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Rapid identification of bacterial infection in blood using procalcitonin as a potential biomarker

Kathirvel Priyanka[1], Prasad Patnam Prathyusha[2], P Kalaiarasi[3], B Thipurasundari[4], Kandaswamy Selvakumar[5*]
[1, 2] PG Student, Valliammal College for Women Chennai, Tamil Nadu, India
[3] Faculty, Valliammal College for Women Chennai, Tamil Nadu, India
[4] Head Department of Biochemistry, Valliammal College for Women Chennai, Tamil Nadu, India
[5] Head Department of Clinical Biochemistry, Billroth Hospitals, Shenoy Nagar, Chennai, Tamil Nadu, India

Abstract
Sepsis is referred to as the presence of infection along with systemic manifestations of infection. Bacterial sepsis is defined as bacteremia with or without organ dysfunction. The presence of bacteria in blood is usually confirmed by blood culture which needs 5-7days for confirmation. Procalcitonin synthesized as a pro hormone of calcitonin which helps to detect the same within hours. The study was conducted using procalcitonin as a biomarker for bacterial infection. Based on the concentration present in the serum are supports to decide whether the blood culture is a desirable one. Ultimately this decision is a favorable one to reduce the patient's unnecessary stress, hospital stay and financial burdens.

Keywords: bacterial infection, biomarker, procalcitonin, sepsis

1. Introduction
Sepsis is a systemic immune reaction to infection by micro-organisms. Sepsis is referred to as the presence of infection along with systemic manifestations of infection. The most common source of infection resulting in sepsis is the lungs, followed by the abdomen, and the urinary tract. It affects with a range of illness from negligible signs and symptoms through to shock and organ dysfunction. Bacterial sepsis is defined as bacteremia with or without organ dysfunction. Sepsis may be related with the direct incursion of micro organisms into the bloodstream via intravenous (IV) infusion (e.g., IV line infections and other device-associated infections).Final Stage of Sepsis may cause multiorgan damage lead to septic shock and finally death occurs. Sepsis most commonly caused due to bacteria, viruses, fungi, or parasites, or it can develop also in noninfectious intraabdominal incidents such as trauma, pneumonia, pancreatitis, and urinary tract infection. Most frequently active sepsis causing micro organism are *Escherichia coli*, *Streptococcus pneumonia*, and *Staphylococcus aureus.* A pro-hormone produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine is called as Procalcitonin (PcT). PcT originate from the calcitonin I (CALC-1) gene on chromosome 11, which acts as an excellent biomarker for bacterial infection in blood (Sepsis) [1, 2].

1.1 Procalcitonin-a biomarker
Earlier 1975, Moya *et al*., [3] found calcitonin in chicken. Biosynthetically these hormones generate as large molecule which splits in to intracellular as Procalcitonin. In human RNA isolated from medullary carcinoma distinct the synthesis of calcitonin as a protein precursor molecule [4]. Finally studies proved calcitonin is secreted sequential Co and post translational modification like glycosylation protiolytic cleavage, etc. [5]. PcT is produced in thyroid C cells, from a CALC-1 gene located on chromosome 11 in healthy individuals. PcT is a peptide precursor of the calcitonin, where its being involved in calcium homeostasis. This 116-amino acid prohormone is comprised of three constituent peptides: a 57-amino acid sequence at the amino terminus (NProCT); the centrally positioned immature CT that contains a terminal glycine; and a 21-amino acid CT carboxy terminus peptide I (CCP-I) [6]. These peptides usually found in the serum of normal individuals. The half-life of calcitonin is 10 minutes, procalcitonin has a 25-30 hours [7].

1.2 Procalcitonin role in sepsis
Neuroendocrine, thyroid parafollicular cells can as produced PcT which originate from the calcitonin I (CALC-1) gene on chromosome 11. Normally procalcitonin acts as a prohormone for synthesis of calcitonin. In the C-cells of thyroid, elevated calcium levels as well as a number of other stimuli, such as the glucocorticoids, CGRP, glucagon, gastrin, or β-adrenergic stimulation, induce expression of the CT gene therefore CALC-1 gene activates endocrine cells of thyroid gland hence CT mRNA is formed, this mRNA converted to PCT in non infectious condition PcT is converted to calcitonin CT. Therefore calcitonin released into blood stream and involved in calcium homeostasis during hypercalcemia it reduces the blood calcium level by inhibiting osteoclasts activity of bone and by resorption of calcium in the kidneys. In bacterial infections PcT-producing calcitonin 1 (CALC-1) gene expression is increasing in multiple extra thyroid tissues throughout the body. In the absence of infection, the extrathyroidal transcription of CALC1 gene is concealed. PcT is "hormokines," a mature protein and the inflammation-related functions of its propeptides. The construction of hormokines is a unknown factors and may be induced either

directly via microbial toxins or indirectly by humoral or cell mediated host response [8-11].

The regulation of ProCT expression is fundamentally different from the regulation of CT expression. In the C-cells of thyroid, elevated calcium levels as well as a number of other stimuli, such as the glucocorticoids, CGRP, glucagon, gastrin, or β- adrenergic stimulation, induce expression of the CT gene, while somatostatin and vitamin D suppress CT production.

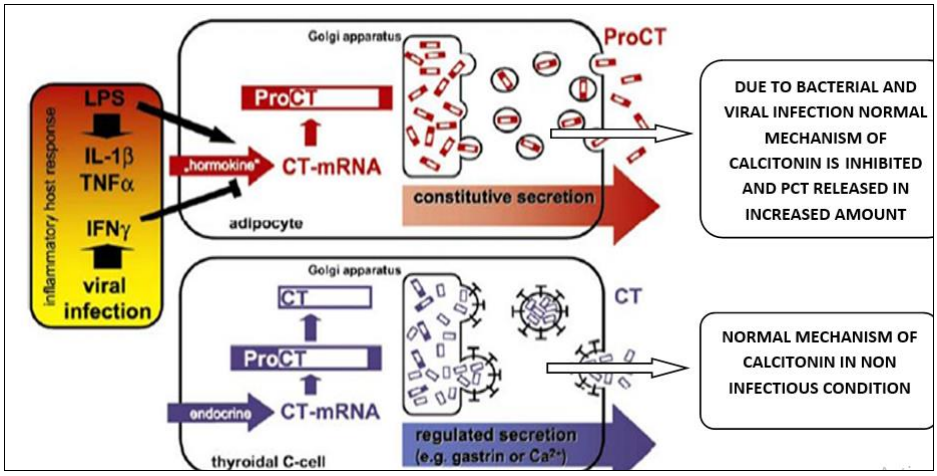

Fig 1: Adopted from (PPT) on Procalcitonin advancing decision making in sepsis by (Sean-Xavier Neath M.D., Ph.D., Assistant clinical professor of medicine, University of California)

The inflammatory release of PcT can be induced in two main ways: lipopolysaccharide induced direct pathway or other toxins released by microbes, and indirect cell-mediated host responses caused by inflammatory cytokines pathway e.g. interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). The molecular mechanisms behind this are still unclear. In bacterial inflammatory processes the level of PcT got increased. In compare to the levels of cytokines which are not specific for particular type of inflammation. These results suggest that numerous modulating factors might be involved in the expression of PcT. Therefore it is clear that PcT measurable in the blood during infection is not produced by C-cells of the thyroid rather by the neuroendocrine cells of lungs or intestine. PcT becomes detectable within few to 4 hours after triggering a event and peaks by 12 to 24 hours [8, 12].

2. Aim

The aim is to prove the Procalcitonin as the potential biomarker in identification of bacterial infection in blood.

3. Materials and methods

3.1 Sample Collection

The study was conducted at Billroth Hospitals, Shenoy Nagar, Chennai 600030 on the ICU patients who already requested for blood culture. The serum samples were taken for the analysis of the procalcitonin. The study was approved by the institutional ethics committee IEC No: BHL/lab projects/2018/007. The serum was separated centrifugation within a hour after collection of the whole blood. The test was performed immediately.

3.2 Methods

The test uses a sandwich immunodetection method, such that the detector antibody in buffer binds to PCT in the serum sample and antigen antibody complexes are captured to another PCT that has been immobilized on test strip as mixture migrates nitrocellulose matrix. Thus the more PCT antigen in serum, the more antigen- antibody complexes accumulated on the test strip. Signal intensity of fluorescence on detector antibody reflects the amount of antigen captured and is processed by QDx InstacheckTM Reader to show PCT concentration in specimen.

3.3 Procedure

Transfer 150 µl of the human whole blood/serum/plasma using a transfer pipette to the tube containing the detection buffer. Close the lid of the detection buffer tube and mix the sample thoroughly with the detection buffer by shaking the tube about 10 times. Pipette out 75µl of this sample mixture from the detection buffer tube and dispense it into the sample well on the test cartridge. For scanning the sample loader test cartridge insert it into the test cartridge holder of the QDx Instacheck™ reader. The proper orientation of the test cartridge should be confirmed before pushing it all the way inside the test holder. An arrow has been marked on the test cartridge especially for this purpose. Press select button on the QDx Instacheck™ Reader to start the scanning process. QDx Instacheck™ Reader will start scanning the sample loaded test cartridge after 12 minutes. Read the test results on the display screen of the QDx Instacheck™ Reader.

3.4 Interpretation

Table 1: Diagnosis of Bacterial Infection/Sepsis

ng/ml	State
PCT <0.5	Local bacterial infection is possible
0.5 – 2.0	Infection is possible
2.0 – 10.0	Infection (sepsis)
>10.0	Severe bacterial sepsis or septic shock.

4. Statistical data analysis

Data were analysed using the percentage calculation and the comparison were also analysed for mild positive, Moderate positive and the severe positive case. Data analysis of blood & urine culture / total count and differential count among procalcitonin positive was described below in Table1.

Table 2

S.No	DATE	UHID	PATIENT NAME	AGE/SEX	PROCALCITONIN	BLOOD	URINE	TC	DC
1	01-12-17	50406468	SIMON GEORGE	86/M	10.03	NEG	NEG	17500	90.2/2.9/1.1/5.3/0.5
2	01-12-17	50406520	SRIDHARAN	62/M	5.55	NEG	NEG	18400	96.9/0.8/0.0/2.3/0.0
3	04-12-17	50406987	VISHALATCHI	55/F	3.93	NEG	NEG	7400	83.4/12.9/0.2/3.0/0.5
4	04-12-17	50406822	MOHAMMED MAKINUDEEN	63/M	30.22	NEG	NEG		
5	04-12-17	50406994	LAKSHMI	72/F	100	E.coli	NEG	20800	94.5/2.0/0.0/3.1/0.4
6	04-12-17	50050751	MURUGESAN	69/M	8.11	NEG	NEG	14200	80.2/9.5/2.2/7.7/0.4
7	06-12-17	50220274	KAMALESH	34/M	55.45	NEG	Klebsiella (u)	16900	91.0/5.9/0.0/3.1/0.0
8	06-12-17	50395536	PURUSHOTHAMAN	57/M	69.45	Enterococcus	NEG	26000	93.6/2.8/0.0/3.5/0.1
9	06-12-17	50406269	RAMBABU	57/M	>100	E.coli	NEG	23800	89.0/2.3/0.2/8.4/0.1
10	08-12-17	50267920	SUNDARA	66/F	13.81	NEG	NEG	9900	93.4/3.4/0.1/3.1/0.0
11	10-12-17	50406948	HEMAVATHY	48/F	3.32	NEG	NEG	15600	77.2/17.6/1.2/3.4/0.6
12	12-12-17	50405600	SUJATHA	61/F	65.95	NEG	Enterococcus (u)	15400	95.7/1.7/2.4/0.2/0.0
13	13-12-17	50407847	DHANASEKARAN	78/M	3.96	NEG	NEG	16300	93.4/2.6/0.0/3.9/0.1
14	14-12-17	50262931	THIRUNAVUKKARASU	57/M	30.97	NEG	NEG	3900	86.5/8.5/4.7/0.3/0.0
15	16-12-17	50408348	CHELLAMMAL	58F	14.57	NEG	E.coli	20700	81.0/6.9/2.3/9.7/0.1
16	17-12-17	50306524	RAMJOHN BEGUM	50/F	42.1	NEG	NEG	10500	74.2/18.1/0.5/6.9/0.3
17	19-12-17	50407497	SELVARJ	59/M	6.56	NEG	NEG		
18	21-12-17	50407497	SELVARJ	59/M	5.2	Klebsiella	NEG	10900	89.2/6.8/0.8/2.9/0.3
19	22-12-17	50347111	SYED MOHAMMED	44/M	4.05	NEG	NEG	18000	92.5/6.6/0.0./0.2/0.7
20	22-12-17	50398290	SRINIVASAN	50/M	3	NEG	NEG	12400	89.2/7.5/0.6/2.6/0.1
21	22-12-17	50229460	SRINIVASAN	79/M	2.51	NEG	NEG	23500	85.1/6.8/0.0/8.1/0.0
22	23-12-17	50408005	ZAHIR HUSSIAIN	50/M	15.89	klebsiella	NEG	14000	89.2/6.8/0.2/2.3/1.5
23	27-12-17	50409581	GANAPATHY	20/M	2.95	NEG	NEG	9500	62.7/18.8/0.4/17.5/0.6
24	28-12-17	50409683	JANNATH JABIRIYA	69/F	6.11	NEG	NEG	17000	75.7/6.5/0.1/17.5/0.2
25	31-12-17	50410075	JOTHI	75/F	21.02	NEG	NEG	39000	94.4/5.5/0.0/0.1/0.0
26	01-01-18	50409431	NAGALLA SUBBURAYUDU	70/M	20.41	NEG	NEG	27000	92.2/4.3/0.4/2.9/0.2
27	02-01-18	70000044	CHANDRASEKAR	78/M	41.27	NEG	NEG	21300	77.1/3.2/0.1/19.6/0.0
28	02-01-18	50348657	ANNAMALAI	53/M	9.49	NEG	NEG	19600	93.3/1.9/0.0/4.7/0.1
29	03-01-18	70000147	DHANAPAL	46/M	18.06	NEG	NEG	8000	80.4/12.8/0.1/6.3/0.4
30	06-01-18	70000479	JOSEPH ABRAHAM	79/M	2.46	NEG	NEG	19800	91.3/4.1/0.3/4.2/0.1
31	06-01-18	70000258	VASU	55/M	4.93	NEG	NEG	13300	79.9/7.9/2.3/9.4/0.5
32	07-01-18	50183629	JAYACHANDRAN	71/M	16.89	NEG	NEG	11100	92.5/2.6/0.0/4.9/0.0
33	09-01-18	70000781	JOTHI	50/F	4.82	NEG	NEG	11300	90.5/4.9/0.0/4.3/0.3
34	10-01-18	70000894	MADHU	65/F	3.3	NEG	NEG	19700	58.5/34.6/1.2/5.2/0.5
35	10-01-18	70000454	SUNDARESA MUDALIAR	86/M	3.4	NEG	NEG	13400	87.3/4.6/0.2/7.6/0.3
36	11-01-18	50137987	SAMPOORNAM	76/F	12.14	NEG	NEG	13000	83.6/5.5/0.1/10.7/0.1
37	11-01-18	70000894	MADHU	65/F	21.46	NEG	NEG	22300	86.2/7.5/0.0/6.0/0.3
38	11-01-18	70000258	VASU	55/M	13.45	NEG	NEG	15000	77.2/9.4/3.3/9.8/0.3
39	13-01-18	70001210	JAMUNARANI	29/F	5.79	NEG	NEG	19300	88.4/6.3/0.2/4.3/0.8
40	13-01-18	50354385	SETHURAMAN	64/M	2.23	NEG	NEG	8500	85.3/6.9/0.4/7.1/0.3
41	13-01-18	50109892	RAMASAMY	81/M	4.02	NEG	NEG	11400	89.7/3.0/0.0/7.3/0.0
42	14-01-18	70000258	VASU	55/M	10.43	NEG	NEG	11300	72.2/10.8/5.5/10.7/0.8
43	14-01-18	50154423	JAGDISH BHATIJA	60/M	2.29	NEG	NEG	17400	82.1/7.2/0.4/6.4/3.9
44	14-01-18	70000149	SUDHAKAR	70/M	3.74	NEG	NEG	15900	65.7/23.8/3.1/7.1/0.3
45	14-01-18	70000482	MUNUSAMY	55/M	10.38	NEG	NEG	14000	14000/92.8/2.9/0.1/4.0
46		50386735	PADMAVATHY	70/F	>100	E.coli	NEG	18600	94.2/5.4/0.1/0.2/0.1
47	20-01-18	70001720	SYED IBRAHIM	57/M	100	E.coli	NEG	19400	88/7/1/4/0
48	23-01-18	70001210	JAMUNARANI	29/F	13.59	NEG	NEG	19600	72.5/16.8/1.7/8.9/0.1
49	23-01-18	50146380	ANANTHA PADMANABHAN	69/M	5.86	NEG	NEG	12800	88.1/3.6/0.1/8.1/0.1
50	23-01-18	70001983	ELLAPPAN	70/M	16.52	NEG	NEG	22000	88.0/3.8/0.1/8.0/0.1
51	24-01-18	50112220	KALIYAMOORTHY	76/M	>100	E.coli	NEG	28400	96.7/2.0/0.0/1.2/0.1
52	24-01-18	70002216	BASKAR	59/M	40.88	NEG	NEG	23000	69.4/27.3/0.1/2.9/0.3
53	24-01-18	50330659	JAYABALAN	74/M	75.99	Klebsiella	NEG	40900	
54	24-01-18	50399914	DAISY	70/F	47.28	E.coli	NEG	21000	88.0/10.0/1.0/1.0/00
55	24-01-18	50404487	PHILIP	81/M	21.28	NEG	E.coli	2700	51.6/33.0/1.3/13.5/0.6
56	24-01-18	50103064	SUNDARAMOORTHY	64/M	34.95	NEG	Klebsiella (u)	12600	94.0/6.0/0.0/0.0/0.0
57	25-01-18	50400016	LAKSHMI SELVARAJ	60/F	4.92	E.coli	NEG	15900	86.0/7.7/1.2/4.7/0.4
58	25-01-18	50404904	VELRAJ	24/M	9.15	NEG	NEG	11600	86.6/5.2/0.1/8.0/0.1
59	25-01-18	50405674	JAYALAKSHMI	59/F	43.7	NEG	NEG	12700	94.5/3.5/0.0/2.0/0.0
60	25-01-18	50078589	SHANMUGARAJ	36/M	45.4	NEG	NEG	19100	81.7/12.7/2.6/2.7/0.3
61	25-01-18	50395313	BALAJI	31/M	3.12	NEG	NEG	8800	76.5/14.0/1.7/7.4/0.4
62	25-01-18	50396345	DEVAN	64/M	11.48	NEG	NEG	8800	
63	25-01-18	50395874	KUTHBUDHEEN	54/M	8.18	NEG	NEG	16700	75.0/12.7/2.5/9.5/0.3
64	25-01-18	50396392	MOHAMED THAKIBSHA	24/M	3.53	NEG	NEG	12100	63.0/28.4/1.1/7.1/0.4
65	25-01-18	50396555	SATHIDEVI	76/F	37.04	NEG	NEG	18900	91.3/6.3/0.0/2.3/0.1
66	25-01-18	50232622	BALADHANDAYUTHAM	79/M	9.04	NEG	NEG	42300	AML
67	25-01-18	50126674	JALAL ZUBAIDA BANU	70/F	14.08	NEG	NEG	15300	88.7/6.1/0.1/5.0/0.1
68	25-01-18	50397554	SHEEBA	19/F	3.75	NEG	NEG	12300	88.4/4.2/2.4/4.9/0.1
69	26-01-18	50269779	GURUPRASAD	20/M	10.3	NEG	NEG	16300	87.2/7.3/1.1/4.3/0.1
70	27-01-18	50393649	MEENAKSHI	51/F	11.14	NEG	NEG	14000	80.0/12.0/0.0/8.0/0.0

5. Results & Discussion

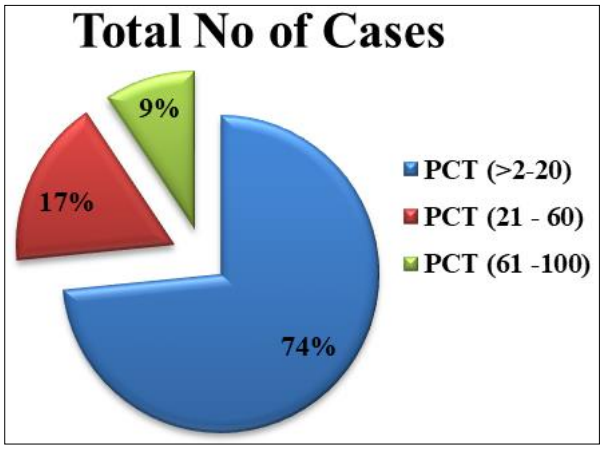

Fig 2: Percentage description of procalcitonin positive classification based on the values

Table 3

Total Number	PCT (>2-20)	PCT (21 - 60)	PCT (61 -100)
Total No of PCT	47	11	6
Bld. C/S Positive	4	2	6
Positive Percentage	9%	18%	100%

Pie chart represents that the total number of positive procalcitonin cases. Based on the biological reference range of procalcitonin, Total numbers of cases were differentiated into 3 groups such as the values are 2-20ng/ml are considered as Mild positive for PCT, values are 21-60ng/ml is considered as Moderate positive of PCT and Severe positive (PCT) values are considered as range falls between 61-100ng/ml. Above 74% of cases are classified as mild positive for PCT, 17% of cases as moderate positive for PCT and only 9% of cases are observed as severe positive for PCT.

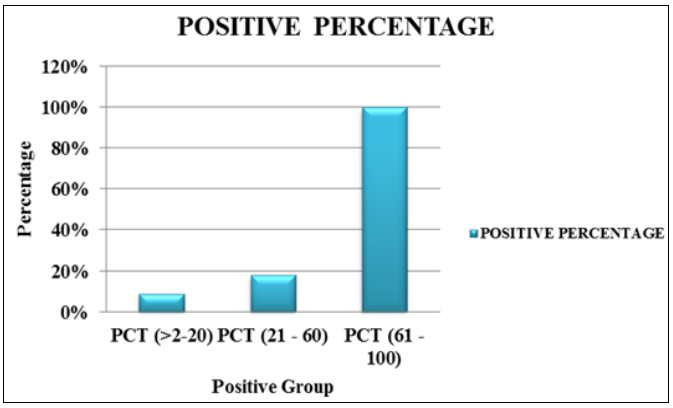

Fig 3: Blood culture positive percentage description of procalcitonin positive classification based on the values

Each bar represents the positive percentage of Procalcitonin vs blood culture. As shown in fig 3 in mild positive cases of PCT, only 9% of blood cultures are positive. In moderate positive cases of PCT, only 18% of blood cultures are positive. Where as in severe positive cases of PCT, all the blood cultures are shown 100% positive.

Sepsis is an invasion of microorganisms of systemic immune response leads to infection. Sepsis is defined as the presence of infection together with systemic manifestations of infection. Bacterial sepsis is a clinical term used to describe symptomatic bacteremia, with or without organ dysfunction. Sepsis can result from bacteria, viruses, fungi, or parasites, or it can develop in noninfectious intraabdominal incidents such as severe trauma, pneumonia, pancreatitis, and other incidents such as urinary tract infection. The microorganism frequency that leads to sepsis shows chances based on sepsis develop inside or outside the hospital. The most frequently encountered active microorganisms in sepsis patients in are *Escherichia coli*, *Streptococcus pneumonia* and *Staphylococcus aureus*.

Proliferation of detrimental strains of bacteria inside the biological system which infect and affect any parts of the human system. Pneumonia, meningitis, and food poisoning are just a few illnesses that may be caused by such harmful bacteria. Bacterial sepsis is associated with high morbidity and mortality. Untreated sepsis may lead to septic shock which in turn leads to death. Sepsis is the second most common cause of death. (1) Sepsis patients can be differentiated as, already infected patient who were came for diagnosis after 2 of 3 days, in this condition diagnosis must done early and treatment should give as soon as possible to rule out the bacterial infection. (2) Next, A hospital-acquired infection, also known as a nosocomial infection, is an infection that is acquired in a hospital or other health care facility. Some patient may prone to get infection due to hospitalization; this is also a one of the way to acquire sepsis. Patient comes without bacterial infection for surgery, may has a chance to get sepsis because of not properly sterilized surgical equipment.

On any situation given above, treatment is necessary as soon as possible, In general to rule out the bacterial infection clinicians prescribe blood culture as a basic and preferred diagnostic tool, but this study says that instead of analyzing blood culture it is preferred to estimate procalcitonin to conform whether the blood culture is required or not. So to find out the bacterial infection in blood procalcitonin serves as a best marker. Generally blood culture reports will be obtaining only after 5 days, so due to this report delay will ultimately delayed in treating the bacterial infection. Blood culture shows positive even on the final day. If the physician depends on those reports will leads to the improper treatment / medication. But if the consultant preferred for the procalcitonin estimation prior to the blood culture it easy pave a path way to the right direction of the treatment at right time using first line of antibiotics for localized infection. This test is also helps to minimize the hospitalization of the patient for more than 5 days in order to waiting for blood culture.

PcT is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine. PcT originate from the calcitonin I (CALC-1) gene on chromosome 11. Expression of the PcT-producing calcitonin 1 (CALC-1) gene is increasing in bacterial infections using multiple extra thyroid tissues throughout the body. Therefore PcT detectable in the plasma during infection is not produced by C-cells of the thyroid rather by the neuroendocrine cells in the lungs or intestine. PcT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24 hours[11]. By analyzing serum procalcitonin if it is exceeds >60mg/dl

then the patient may be prescribed with blood culture because to identify the organism, but the presence of bacteria in blood is confirmed by procalcitonin test to starts the first line of basic antibiotics. If the procalcitonin level is below 60mg/dl there is less or no possibility of bacterial infection and hence for that case of patient blood culture diagnosis is not needed. During data analysis, comparisons of procalcitonin vs blood culture have been monitored to prove procalcitonin as a potential biomarker for bacterial infection in blood. In this study most of the patients have been prescribed either blood culture or PcT. In some cases only both test have been prescribed. The patients who were asked for both procalcitonin and blood culture were selected and the data of both the report were compared. In this study all the PcT positive cases are not positive to blood culture. Only when the PcT becomes severe positive (>60mg/dl) according to the biological value it is positive to blood culture. So patients who were prescribed for blood cultures were tested for Procalcitonin and both were compared. Finally the study reveals that blood culture becomes positive only for the patients who were severe positive to procalcitonin that is values >60mg/dl.

6. Conclusion

This study proves that the definite blood culture becomes positive, when the level of procalcitonin reaches above 60mg/dl (severe positive). Therefore the estimation of procalcitonin will ultimately help the clinicians to decide whether the patient needs the blood culture or not, this prior estimation of procalcitonin surely helps to minimize the nosocomial infection, hospitalization of patient, stress during the stay in hospital, loss of the blood during culture (volume of blood for blood culture 8ml for each aerobic and anaerobic) and increases the speedy medication if positive occurs. Existing literature proves that in those patients with chronic obstructive pulmonary disease, a single serum PcT determination at the time of admission reduced the mean length of stay from 7.1 days to 4.8 days (Kristofferson *et al.*, 2009) [13]. TAT for blood culture is more than 5 days, which affects treatment if the clinicians depend of the report of blood culture. Hence this study proves that procalcitonin is a best biomarker for bacterial infection.

7. References

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