



What's More Alarming? Gram Negative or Gram Positive Bacteria in Sepsis

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ABSTRACT

Bacterial sepsis is one of the major causes for mortality and morbidity in the developing countries. Infections with multidrug-resistant organisms are also increasing in incidence. The objective of this review is to identify the leading cause of bacterial sepsis: Gram negative bacteria or Gram-positive bacteria. The study includes combination of cohort study and administrative data to identify the leading cause of bacterial sepsis. Among 100 cases sent for lab investigation, 70 blood cultures were positive for sepsis and showed growth on culture plate. And the result showed a great variation in different decades. In early 1980s, gram positive bacteria were the leading cause of sepsis (40cases) while just 20 cases showed the presence of gram-negative bacteria causing sepsis. In 1960s, gram negative bacteria causing sepsis cases were found to be 50, while gram positive bacteria causing sepsis where just 10cases. Recently, it was seen that gram-positive bacteria causing sepsis cases where 40cases and gram-negative bacteria causing sepsis where just 30cases. In early 1980s the primary cause for causing sepsis were gram positive bacterias. After the introduction of antibiotics in early 1960s to 1980s it was seen that gram-negative bacteria were the leading cause for causing sepsis as the antibiotics were showing more activity against the gram positive bacteria. In contrast the current situation showed increase in gram positive bacteria causing sepsis due to antimicrobial resistance.

Keywords: Bacterial sepsis, gram positive bacteria, gram negative bacteria, antibiotics.

INTRODUCTION

Sepsis is one of the commonest causes of morbidity and mortality in India compared to the developed countries¹. Despite considerable efforts in the past century to improve therapy for sepsis, mortality rates remain unacceptably high. Microorganisms can induce the host to produce many constituents that can result to immune dysregulation, tissue damage and death. The micro-organism produced endotoxins which are important in causing gram negative infection, gram positive bacteria can also play a dominant role¹. Diseases severity partly determines the outcome. Development of organ dysfunction is due to the presence of sepsis. The risk of death from sepsis is as high as 30%, from severe sepsis as high as 50% and from septic shock as high as 80%². Large epidemiologic studies show Gram-positive organisms superceding Gram-negatives in the early- to mid-1980s as the most common cause of sepsis in the USA. According to the most recent estimates in sepsis, there are approximately 200,000 cases of Gram- sepsis each year, compared with approximately 150,000 cases of Gram negative sepsis.³

In 1992, a panel of experts from The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference⁴ was the latest in a series of on going attempts⁵⁻⁹ to provide a conceptual and practical framework in which to define the systemic inflammatory response to infection that often underlies sepsis. Sepsis was defined as the presence of infection in the setting of the systemic inflammatory response syndrome (SIRS),

whereas severe sepsis was defined as a life threatening condition that arises when the body's response to infection causes injury to its own tissues and organs.¹⁰ Common location for the primary infection includes the lungs, brain, urinary tract, skin, and abdominal organs.¹¹ Severe sepsis is sepsis causing poor organ function or insufficient blood flow. Sepsis is more common among males than females.^{11,12}

Incidence

Sepsis is not a reportable disease but it is possible to cause death due to sepsis, are attributed to be the complication of many disease when mortality rate statistics are taken. A 2010 study from Ahmedabad reported a clear trend in the emergence of gram positive bacteria in blood stream infections with Staphylococcus constituting up to 27.4% of all blood culture specimen isolates¹³. About 300000 cases of sepsis per year in united states, the estimated death by sepsis caused by gram negative organism ranges from 20-50 % of the total death. Data from our longitudinal study for the year 2000 found severe sepsis to occur at the rate of 81 cases per 100,000 people in the United States¹⁴. Finfer et al. found severe sepsis to occur at the rate of 77 cases per 100,000 people in Australia and New Zealand. Surveying patients within the first 24 hours of ICU admission, Padkin et al.¹⁵ reported 51 patients with severe sepsis per 100,000 people in the United Kingdom. In contrast¹⁶, Angus et al. reported 300 patients with severe sepsis per 100,000 in the United States population for the year 1995. The sepsis is more frequent in younger



individuals and the gram negative organism is more likely to cause it.¹⁷

Etiologic Agents in Sepsis

Site of origin	Etiologic agents	frequent precipitating events
Skin	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i>	Intravenous catheter
Respiratory tract	Out of hospital: <i>Streptococcus pneumoniae</i> <i>Streptococcus pyrogenes</i> In hospital: <i>Pseudomonas aeruginosa</i> , <i>Serratia</i> <i>Enterobacter</i> , <i>Acinetobacter</i>	Aspiration
Genitourinary tract, Bladder catheter,	<i>E.Coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Proteus sp.</i> , <i>Pseudomonas aeruginosa</i> .	ureteral obstruction, cystoscopy
Gastrointestinal tract, Biliary tract	<i>E.coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i>	Cholangitis, biliary stent
Bowel abscess	<i>E.coli</i> , <i>Klebsiella</i> <i>Enterobacter</i> , <i>Serratia</i> <i>Salmonella</i> , <i>Bacteroides</i>	Perforation
Reproductive system	<i>Streptococcus</i> , <i>E. coli</i> , <i>Bacteroides</i>	Postpartum, instrumentation

Bacterial Organisms

Infections are mainly caused by bacteria, but also by fungal or viral. Bacterial infections are mainly caused by gram positive and gram negative bacteria. Fungal sepsis accounts for approximately 5% of severe sepsis and septic shock cases, the most common cause of fungal sepsis infection is caused by candida species of yeast. Typically 50% of all sepsis cases leads to lung infection.¹⁸

Sepsis and septic shock have been produced by all species of aerobic and anaerobic bacteria. Microorganisms from many classifications have the capability of establishing sepsis and septic shock¹⁹. These syndromes have been associated with infections caused by viruses (for example, dengue fever), by rickettsia (for example, Rocky Mountain spotted fever), by fungi, including *Candida* species and *Histoplasma capsulatum*, and by bacteria. Perhaps because bacteria are the most common microorganisms associated with sepsis and septic shock, they have been

best studied. Gram negative aerobic bacillary organisms particularly *E. coli*, the Enterobacteriaceae (like *Klebsiella*, *Serratia*) and the Pseudomonads have increased in frequency not only as causes of serious community acquired infections but also as causes of serious hospital-acquired infections throughout the 1960's, 1970's, 1980's, and 1990's²⁰.

Gram-positive bacteria	Gram-negative bacteria
<i>Streptococcus species</i>	<i>Proteus mirabilis</i>
<i>Staphylococcus species</i>	<i>Klebsiella pneumoniae</i>
<i>Enterococcus faecalis</i>	<i>Enterobacter aerogenes</i>
<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
	<i>Pseudomonas aerogenosa</i>
	<i>Citrobacter species</i>
	<i>Klebsiella oxytoca</i>
	<i>Citrobacter freundii</i>
	<i>Salmonella paratyphi</i>

Gram Positive Bacteria

Gram-positive bacteria are bacteria classified by the colour they retain in the staining method. Hans Christian Gram developed the staining method in 1884. The staining method uses crystal violet dye which is retained by the thick peptidoglycan cell wall found in gram-positive organisms.

Gram positive bacteria were predominant cause of sepsis before the introduction of antibiotics in the 1950s. After the introduction of antibiotic gram negative bacteria became the predominant causes of sepsis from 1960s to 1980s²¹. After the 1980s most common staphylococci are thought to cause more than 50% of case of sepsis. Gram positive pathogens which include streptococcus pyrogenes, staphylococcus aureus, streptococcus pneumonia and enterococcus produce super antigens. These cause septic shock but in a different way. These peculiar antigens are the strongest known activators of immune cells called T lymphocytes binding up to 20% of these cells, bypassing normal immune mechanism. The resulting flood of cytokines into the patient's system results in lethal shock. Despite their thicker peptidoglycan layer, gram-positive bacteria are more receptive to certain cell wall targeting antibiotics than gram-negative bacteria, due to the absence of the outer membrane.

In fact, some of the original studies of sepsis bore out that Gram-positive bacteria were among the most common causes of sepsis²².

In 2019, Atul P. Kulkarni et al, Current Perspectives on Treatment of Gram-Positive Infections in India proposed that the emerging antimicrobial resistance leading to gram-positive infections (GPIs) is one of the major public health threats worldwide. GPIs caused by multidrug resistant bacteria can result in increased morbidity and mortality rates along with escalated treatment cost.²³



In the review of Neil Woodford, David M. Livermore²⁴ about infections caused by Gram-positive bacteria, states that Infections caused by multidrug-resistant Gram-positive bacteria represent a major public health burden, not just in terms of morbidity and mortality, but also in terms of increased expenditure on patient management and implementation of infection control measures.

In a study from the USA performed in the year 2000 showed that Gram-positive bacteria accounted for 52.1 % of hospital admissions with sepsis, compared to 37.6 % for Gram-negative organisms²⁵. Moreover, whereas mortality related to Gram-negative organisms has decreased that due to Gram-positive infections remains the same and the overall mortality resulting from Gram-positive septicemia is higher than that from Gram-negative bacteria²¹.

Gram Negative Bacteria

Gram-negative bacteria are bacteria that do not retain the crystal violet stain used in the gram-staining method of bacterial differentiation²⁶.—Originally sepsis was described, and strongly considered to be, a disease specifically related to Gram-negative bacteria²⁴. This is because sepsis was considered to be a response to endotoxin – a molecule that was thought to be relatively specific for Gram-negative bacteria. They are characterized by their cell envelopes, which are composed of a thin peptidoglycan cell wall sandwiched between an inner cytoplasmic cell membrane and a bacterial outer membrane. The gram negative pathogens which include E-coli, Klebsiella pneumonia, Enterobacter and Pseudomonas aerogenosa. Their cell walls contain toxic chemicals called endotoxins, chemically composed of fats and carbohydrates called lipopolysaccharides [LSP]. When these cells are dying they release LSP which activate a type of immune cell called a macrophages this stimulate the release of chemical that widen blood vessels this results in over whelming inflammation and septic shock. Several classes of antibiotics have been designed to target gram-negative bacteria, including aminopenicillins, ureidopenicillins, cephalosporins, beta-lactam-betalactamase combinations (e.g. piperacillin-tazobactam), Folate antagonists, quinolones, and carbapenems. Many of these antibiotics also cover gram positive organisms. The drugs that specifically target gram negative organisms include aminoglycosides, monobactams (aztreonam) and Ciprofloxacin²⁷.

According to the study of “Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia” by Ryuzo Abe, Shigeto Oda, Tomohito Sadahiro, Masataka Nakamura, Yo Hirayama, Yoshihisa Tateishi, Koichiro Shinozaki, Hiroyuki Hirasawa²⁸ concludes that The incidence of Gram-negative bacteria and CRP and IL-6 blood level were significantly higher in the septic shock group than in the sepsis and severe sepsis groups. Furthermore, CRP and IL-6 blood level measured concomitantly with sampling for blood culture were significantly higher in Gram-negative bacteremia than in Gram-positive bacteremia.

A clinical microbiological review on Jan.1993 by ROGER C. BONE⁹ on the topic “Gram-Negative Sepsis: a Dilemma of Modern Medicine” clearly states that Gram-negative sepsis remains a significant cause of morbidity and mortality in spite of the on going development of new antimicrobial agents. This may be because antimicrobial therapy fails to address the underlying pathogenetic mechanism involved in the systemic inflammatory response. It is the triggering of mediators by bacterial endotoxin that produces the symptoms of gram-negative sepsis.

A study done by Hardik V Vaniya, Nirav M Patel, Jitendra M Agrawal, Hiren R Trivedi, Jatin V Dhanani, Jayesh D Balat based on the topic “Antimicrobial culture sensitivity pattern in neonatal sepsis in a tertiary-care hospital” was mainly focused on the spectrum of bacteria that cause neonatal sepsis and concluded that Gram-negative organisms comprised the majority of the neonatal infections, with Klebsiella being the most prevalent.²⁹

In a 2017 study by Poonam Dalal et al, A total of 28927 neonates 81.18% cases of sepsis was caused by gram negative bacteria whereas 18.82% cases were with gram positive microorganism.³⁰ Similarly studies conducted in 2013 by Bhat et al. gram negative organism causes most of the sepsis cases.³¹ And also by Shrestha et al. also stated that 60.64% of gram negative bacteria are the source of infection for sepsis.³²

CONCLUSION

Our understanding regarding the topic specifies that epidemiology of sepsis has increased dramatically since the development of an expert researches, nearly 15 years ago. Information were obtained from the combination of cohort studies and administrative data have permitted a better understanding of factors that influence the risk of disease and subsequent, relevant clinical outcomes. In early 1980s the primary cause for causing sepsis was gram positive bacteria. After the introduction of antibiotics in early 1960s to 1980s it was seen that gram negative bacteria were the leading cause for causing sepsis as the antibiotics were showing more activity against the gram positive bacteria. In contrast the current situation showed increase in gram positive bacteria causing sepsis due to antimicrobial resistance.

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