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Evaluation of Bloodstream Infections Associated with Carbapenem-Resistant Enterobacteriaceae in Paediatric and Adult Patients

Sunil Kumar[1], Dinesh Narayan Nalage[2], Mohammad Aslam[3], Shoorvir Singh[1*] and Umesh Kumar[4*]

[1]*Department of Biotechnology, GLA University, Mathura 281406, Uttar Pradesh, India.*
[2]*Institute of Biosciences and Technology, MGM University, Aurangabad 431003, Maharashtra, India.*
[3]*Department of Surgery, JN Medical College, Aligarh Muslim University, Aligarh 202001, Uttar Pradesh, India.*
[4]*Department of Biosciences, Institute of Management Studies Ghaziabad (University Courses Campus), NH09, Ghaziabad 201015, Uttar Pradesh, India.*

Abstract

THE majority of infections that affect the bloodstream are caused by bacteria, though infections caused by viruses and fungi can also occur. Common sites of infection include the skin, intestines, urinary tract, and lungs. When viable, reproducing bacteria are detected in the blood, the condition is known as bacteremia. This type of illness impacts the bloodstream. Bacteremia is classified into two types: primary and secondary. In primary bacteremia, bacteria are introduced directly into the bloodstream, which can occur, for example, through drug injection. The methods available in the past were laborious and often ineffective, even if the patient had taken antibiotics. Infections acquired in the community or through medical treatment are typically caused by gram-negative bacteria belonging to the Enterobacteriaceae family. Severe or high-risk bacterial infections are often treated with carbapenems, a class of beta-lactam antibiotics known for their effectiveness. This class of antibiotics is typically reserved for bacterial infections that are multidrug-resistant or suspected to be so. In some cases, bacteria produce carbapenemases—enzymes that degrade the β-lactam ring of carbapenem antibiotics. Since the genes for carbapenemases are carried by easily transferable mobile genetic elements (such as plasmids or transposons), the rapid global spread of carbapenem-resistant Enterobacteriaceae (CRE) is largely attributed to the presence of these enzyme-producing bacteria. The present study aims to determine the most prevalent blood-borne infections across 100 patients of various age groups, along with evaluating carbapenem-resistant Enterobacteriaceae.

Keywords: Antibiotics, Bacteraemia, carbapenems Enterobacteriaceae, Infection.

Introduction

Although infections caused by viruses (viremia) and yeasts or other fungi (fungemia) are also possible, the most common cause of bloodstream infections is bacteria (bacteremia). Sepsis occurs when an existing infection triggers a cascade of events in the body. According to recent studies, the incidence of bloodstream infections has been increasing, with significant impacts on patient outcomes [1, 2]. Common sites of infection for sepsis include the skin, intestines, urinary tract, or lungs. Delays in treatment for sepsis can hasten the deterioration of organ function, harm to tissues, and potentially mortality. When viable, reproducing bacteria are detected in the blood, the condition is known as bacteraemia. The bloodstream is affected by this type of illness. There are two ways to classify bacteraemia: primary and secondary. In primary Bacteraemia, the bacteria are injected directly into the bloodstream. Primary bacteraemia can occur as a result of injecting drugs [3]. The use of contaminated blood vascular catheters in healthcare facilities is another potential cause of primary bacteraemia. Secondary bacteriaemia occurs when bacteria enter the body through an alternate route, such as a skin cut, the respiratory tract, the gastrointestinal tract, the urinary tract, the genitalia, or the mucous membrane of the lungs. Bacteria may enter the body through

*Corresponding authors: Umesh Kumar, E-mail: umeshkumar82@gmail.com, Tel.: +919899952297
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these points and then spread to the lymphatic and bloodstream systems. Bacteraemia can also be characterised by the length of time that bacteria are present in the bloodstream, whether it is transient, intermittent, or persistent. Bacteraemia, which causes transitory bloodstream infections in healthy people, typically has no long-term effects because the bacteria only stay in the bloodstream for a short period of time before being eliminated [4].

New infections caused by *Staphylococcus pyogenes, Staphylococcus viridians*, and *Staphylococcus aureus* are all potential causes of bloodstream infections (BSIs) in children, adolescents, and young adults after an influenza pandemic. Some examples of the first group include Salmonella typhi and non-typhi in certain parts of the world, as well as aureus bacteraemia [5]. These infections usually manifest in the community, but sometimes they are discovered just after a patient has been admitted to the hospital. Worryingly, meningitis and community-acquired BSI in otherwise healthy hosts have been warned about time and again by various authorities not to use antibiotics unless absolutely necessary; otherwise, you run the risk of missing a potentially dangerous infection that looks harmless at first glance. At first glance, a viral infection might seem similar to a more serious, sneaky bacterial disease. The second group of bloodstream infections (BSIs) includes patients whose immune systems are either immature or older [6]. For example, infections caused by *Listeria*, *pneumococcal*, group *B streptococcal*, and *E.coli* In the latter stages of life, E. coli, Klebsiella spp., and Candida frequently exhibit surprising similarities. Almost any pathogen, including fungi, Gram-positive and Gram-negative bacteria, and infections acquired in hospitals, can cause bloodstream infections (BSI) in the third category [7]. Infections in people with impaired immune systems, whether hereditary or acquired, are part of this category. People with diabetes and other conditions that increase the risk of infection also fall into this category. Lastly, there are nosocomial infections, which are common in modern medicine and have close ties to healthcare. This is especially true in settings where immunosuppressive and cytotoxic treatments are commonly used [8].

Worldwide, Carbapenem-Resistant Entero-bacteriaceae (CRE)-related bloodstream infections (BSIs) represent a serious risk to public health. Because there are few available treatments for CRE infections and their high fatality rates, the discovery and spread of this virus have raised serious concerns [9]. With only a few active antimicrobials remaining, the available therapy alternatives for CRE are restricted. The aminoglycosides, carbapenem, colistin, and tigecycline are often the only alternative antimicrobials accessible. Only isolates having a meropenem MIC of less than 8 mg/L benefit from carbapenem. Nephrotoxicity and heterogeneous resistance have been documented with colistin, making it the last resort for treating infections brought on by Gram-negative bacteria that are resistant to many drugs [10, 11]. The present study employs the use of Instruments such as the Vitek 2 compact, which provides the MIC value and the Bact Alert 3D system and aims to identify the pattern of carbapenem resistance in the blood sample procured from the patients.

Material and Methods

Sample collection site and ethical clearance

The samples were collected from patients at the Amrita Institute of Health Sciences, Faridabad. Ethical approval was obtained from the Institutional Ethics Committee of JNU College and Hospital, Faculty of Medicine, Aligarh Muslim University, Aligarh, India. (Ref. No. IECJNMC/1258).

Sample collection

Blood from several bacteraemia or septicaemia patients was placed in a biomerieux blood culture bottle. The positive control group had fifty confirmed cases and the negative control group fifty healthy people. A bar code with the patient's name, age, and gender was applied to the samples sterilely. Use a separate sterile needle and disinfect the blood culture bottle mouth before adding blood. Syringes and needles were used to draw the blood samples into the blood culture containers, and a holder was used when collecting blood into the containers to maintain proper technique [12].

Incubation of blood samples

Blood culture bottles are incubated with Bac TAlert 3D biomerieux instruments. These instruments keep bottles at 37 degrees and provide optimal agitation, which promotes the growth of readily available bacteria. The bottles incubate for five days in this device. The organism produces carbon dioxide during metabolism. This changes the colour of the sensor at the bottom of the bottles, triggering an alarm for positive blood cultures. When white blood cell counts are high, bottles may give false positives. This happens because the excessive breakdown of leukocytes releases carbon dioxide, altering the sensor’s color in the blood culture bottle. As a result, the BacT/ALERT machine may register false positives. We found no growth in the bottle after gramme staining [13].

Culturing of samples and staining

Cultures that tested positive underwent a primary Gram stain, followed by subculturing on appropriate solid media. Mixtures of 5% sheep blood agar (SBA) and MacConkey agar were inoculated with a single drop of blood and incubated at 37°C with 5-10% carbon dioxide for 18-24 hours. The initial techniques for bacterial identification included assessing colony morphology and performing Gram

staining. After 24 hours, blood, MacConkey, and chocolate agar were streaked using a sterile inoculating loop, and the growth was observed [14].

Antibiotic sensitivity test

By using the disc diffusion method, we are able to determine the antibiotic sensitivity of Muller-Hinton agar by placing antibiotic disc over the grass cultivation of bacterial solution it does not provide the minimum inhibitory concentration (MIC). Because of this, we are utilising the Vitek 2 compact equipment, which provides the minimal inhibitory concentration. the minimal concentration number that is enough to kill bacteria. The identification of the organism and the drug sensitivity were carried out on a Biomerieux instrument called the Vitek 2 compact. The calorimetric test was used to determine the drug sensitivity, and the results were then observed for drug resistance [15].

Results

The results indicated that *E. coli* was the most frequently isolated bacterium. In addition to *E. coli*, *S. typhi, Klebsiella pneumoniae, S. enterica,* and *S. paraty*phi were also identified in the samples, as shown in Fig 1. Which displays the frequency of bacterial species identified across the sampled population. Data were compiled in a bar chart format, with the x-axis representing different bacterial species and the y-axis indicating the number of occurrences. Statistical analysis involved calculating the percentage of each species relative to the total number of bacteria identified.

Fig. 2 illustrates the age-wise distribution of the identified bacteria. Data were presented in a stacked bar chart, with age groups (0-10 years, 40 years and above, etc.) on the x-axis and the prevalence of each bacterial species on the y-axis. The distribution was analyzed using a Chi-square test to assess the association between age groups and bacterial occurrence.

Other observations made also include the age wise distribution of the identified bacteria from the blood sample which gave a clear picture as give in figure 2. It could be seen that the *S.typhi* was found much more prominent in the samples drawn from NICU and neo-natal care units which includes children of 0-10 years. However, the in case of *E. coli* which was found in much more number of samples from the elderly population as we have rated from 40yrs and above. This could be concluded in the terms that the children showing *S.typhi* infestation are could also have typhoid as the primary reason for admission which is accountable to the lower age and lower immunity of the children making them prone to *S.typhi.* On the other hand, the *E.coli* is mainly a water and food borne pathogen and its infestation arise in the form of infection in stomach which could be related to the fact that it was found to be prominent in the elderly age group people.

The antibiotic resistance could be seen in figure 3 where it could be observed from the anti-biotic susceptibility test that the resistance was found in the sample showing *E.coli* and *Klebsiella pneumonia.* Where the *Klebsiella pneumonia* was found to show resistance against the carbapenem.

Discussion

Typically, bacteraemia causes bloodstream infections that develop into sepsis; these infections can start in the skin, urinary tract, lungs, or gastrointestinal tract. Severe infection, or sepsis, can swiftly lead to organ failure, tissue damage, and death if not treated [16]. Persistent bacteraemia can be caused by a variety of infectious diseases, including typhoid fever, brucellosis, and bacterial meningitis. Infections that cause persistent bacteraemia, if left untreated, can be fatal [17]. Bacteria of the gram-negative *Enterobacteriaceae* family are the most common cause of infections contracted in both healthcare settings and the general public. An effective weapon in the battle against harmful bacteria and other infections is the carbapenem family of beta lactam antibiotics [18, 19]. A sad reality is that some bacteria become resistant to antibiotics over time. Overtreatment has also been linked to increased mortality rates in certain patients with infections. The CLSI-approved Vitek 2 compact system was utilized to detect drug-resistant bacteria. To reduce mortality from bloodstream infections caused by Carbapenem-resistant Enterobacteriaceae strains, a comprehensive assessment of the appropriateness of antibiotics and the severity of infections is necessary, along with a focus on the specific bacteria involved [20]. Our goal in conducting this study is to determine which antibiotics are most effective against Carbapenem-resistant Enterobacteriaceae and which age groups are most affected by these infections. The majority of blood-borne infections in people of all ages are caused by the carbapenem-resistant Entero-bacteriaceae family, which will be excluded from this discussion. Combination therapy was used to evaluate the synergistic effects of different antibiotics in order to control blood stream infections and sepsis. The worldwide healthcare systems are under a great deal of stress due to antibiotic resistance. Predictive statistical models (Antimicrobial Resistance, 2022) estimate that 1.27 million deaths in 2019 were directly caused by bacterial antibiotic resistance, out of an estimated 4.95 million deaths associated with bacterial resistance [21]. According to Wozniak et al. (2019), the economic burden is increased by €3,200 for every third-generation cephalosporin-resistant Enterobacter bloodstream infection, and by an additional €9473 for each broad-spectrum β-lactamase-resistant

Enterobacteriaceae bloodstream infection [22]. In addition, resistance rates are greater in low-income nations compared to high-income ones.

From the study is was observed that the *E.coli* infection was prominent in the elderly patients where the *S. Typhi* infection was prominent in the children's. Often referred to as "commensal," "intestinal pathogenic," or "extraintestinal pathogenic," Escherichia coli is both a pathogen and an organism that naturally occurs in the mammalian intestine. Diarrhoea is typically caused by intestinal pathogenic isolates, which infect and damage the mucosa lining the intestines and release toxins. Toxins, adhesins, polysaccharide capsules, siderophores, and invasins are produced by extraintestinal pathogenic isolates (ExPEC), which allow them to evade host defences and invade host tissues, causing urinary tract infections (UTIs) and bloodstream infections (BSIs) [23]. The majority of E. coli infections in both humans and livestock can be attributed to five main lineages, according to molecular research. The food animal reservoir might have played a role in the observed changes in human infection epidemiology, according to matches between clinical isolates and isolates from food animals [24,25]. The study's findings indicate a significant epidemiological trend where E. coli infections are more prevalent among elderly patients, while S. Typhi infections are notably higher in children. This age-related distribution raises important questions about the underlying mechanisms that contribute to these patterns.

E. coli is a highly diverse bacterium, existing in various pathogenic forms, including commensal strains that are part of the normal gut flora and pathogenic strains that can cause serious infections. The intestinal pathogenic variants are often responsible for diarrheal diseases, particularly in children and immunocompromised individuals. In contrast, extraintestinal pathogenic E. coli (ExPEC) strains are known to cause urinary tract infections (UTIs) and bloodstream infections (BSIs).

On the other hand, *Salmonella enterica serovars Typhi* and *Paratyphi* A, B, and C are Gram-negative bacteria that can cause enteric fever, a systemic infection which are reported in our study to occurrence predominately in 0-10 years of children from NICU samples. There is a high mortality rate associated with the disease, which is estimated to impact around 11–21 million people worldwide every year [26]. Enteric fever is responsible for around 200,000 fatalities per year, according to recent statistics. Asia bears the brunt of enteric fever; the continent accounts for 93% of all reported cases worldwide. Among the regions, Southeast Asia has the third-highest incidence, with around 110 cases per 100,000 people. Pakistan had an estimated 413/100,000 cases of enteric fever in children ages 2-4 and 573/100,000 cases in children ages 5-15 [27]. The emergence of multi-drug resistant *Salmonella Typhi* (MDR *S.Typhi*) is a consequence of the long-term development of antibiotic resistance in *Salmonella Typhi*. The first-line antibiotics ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole have been ineffective against these strains. Nevertheless, third-generation cephalosporins are ineffective against them [28].

A major issue in public health is the emergence of drug-resistant microorganisms. Resistance to several different types of cytotoxic chemicals, many of which are anticancer agents, is the most prominent trait of this complicated phenotype. A major concern to public health around the world this century, multidrug resistance may have ties to antimicrobial medications. Treatment failures and the associated rise in healthcare expenditures have contributed to an increase in mortality and morbidity caused by this phenomenon. Bacteria that are harmful to humans, farm animals, and even fish in aquaculture have evolved to be resistant to a wide range of antibiotics [29].

Conclusion

Due to a lack of awareness, individuals experiencing symptoms of bacteraemia may not seek treatment at a physician's clinic. Bacterial infections are becoming increasingly lethal as their rate of spread increases over extended periods of time. In rare cases, treating an infection that has persisted for a long time might lead to organ failure. The (bact alert 3d) blood culture system is prone to false positives due to inaccurate sample collection, which in turn affects the accuracy of the results. We can thank the colorimetric test for this. Avoiding the needless labour of cultivating each blood sample on blood, MacConkey, and chocolate agar is made possible by the Bact alert 3D system. It operates on the principle of a calorimetric assay and sounds an alarm when the blood culture bottle within comes back positive. The membrane of the blood culture bottle underwent a change whenever carbon dioxide was produced as a result of bacterial metabolism. In contrast to Vitek 2 compact, the Kirby Bauer method is unable to provide MIC information. To prevent contamination, always disinfect the mouth of the blood culture bottle before inserting the needle. This cutting-edge method of determining the minimum bactericidal concentration (MBC) for a given microbe was unavailable many years ago. The minimum effective concentration (MBC) of an antibiotic is the concentration at which a given microbe will be killed. This is provided by the CLSI-based Vitek 2 compact, as opposed to more antiquated methods such as the Kirby Bauer method, which do not provide MBC. Our study was supported by these methods, which allowed us to conclude that the patient did not have a primary infestation of any kind of bacteria that were screened. It is important to

understand and screen the bacteria from blood samples because the distribution of bacterial occurrence could be observed in a different pattern among the age groups. Inappropriate empirical antibiotic treatment poses risks; patients without resistant organisms who develop community-onset sepsis are more likely to receive broad-spectrum antibiotics, which can adversely affect their prognosis. Broad-spectrum antibiotics negatively impact the health of infected individuals. By conducting rapid and accurate blood pathogen analyses, medical professionals can better assist patients in need and ensure that future generations can withstand multidrug-resistant infections. The patterns observed in this study emphasize the importance of targeted interventions for different age groups and the need for ongoing research into the epidemiology of bacterial infections. By understanding the factors contributing to the prevalence of *E. coli* and *S. Typhi* infections, public health officials can better implement prevention strategies, improve treatment protocols, and ultimately reduce the burden of these infections on vulnerable populations.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

The ethical permission was obtained from the Institutional Ethics Committee, JNU College and Hospital, Faculty of Medicine, Aligarh Muslim University, Aligarh, India (Ref. No. IECJNMC/1258).

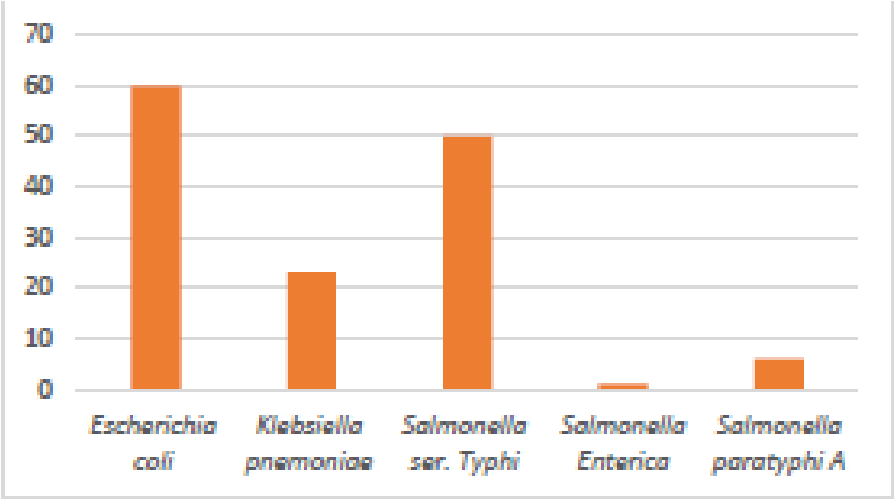

Fig. 1. Occurrence of microbial infection in the examined samples from patients.

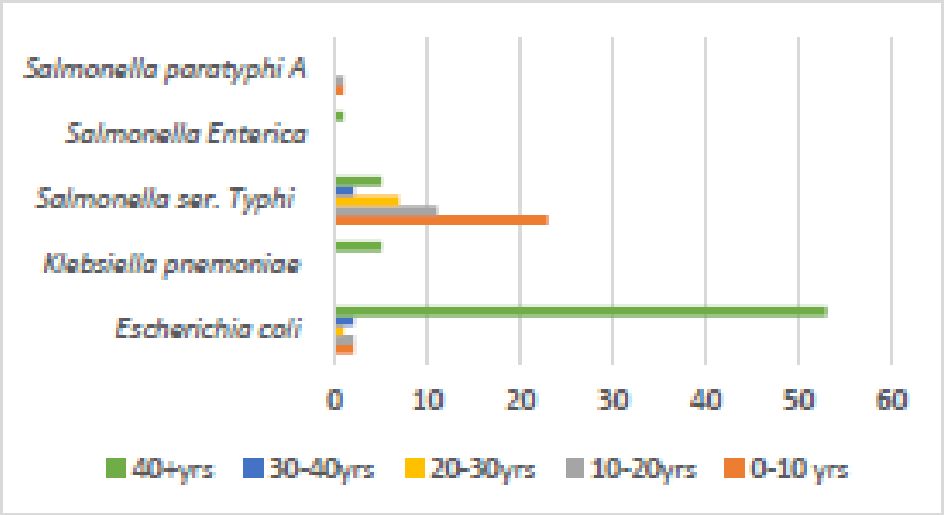

Fig. 2. Age-wise distribution of occurrence of microbial infection in the examined samples.

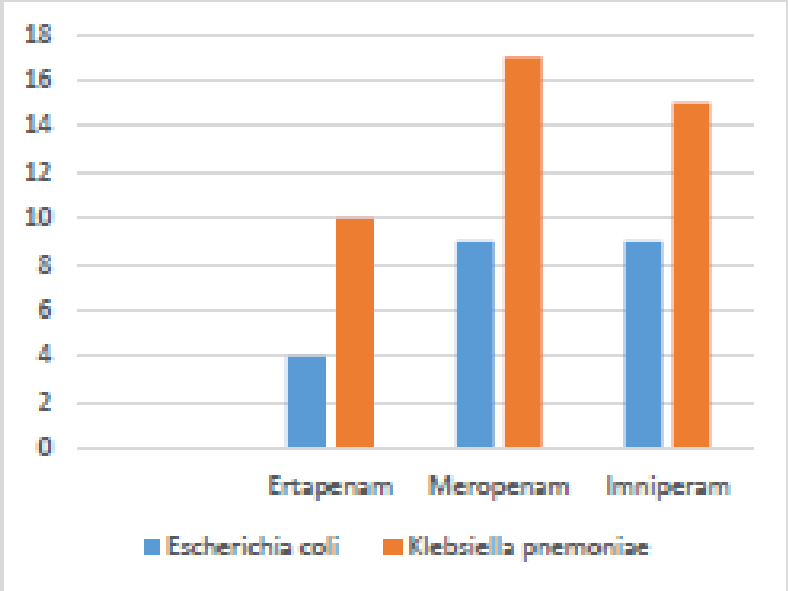

Fig. 3 : P**resents the prevalence of carbapenem-resistant bacteria as a bar graph, with the x-axis representing different bacterial species and the y-axis indicating the percentage of resistant isolates. Each bar represents the percentage of isolates that showed resistance to at least one carbapenem antibiotic.**

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