995). A possible association of *Pseudomonas* sepsis and Noma, with malnutrition playing a central role in causing both the diseases were highlighted in these patients (Vaidyanathan et al., 2005).

### *Enterobacter*

All biochemical analyses showed statistically significant increase in the measured parameters due to bacterial infections except for urea which appear to be normal. A significant positive correlation was observed between lactate dehydrogenase (LDH) with creatinine. In the 7 days group, there were significant positive correlations between aspartate aminotransferase (AST) and alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR) with Urea and alkaline phosphatase (ALP) with C-reactive protein (CRP). Many of these biomarkers will provide important new insights into pathophysiology and aid in the diagnosis and management of cardiovascular patients (Kholoud et al., 2013).The mean age of the patients with urinary tract infection (UTI) was 2.75 +/- 3.49 yr, which was significantly lower than in those without UTI. Levels for white blood cells, thrombocytes,

ALT, and ALP were significantly higher in patients with UTI than in those without UTI. There were no significant differences between the groups with regard to serum albumin, bilirubin, AST, Gamma-glutamyl transferase (GGT), BUN, or creatinine levels, glomerular filtration rate, duration of disease, and Pediatric liver transplantation (PELD) scores. UTI is common in children with cirrhosis. It occurs more frequently in patients with biliary atresia than it does in patients with other types of chronic liver disease (CLD). In febrile children with chronic liver disease, UTI should be considered in the differential diagnosis (Baskin et al., 2007).

Quantitative metabolomics profiling of serum, plasma and urine discriminates between healthy and inflammatory bowel disease (IBD) subjects. However, our results show that the metabolic differences between the Crohn's disease (CD) and ulcerative colitis (UC) cohorts are less pronounced (Rudolf Schicho et al., 2012). Levels of blood urea nitrogen (BUN) and serum creatinine increased in two patients but returned to pre-treatment levels within two weeks after therapy. No other adverse reactions were noted. Amikacin may replace gentamicin as initial therapy in serious gram-negative bacillary infections, particularly when resistance to gentamicin is a problem (Daikos et al., 1976) Using the Cockcroft and Gault method, the estimated creatinine clearance was ~20 mL/min.1 Urinalysis showed pyuria with >50 white blood cells and many bacteria and patient was empirically treated with vancomycin and piperacillin/tazobactam (Brust et al., 2014).That alteration in the biochemical marker cytokine by the administration of staphylococcal enterotoxin B (SEB) to mice may be used as indicators of toxicity (Wood et al., 1995). Even in the course of a bacteraemia, there is a significant increase in the non-specific inflammatory parameters indicating the gravity of bacteraemia as well, with a constant risk of developing sepsis and septic shock. The importance of running and following-up the laboratory parameters herewith is emphasised for the purpose of detecting sepsis in a timely manner and administering an adequate therapy (Lukovac et al., 2013)

The two bacterial wall components, Staphylococcus aureus, peptidoglycan (PepG) and lipoteichoic acid (LTA), work together to cause systemic inflammation and multiple systems failure associated with Gram-positive organisms (De kimpe et al., 1995). A study suggest the status of patients with methicillin-resistant *Staphylococcus aureus* (MRSA)bacteraemia who did not survive was worse than those who did survive, but that infection-control team (ICT) consultation might significantly affect survival by recommendation of appropriate care and anti-MRSA drug use (Isobe et al., 2012). Significant factors for therapeutic effect were found to be platelet count, BUN, creatinine, and CRP, each measured before starting administration of anti-MRSA drugs; whether blood drug concentration was measured; and whether pneumonia or septicaemia was present. Consideration should be given to these five important factors when treating MRSA patients (Hayashi et al., 2005). All patients with a febrile, exanthemata's, multisystem illness, particularly one associated with menstruation or a staphylococcal infection, should be promptly evaluated and empirically treated for toxic shock syndrome (Tofte et al., 1982)

Treatment with 63.85 mg/kg of BT2-peg2-vancomycin every 12 hours was more active than all other treatment regimens evaluated, but was associated with high plasma BT2-peg2-vancomycin levels, decreased animal weight, increased kidney size, creatinine and BUN, and leucocytosis with tubulointerstitial nephritis. With optimization of pharmacokinetic parameters to prevent toxicity, BT2-peg2-vancomycin may be useful in the treatment of MRSA osteomyelitis (Karau et al., 2013). Vancomycin levels were not consistently measured in all neonates, resulting in late detection of subtherapeutic trough levels. Rifampin may be effective in the treatment of persistent Coagulase negative staphylococci (CoNS) infections in neonates. Outcome may be improved by adequate monitoring of vancomycin trough levels (van der Lugt et al., 2010). Infection is an important risk factor for morbidity and mortality in patients with systemic lupus erythematosus (SLE) and major infection accounts for 32% of deaths in SLE. The long-term use of corticosteroids and immunosuppressive agents contributes to this risk Corticosteroids lead to fibrotic and retracted cardiac valve leaflet tissue, which increases the risk of valvular dysfunction and infective endocarditis (IE) in patients with SLE. A patient with SLE who developed *S. aureus* endocarditis with multiple brain and cutaneous septic emboli following dental work (Liao et al., 2004)

Distamycin could be prescribed in some patients with elevated CK values. A cut-off value of baseline CK for use of daptomycin needs to be determined (Olivia et al., 2013). Thromboelastographic showed increasing hypercoagulability from 12 h and onwards, whereas the platelet numbers declined slightly throughout the

experiment. The levels of serum AST and bilirubin were elevated at 24 and 36 h, suggesting that sepsis and severe sepsis were induced as evidenced by dysfunction of the blood clotting system and the liver (Leifsson et al., 2010). The elevation of rectal temperatures and white blood cell counts related well with clinical observations. The serum iron levels proved very helpful in predicting the severity of clinical signs and often dropped before the onset of clinical signs and pyrexia (Varma et al., 1984) Uraemia also indicates a poor prognosis in patients with Pneumococcal pneumonia. Serum (CK) is a simple test that may allow early recognition of *Streptococcus* pneumonia in patients who are at an increased risk for a poor outcome, and permit timely therapeutic intervention (Garcia et al., 2002) Neither postural hypotension nor reflex tachycardia accompanied the therapeutic effect of captopril. BUN, serum creatinine and creatinine clearance did not change significantly after therapy in either study group. Three days after initiating treatment, the 24 h urinary catecholamine output increased significantly in children who received captopril but did not change in children treated with furosemide and reserpine (Morsi et al., 1992)

A provisional diagnosis of meningococcal septicaemia was made and on microbiological advice treatment was commenced with a third generation cephalosporin and teicoplanin by intravenous route. Vital parameters were supported with intravenous fluids and oxygen therapy by mask. Intake output chart was strictly maintained (Madhusudhan et al., 2007). Bacterial infections are a serious complication of end-stage liver disease (ESLD) that occurs in 20% to 60% of patients. Ascitic fluid in patients with peritonitis showed a median white blood cell count of 466 cells/mm(3) (range, 250-12,822 cells/mm(3)), with 66% polymorphs, protein of 0.9 gm/dL, and albumin of 0.4 gm/dL. *Streptococcus salivarius* may cause primary bacteremia and spontaneous bacterial peritonitis (SBP) in liver transplantation candidates despite quinolone prophylaxis (Gautam et al., 2007).

Portal vein thrombosis is a rare complication of inflammatory bowel disease and has been described in only 10 patients thus far. Multiple etiologic factors may be responsible in relation to inflammatory bowel disease, such as hypercoagulability, thrombocytosis and abdominal sepsis. In patients with inflammatory bowel disease, unexplained sepsis and abnormal liver function tests, the possibility of an acute portal vein thrombosis should be considered and investigated, because unrecognised it may have serious long-term complications (Mijnhout et al., 2004) Pulmonary infection with *Streptococcus milleri* may result in considerable morbidity and mortality, and is characterised by a strong male predominance, non-specific symptoms (often without toxicity), the presence of predisposing factors, pleural loculation, pneumothorax, and a protracted stay in hospital (Wong et al., 1995).

The mean PCT level was0.374, 0.105 and 0.02 ng/mL in the Streptococcal, nonbacterial tonsil opharyngitis and control groups, respectively. PCT had a greater specificity than CRP for detection of bacterial tonsil opharyngitis (Elsammak et al., 2006) The Centor criteria and the streptococcal rapid antigen detection test (RADT) are commonly used to differentiate sore throat patients with group A streptococci (GAS) from patients with other pathogens. The sensitivity, specificity, and area under the curve of the RADT were higher than those of the 4 measured infection markers in the differentiation between GAS and non-GAS acute tonsillitis patients. The infection markers did not increase the diagnostic accuracy when added to the Centor score and RADT. When RADT is not available, measurement of CRP or absolute neutrophil count (ANC) may increase the diagnostic accuracy in the detection of GAS-positive patients (Christensen et al., 2014) Biomarker levels vary depending on the clinical status. However, the identification of the etiology of infectious exacerbation by means of circulating biomarkers is encouraging, but its main disadvantage is the absence of a microbiological gold standard, to definitively demonstrate their value. High biomarker levels during an exacerbation episode correlate with the short-term prognosis, and therefore their measurement can be useful for chronic obstructive pulmonary disease (COPD) management (Lacoma et al., 2011).

The sensitivity was 94.4% for PCT (cutoff: 1.5 ng/mL) and 91.9% for CRP (cutoff: 100 mg/L). A value≤0.5 ng/mL of PCT ruled out P-CAP in >90% of cases (negative likelihood ratio: 0.08). Conversely, a PCT value≥1.5 ng/mL associated with a positive pneumococcal urinary antigen had a diagnostic probability for P-CAP of almost 80% (positive likelihood ratio: 4.59).PCT and CRP are reliable predictors of P-CAP. Low cutoff values of PCT allow identification of children at low risk of P-CAP. The association of elevated PCT or CRP with a positive pneumococcal urinary antigen is a strong predictor of P-CAP (Galetto

et al., 2013). SP septicaemia is commonly seen in children aged under 2 years. The most common clinical manifestation is fever, accompanied by elevated WBC, CRP and PCT levels, and it is usually complicated by pulmonary or brain infection. Resistance to multiple antibiotics is very common in SP strains, so it is important to properly use antibiotics according to drug sensitivity test results. Patients who receive active treatment have a good clinical outcome (Su et al., 2013). In EBV patients under age 5 years, plasma PCT was normal, whereas ESR, WBC count, and CRP concentrations overlapped those found in severe bacterial infections. There is need for a study of a different design to assess the utility of a diagnostic test. Further studies of diagnostic accuracy performed prospectively with large samples are required to confirm these findings (Matesanz et al., 2003).

In a secondary analysis of all 51 study neonates, CRP and PCT did not provide additional benefit over neutrophil values (NV) in differentiating neonates with pneumonia. Four days of AT appears to be adequate for selected term neonates with pneumonia; however, 2 days of AT appears to be inadequate for this population. Relative to NV, CRP and PCT appear to have a limited role (William et al., 2003). Procalcitonin and CRP alone and their combination had a moderate ability to detect pneumonia of mixed bacterial infection during the 2009 H1N1 pandemic. Considering high specificity, combination of low CRP and PCT result may suggest that pneumonia is unlikely to be caused by mixed bacterial infection (Ahn et al., 2011). Although PCT testing may not currently be available at many institutions, its superior ability to distinguish bacterial infection from other causes of inflammation makes it a useful tool in the evaluation of hospitalized children, and it most likely will soon augment or replace other inflammatory markers. Pediatric hospitalists will need to learn the indications, cutoffs, and nuances of this new tool (Behere and Garber, 2013).

Serum procalcitonin level has a better diagnostic and prognostic value than CRP or leukocyte counts to distinguish between bacterial and viral meningitis. It is also a good indicator of the efficacy of treatment of bacterial meningitis (Alkholi et al., 2011).

Its addition to Pneumonia Severity Index (PSI) and CURB-65 significantly improved their prognostic accuracy. A MR-proADM cut-off of 0.646 $nmol \cdot L^{-1}$ identified 92% of patients scored as PSI classes IV and V as high risk. MR-proADM outcome prediction power was not affected by different aetiologies. Midregional Proadreno medullin (MR-proADM) MR-proADM has high short- and long-term prognostic accuracy, and increases the accuracy of clinical scores. The prognostic value of MR-proADM is not modified by different possible CAP aetiologies (Bello et al., 2012). The linear correlation between plasma PCT concentrations and the four categories was much stronger than in the case of CRP (Spearman's rho, 0.73 vs. 0.41; $p<0.05$). A rise in sepsis-related organ failure assessment score was related to a higher median value of PCT but not CRP. PCT is a better marker of sepsis than CRP. The course of PCT shows a closer correlation than that of CRP with the severity of infection and organ dysfunction (Luzzani et al., 2003).

## Conclusions

The contents of this review article presents the latest research findings on the role of biochemical tests as additional laboratory diagnostic tools in the diagnosis of Bacteraemia. The important biochemical tests recommended as per the contents of this review article are: AST and ALT for liver function, BUN and creatinine for kidney function, AST, CK, LDH for cardiac function and PCT, CRP as clinically useful inflammatory markers, their merits and demerits in various types of bacterial infection. This contents found in this review article will be very useful for researchers to explore more research in this filed to establish additional diagnostically useful markers for every type of bacterial infection.

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