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RESEARCH ARTICLE

CLAINICO-BACTERIOLOGICAL SPECTRUMAND ANTIMICROBIAL RESISTANCE PROFILEIN BACTEREMIA COINFECTING COVID-19 PATIENTS IN A TERTIARY CARE HOSPITAL IN TRIPURA

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Abstract

Background- Secondary bacterial infections including bacteremia have been implicated as a major cause of morbidity and mortality in COVID-19 patients So, it is important to determine the bacteriological profile of organisms responsible for bacteremia among COVID-19 patients along with their antimicrobial resistance pattern Objectives- To determine the bacteriological profile, antimicrobial resistance pattern and clinical outcome among COVID-19 patients with bacteremia as manifestation of secondary bacterial infection. Study design- Single center, cross sectional study Methods- Blood cultures were obtained from COVID-19 patients with features of bacteremia and sepsis based on Sepsis-3 criteria and serum procalcitonin level. Identification and AST were performed and the patients were followed until final outcome or discharge from hospital. Results- Among 43 blood samples obtained. 8 were positive in culture for pathogenic bacteria (18.6%). Mean age of the patients were 53.4 ± 14.9 years with male preponderance (62.5%). Mean procalcitonin level was 6.5±5.7 ng/ml. Positive history of contact was the major risk factor (62.5%) and mean duration of hospital stay was 11.1± 3.9 days. Mortality rate was 37.5%. Gram negative bacilli were the major isolates (75%) and one case was caused by an unusual organism Erysipelothrixrhusiopathiae. Among the Gram negative bacilli, maximum resistance was against Amikacin (100%) and minimum against Meropenem (16.7%). Out of GNB isolates, one isolate of Pseudomonas aeruginosa was Metallo ? lactamase enzyme producer and another one was multidrug resistant strain.

Conclusion- Bacteremia among COVID-19 patients is a serious form of bacterial co-infection, leading to increased morbidity and mortality among the patients. High degree of clinical suspicion and increasing prolactin level must be complemented with blood culture to rule out bacteremia in these patients, where timely intervention and proper antimicrobial therapy can be lifesaving. Keywords- COVID-19, SARS-CoV-2, Coronavirus, Bacterial coinfection, Bacteremia, Antimicrobial resistance.

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Introduction:-

From December 2019, the world is experiencing a pandemic created by corona virus disease 2019 or COVID-19. The virus, belonging to β-coronavirus of Group 2b,[1] is thought to have originated from Huanan sea food market in Wuhan city, China.[2] On 11th February 2020, World Health Organization (WHO) officially named the disease as COVID-19 and on the same day, International Committee on Taxonomy of Viruses (ICTV) named the virus as severe acute respiratory syndrome coronavirus2 (SARS-CoV-2).[3]

Zhouand colleaguesshowed that secondary bacterialinfections accounted for about 50% mortality in COVID-19 patients.[4]Bacterial co-infection among COVID-19 patients is 7% among hospitalized and 14% among ICU patients, with*Mycoplasma pneumoniae*being the most common co-infecting organism (42%) followed by *Pseudomonas aeruginosa* (12%) and *Haemophilus influenzae* (12%).[5]

Bacteremia has been described as one of the complications in COVID-19 patients. Conflicting reports exist about bacteremia in COVID-19 patients, ranging from 3.8% to 7.7 %. [6,7] Y He and colleagues reported that bacteremia occurred in 24.6% of COVID-19 patients with nosocomial infections.[8] In COVID patients, bacteremia has been mainly associated with history of long-term inhaled corticosteroids in asthma and Chronic Obstructive Pulmonary Disease (COPD). [8]Moreover, the role of empirical antimicrobial therapy in the bacteremia patients in setting of SARS-CoV-2 coinfection is still unproven.[6]

In India, AMR Surveillance data (ICMR, 2019) shows thatNon- fermenting Gram-Negative Bacilli (NFGNB-*Pseudomonas aeruginosa, Acinetobacter baumanii, Burkholderiapseudomallei*) were the predominant Gram-negative organisms (12.5%)isolated from blood, following *Staphylococcus aureus* (24.4%) and *Enterococcus spp.*(14.5%). [9]These organisms are inherently resistant to a wide variety of antimicrobials and can acquire resistance genes easily by horizontal transfer. [10]

Blood stream infections caused by multidrug resistant organisms themselves possess clinical challenges as they severely limit the therapeutic options in these patients. Therefore, they significantly increase the mortality and morbidity among COVID-19 patients. Moreover, co-infection with atypical and unique organisms (e.g., *Bacillus cereus, Erysipelothrixrhusopathiae*) also compounds these problems as there should be a high degree of clinical suspicion to diagnose these cases.[11]

This study aims toshow the bacteriological profile of organisms responsible for Blood stream infections among COVID-19 patientsisolated in a tertiary care center in Tripura, North Eastern India, with their antimicrobial resistance patterns which may be beneficial to further formulate diagnostic and therapeutic strategies.

Materials And Methods:-

The study was a single center cross sectional study which was conducted at Department of Microbiology, Agartala Government Medical College and GBP Hospital, Agartala, Tripura, India. The period of study was 3 months (15th May, 2020 to 14th August, 2020). Blood samples for culture and sensitivity was collected from the laboratory confirmed patients with COVID-19 presenting with features of sepsis or septic shock, defined as per 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[12]along with abnormal procalcitonin level (normal level ≤ 0.05ng/ml).

Blood collection was performed by peripheral venepuncture under strict aseptic precautions as per WHO protocol.[13] Two different sets were collected from two different sites, with each set comprising of two blood culture bottles (BacT/Alert FA Plus, BioMérieux), each being inoculated with 8-10 ml of blood. First set was collected before the start of antibiotic therapy and second set was collected just before administration of next dose. After collection, the bottles were incubated in BacT/Alert 3D 60 automated blood culture system (BioMérieux) as per manufacturer's protocol.[14]

If there was positive signal within 5 days, the bottle was taken out and subculture was performed in Blood and MacConkey agar plates and Gram's stain was performed from the media in the bottle. Gram's stain report was immediately communicated with the treating Physician. After 24 hours incubation, organism was identified up to

species level by standard biochemical tests.[15] Confirmation was also done using Vitek-2 Compact identification and AST system (BioMérieux) as per manufacturer's protocol.[16]

Antimicrobial sensitivity test was performed using Kirby- Bauer's disc diffusion test [17] as per CLSI protocol M100-E30, 2020[18] and CLSI protocol M45-E3,2015[19] (for *E. rhusopathiae*). AST was also confirmed by detection of MIC values as per CLSI protocol using Vitek-2 compact machine.

Production of Carbapenemase was confirmed by Modified Hodge test. [20] Production of Ambler Class B Metallo ß lactamase was confirmed phenotypically by double disc diffusion test (Imipenem 10µg and Imipenem-EDTA 10/750µg, Himedia, India). [20]

Statistical analysis was done using MS Excel (Office 365®, Microsoft) and IBM SPSS® Statistics Software, version 26. Results are expressed as Percentageand Mean value of the samples.

Results:-

Out of 477 of patients admitted in AGMC & GBP Hospital COVID Care Centre over 6 months, 43 blood cultures were obtained with order rate of 9% (43/477). Out of 43 blood cultures, pathogenic organisms were isolated from 8 samples with positivity rate of 18.6% (8/43). The clinic-demographic and investigational profiles are enumerated in table no. 1.

Out of 8 (eight) cases of bacteremia, 6 (Six) were caused by Gram Negative Bacilli(75%), onecase was caused by Gram Positive coccus and one by Gram Positive bacillus. Distribution of isolated organisms are shown in Figure 1 and the colonies of organisms isolated from blood are shown in Figure 2.

Antimicrobial resistance patterns among Gram Negative Bacilli are shown in Figure 3.

E. rhusopathie was sensitive toAmpicillin (≤ 0.25µg/ml), Cefepime (≤ 1µg/ml), Imipenem (≤ 0.25µg/ml), Levofloxacin (≤ 0.5µg/ml) and resistant to Erythromycin (2µg/ml).*S.aureus* was sensitive to Gentamycin (GEN 10µg), Doxycycline (DO 30µg), Vancomycin (VAN, MIC≤ 2µg/ml), Cotrimoxazole (COT 1.25/23.75µg), Levofloxacin (LE 5µg) and resistant toAzithromycin (AZ 15µg).

Modified Hodge Test in the meropenem resistant strain of *Pseudomonas aeruginosa*showed it to beCarbapenemase producer and Double disc diffusion test confirmed it to be Metallo ß lactamase (MBL) producer as shown in Figure 4.

Discussion:-

Studies around the world have shown bacterial co-infection as significant causes of morbidity and mortality among COVID-19 patients. [5, 21] According to Langford et al (May,2020),overall bacterial co-infection rate was 6.9% with 71.8% patients requiringantibiotic prescription between December 2019 to March 2020.[21], Lansbury et al also reports an overall coinfection rate of 7% among COVID-19 patients.[5]

Bacteremia is described as one of the complications in COVID-19 patients. Several studies show variable occurrence of bacteremia among these patients, ranging from 3.8% to 7.7%. [6,7] In our study, bacteremia was present in 1.7% of overalllaboratory confirmed COVID-19 cases (8/477, 1.7%), which is lower than the rate described in the studies.43 blood culture samples were received (blood culture order rate 43/477, 9%) and positivity rate was 18.6%, which is higher than that described by Sepulveda et al. [6]

In the study, mean age of the patients was 53.4 ± 14.9 years. The distribution is similar to normal adult age group among COVID-19 patients as shown in studies by Chen N et al (mean age 55.5± 13.1 years)[22] and Chen T et al (median age 54 years).[23]Males were more affected with bacteremia than females (62.5%) in our study. Although no other study shows difference in gender among bacteremia patients in COVID-19, gender difference is similar to overall trend in COVID-19 patients as shown by Chen N et al (male 67% affected). [22]

In the study, contact with lab confirmed case was the major risk factor which was present in 62.5% patients (5/8, 62.5%). Other risk factors include history of asthma with inhalational corticosteroid use (1/8, 12.5%), Chronic

Kidney Disease (2/8, 25%) and Diabetes Mellitus (2/8, 25%). Mean duration of hospital stay after admission was 11.1± 3.9 days. 50% of the patients required admission to Intensive Care Unit (ICU). Mortality among the patients was 37.5% (3/8, 37.5%). This shows that bacteremia can cause severe manifestation among the COVID-19 patients requiring ICU admission. Also, it may lead to fatal outcomes even after intensive treatment, thus emphasizing the need for early detection of bacteremia among COVID-19 patients.

Mean Procalcitonin level in our study was 6.5±5.7 ng/ml which shows that higher procalcitonin level (normal ≤ 0.5 ng/ml) is a good predictor of bacteremia and sepsis among COVID-19 patients. As risingProcalcitonin level in COVID-19 patients is positively associated with severity of the disease [24] and worsening prognosis, [25] it can also be considered as indication of blood culture among the patients, leading to early diagnosis and timely treatment of bacteremia reducing morbidity and mortality.

In our study, Gram negative bacilli were the predominant isolates from blood (6/8, 75%). *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were the major isolates, each accounting for 25% of overall organisms isolated from blood. Other GNBs include *Acinetobacter baumanii*(12.5%) and *Burkholderiapseudomallei* (12.5%). *Staphylococcus aureus* (12.5%)and *Erysipelothrixrhusiopathiae*(12.5%)are the other organisms which were isolated from the patients.

Antimicrobial sensitivity profile in our study shows that the Gram-negative isolates had maximum resistance to Amikacin (100%) and minimum resistance to Meropenem (16.7%). The resistance pattern to other groups of antimicrobials include Piperacillin-Tazobactam (33.3%), Ceftazidime (50%), Levofloxacin (33.3%) and Colistin (50%). Our study shows increased resistance to Amikacin and Colistin among Gram Negative isolates compared to AMR surveillance data, 2019 which is a matter of great concern. [9] Increased resistance to antimicrobials and isolation of multidrug resistant strains severely limits therapeutic options among the COVID-19 patients with bacterial co-infection, as most of them are already immunocompromised due to old age, Diabetes mellitus, Chronic Kidney Disease, malignancy, steroid therapy due to asthma or COPD and other systemic illnesses.[21, 22]

Out of the two strains of *Pseudomonas aeruginosa* isolated in our study, one strain was multidrug resistant, being only sensitive to Meropenem and the other strain wasMetallo β lactamase (MBL) producer. *Pseudomonas aeruginosa* has been shown to be the second most common bacteria coinfecting COVID-19 patient (12%) by Lansbury et al. [5]Also, the bacteria is inherently resistant to a wide variety of antimicrobials and is known to transmit the resistance factors by horizontal transmission.[10,26]Bacteremia caused by MBL producing Carbapenem resistant strain and Multi drug resistant strain of *Pseudomonas aeruginosa* in COVID-19 patients, who already are suffering from compromised immune system, indicates grave outcome in the future.

In our study, one case of bacteremia was due to *Erysipelothrixrhusiopathiae*. There was no history of any occupational exposure and the patient had history of long-term steroid use due to childhood asthma. There was mortality of the patient as she was immunocompromised due to old age and steroid therapy.

Erysipelothrix rhusiopathiae, which is considered an occupational pathogen, mainly manifests in the form of typical cutaneous lesions called erysipeloid. [27] Bacteremia by this organism is a primary infection and not secondary dissemination from cutaneous lesions. [28] Also, bacteremia due to *Erysipelothrix rhusiopathiae* is usually associated with long term high dose steroid use. [27] This shows the need of high degree of clinical suspicion as COVID-19 patients may also suffer from bacteremia due to unusual organisms like *Erysipelothrix rhusiopathiae*. There is necessity to rule out these organisms as they can have serious outcome among COVID-19 patients.

Burkholderia pseudomallei, causative agent of meliodosis, was isolated in one of the patients suffering from bacteremia. This organism is ubiquitous in nature and is transmitted from wet soilsand stagnant waters in the endemic regions through wounds in the skin and occasionally through ingestion. Most severe manifestation of meliodosis includes septic shock associated with severe pneumonia. [29] The patient had history of Type 2 Diabetes mellitus and soft tissue infection in right leg, following which he developed bacteremia. Association with pneumonia couldnot be ascertained as his lungs were already compromised due to SARS-COV-2 infection.

In our study, sample size is very less (forty-three) and out of that, only 8 were positive in blood culture. The study was conducted for a very short time (six months). Further studies with larger sample sizes and over longer durations are necessary to elucidate the effect of bacteremia among COVID-19 patients. It is also important to elucidate the

molecular mechanisms underlying the drug resistance among the bacteria coinfecting COVID-19 patients, so that judicious use of antimicrobials can be instituted through stewardship programs, thus preventing morbidity and mortality among the patients.

Table 1:- Clinico-Demographic And Investigational Profile Of Covid-19 Patients With Blood Stream Co-Infection.

VARIABLES	VALUES
MEAN AGE (YEARS)	53.4 ± 14.9 (Range 38-85 years)
GENDER • MALE • FEMALE	 5 3
RISK FACTORS • H/O CONTACT WITH LAB CONFIRMED CASE • ASTHMA WITH STEROID USE • CKD • TYPE 2 DIABETES MELLITUS	 5 1 2 2
MEAN DURATION OF HOSPITAL STAY FOLLOWING ADMISSION (DAYS)	11.1± 3.9 (Range 6-15 days)
CLINICAL OUTCOME • RECOVERY • ADMITTED TO ICU • MORTALITY	 5 4 3
MEAN PROCALCITONIN LEVEL (ng/ml)	6.5±5.7 (Range 3.2-20.0 ng/ml)

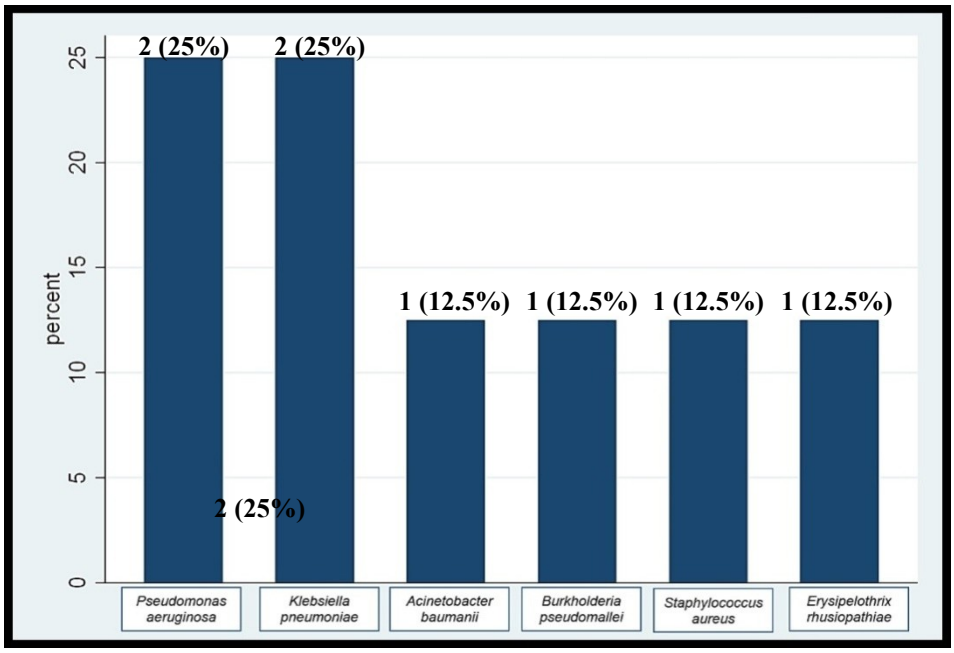

Fig 1:- Distribution Of Organisms Isolated From Blood In Covid-19patients.

Fig 2:- Colonies Of Different Organisms Isolated From Blood.

A. Green diffusible pigmentation of *P. aeruginosa* on nutrient agar
B. Lactose fermenting mucoid colonies of *K.* pneumoniae on MacConkey agar
C. Non- lactose fermenting colonies of *A.baumanii*on MacConkey agar
D. Non- lactose fermenting irregular colonies of *B. pseudomallei*onMacConkey agar
E. Non diffusible golden yellow pigmentation of *S. aureus* on Nutrient agar
F. Non- hemolytic, greyish white, smooth colonies of *E. rhusiopathiae* on Blood agar.

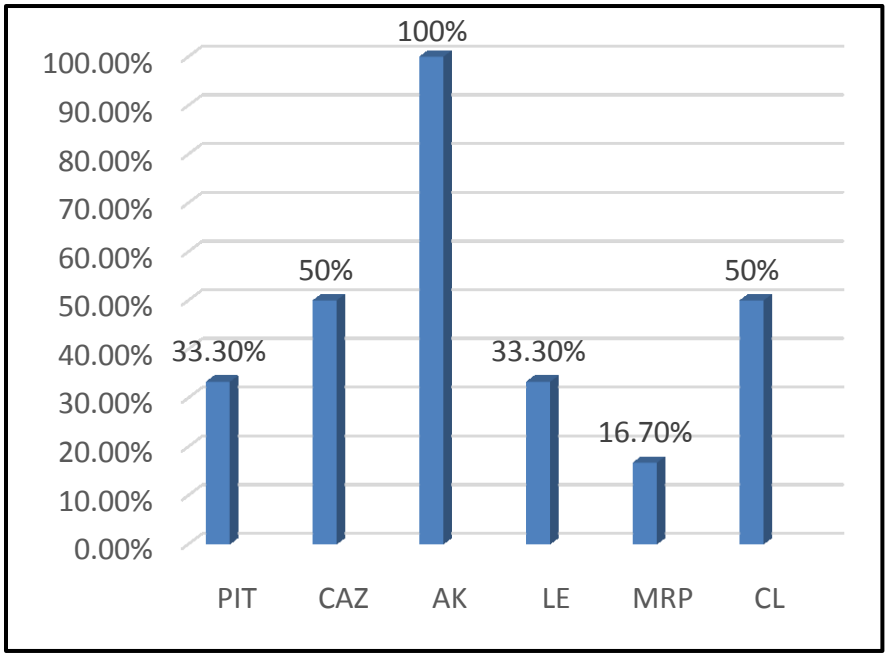

Figure 3: Antimicrobial sensitivity pattern of Gram negative bacilli

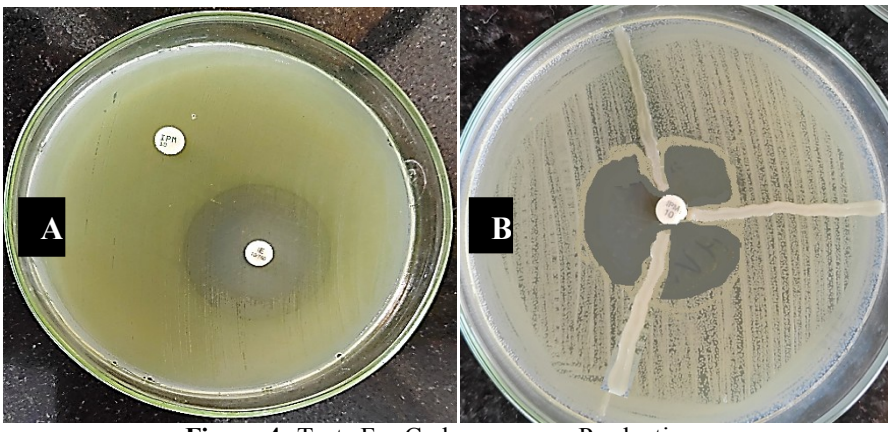

Figure 4:-Tests For Carbapenemase Production.

A. Modified Hodge Test To Detect Carbapenemase

a. Organism isolated from sample- positive result.
b. Known carbapenemase producing strain - positive result.
c. Known carbapenemase non producing strain - negative result.

B. Double Disc Diffusion Test To Detect Mbl

Conclusion:-

Bacteremia among COVID-19 patients is a serious form of bacterial co-infection, which may lead to increased morbidity and mortality among the patients. Most of the patients suffering from bacteremia are in their 5th and 6th decades of life and have compromised immune system due to various systemic illnesses or malignancy. High degree of clinical suspicion and increasing prolactin level must be complemented with blood culture to rule out bacteremia in these patients, where timely intervention and proper antimicrobial therapy can be lifesaving.

Out of total 477 COVID-19 patients admitted during this period, only 43 blood culture samples were received. An increase in blood culture samples depending on clinical criteria and measurement of prolactin level must be considered to rule out bacteremia among COVID-19 patients.

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