

Bloodstream Infection

¹Ketki Halnor, ²Shubham Lahane, ³Mahendra Khandare, ⁴Anjali Mali,
⁵Dr.Gajanan Sanap

¹Student, ²Student, ³Assistant Professor, ⁴Assistant Professor, ⁵Principal
^{1,2,3,4,5}Department of Pharmacy

^{1,2,3,4,5}Late Bhagirathi Yashwantrao College of Pharmacy, Pathri, Chatrapati Sambhajnagar, Maharashtra,
India, 431001

Submitted: 20-03-2023

Accepted: 30-03-2023

ABSTRACT :-

Bloodstream infections, also known as bacteremia, are a serious and potentially life-threatening medical condition. It occurs when bacteria, viruses, fungi, or other microorganisms enter the bloodstream and cause an infection. This can be a result of a medical procedure, such as an IV catheter, a surgical wound, or a weakened immune system due to an underlying medical condition like diabetes, AIDS, or cancer. It is important to note that some people are more likely to develop a bloodstream infection than others. Those with weakened immune systems due to cancer, HIV, or other medical conditions are particularly prone to developing bacteremia. It is essential to take the necessary steps to prevent a bloodstream infection. This includes washing your hands and any surfaces that come into contact with your body fluids, wearing clean clothing, and avoiding contact with people who are known to have infectious diseases. If you develop any of the symptoms associated with bacteremia, it is important to seek medical attention immediately.

Keywords :- Bloodstream Infection, Iv Catheter, Bacteria,

I. INTRODUCTION:-

Definition:-

Bloodstream infection are infectious disease defined by the presence of viable bacterial or fungal micro-organisms in the bloodstream that elicit or have elicited an inflammatory response characterized by the alteration of clinical laboratory. [1]

History:-

It has been known for more than a century that bacteraemia or the presence of bacteria in the bloodstream, exists. Two cases of bacteraemia in children with streptococcal illness who also had bloody diarrhoea were reported by Libman in 1897.[2] He released a study of over 700 blood

cultures with instructions on how to conduct them nine years later. Nine years later, he released a research series with instructions on how to conduct more than 700 blood cultures.[3] Since then, conventional procedures for obtaining blood have helped to advance the identification of bloodstream infections. The use of automated technologies, enhanced culture conditions, and sample analysis to identify bacterial or fungal growth. The importance of blood cultures is crucial. Blood cultures are the gold standard for identifying bloodstream infections in patients with fever in microbiological laboratories. The future development of bloodstream infection detection techniques will concentrate on enhancing sensitivity, accelerating diagnosis, and minimising drug inhibitory effects. A quicker detection of bloodstream infections enables the administration of the proper antibiotic therapy early, which lowers morbidity and death. The best approaches for detecting bloodstream infections have been proposed during the past few decades; those based on molecular detection, such as fluorescent hybridization probes and PCR, appear to be the most promising. The development of molecular methods ushers in a new age in the detection of bacteraemia, necessitating a complete re-evaluation of existing theories and deeply held ideas about how and when the more recent molecular methods might make a therapeutic impact.

The following factors can lead to the start of BSI:

- Immunosuppression
- Broad spectrum antimicrobial medicines can suppress the natural flora, which promotes the growth of bacterial strains that are resistant to them.
- Major surgeries or invasive treatments that give microorganisms access to the blood
- Prolongation of sick patients' lives.

Bloodstream Infection Types:

Bloodstream infections can be divided into two main groups:

1. Intravascular bloodstream infection
2. Extravascular bloodstream infection

1. Intravascular Bloodstream Infection

The following are examples of intravascular infections that start within the circulatory system:

- Bacterial endocarditis
- Aneurysm with fungi
- CRBSI (catheter-related blood stream infection).

These infections, which are present in the vascular system, cause ongoing bacteremia, which results in dangerous and potentially fatal situations.

A. Bacterial endocarditis:-

It is an endocardial infection that is defined by the presence of “vegetation” made up of a mass of platelets, fibrin, and microcolonies of bacteria, and sparse amounts of inflammatory cells.

The mural endocardium, low-pressure side of a ventricular septal defect, and heart valves are where vegetation is most frequently found.

Endocarditis can be categorised according to:

- Onset: subacute (slow evolution, metastasizes slowly)
- Acute (fast destroys the heart structures, spreads to extracardiac site, rapidly deadly).
- The affected valve type can be either a natural or artificial valve.
- It may be related to intravenous drug abuse.

Treatment :- Vancomycin and gentamicin/ceftriaxone are the main components of empirical treatment. If prosthetic valve endocarditis is thought to be present, rifampin may be added to the treatment plan.

B . CRBSI (Catheter-Related Bloodstream Infection)

Patients in ICUs who are critically ill are frequently given central lines, which facilitates the administration of medication and parenteral nutrition. Mishandling of central lines during insertion or daily maintenance might cause an infection that results in the development of CRBSI.

The diagnosis of catheter-related blood stream infection (CRBSI) :

Catheter Criteria:- existing central line

Clinical Standards:- Sepsis symptoms and signs include fever, hypotension, and tachypnea.

Cultural Standards:- (Time difference to positive)

The same pathogen must be detected by culture in both central line and peripheral line blood specimens, with the central line bottle flagging positive at least two hours or more earlier than the peripheral line bottle.

2. Extravascular Bloodstream Infection:-

The majority of clinically important bacteremia cases are extravascular in nature. The organisms proliferate at the primary site, such as the lungs, and are evacuated by the lymphatic system before entering the bloodstream. The germs are either eliminated by the reticuloendothelial system's cells or they spread out more and result in septicemia. A point of entry The genitourinary tract (25%), respiratory tract (20%), abscesses (10%), surgical site wound infections (5%), and biliary tract (%) are the most frequent ports of entry for bacteremia. Up to 25% of the time, the portal of entry is still unknown.

Extravascular Bloodstream Infection (BSI)-Causing Bacteria And Their Typical Origins:-

H. influenzae type B – Meninges, epiglottitis, lungs

Pneumococcus:- Meninges, lungs

Brucella:- Reticuloendothelial system[5]

Pathophysiology Of Bloodstream Infection:-

Pathophysiology of Sepsis:

The symptoms are extremely variable and include fever, chills, hypotension, hypothermia (especially in the elderly), diaphoresis, anxiety, change in mental status, tachypnea, tachycardia, hyperventilation, reduced vascular tone, and the potential for organ dysfunction due to the widespread immune response[6]. When the human immune system is confronted with infectious agents in the bloodstream. Thrombocytopenia, toxic neutrophil granulations, disseminated intravascular coagulation, and neutrophilic leukocytosis are examples of hematologic findings. Other metabolic signs include cholestatic jaundice, elevated transaminase levels, or hypoglycemia. Renal signs like acute tubular necrosis, oliguria, or anuria. Gastrointestinal signs like upper gastrointestinal bleeding.

1. Sepsis remains one of the world's leading causes of death despite modern advancements [7]. If neglected, sepsis can progress to septic shock (sepsis complicated by hyperlactatemia or hypotension that is resistant to fluid resuscitation), which can lead to organ failure and death [8]. The term “sepsis” has numerous accepted definitions. The diagnosis of all conditions is based primarily

on the clinical recognition of symptoms, which is then supported by laboratory testing.[9]

2. Bacteremia is the term used to describe the presence of live bacteria in the blood. The syndrome of systemic inflammatory response is a systemic inflammatory reaction to physical injury (for instance, due to an infection, burns, or trauma) that calls for some of the following circumstances:

- A. A fever or cold temperature
- B. Tachycardia
- C. Tachypnea.
- D. Leukopenia or leukocytosis
- E. An increase in C-reactive protein
- F. High plasma procalcitonin levels
- G. A change in mental state
- H. Profound edema or a favourable fluid balance
- I. Hyperglycemia
- J. Arterial hypotension,
- K. Organ malfunction
- L. Hyperlactatemia
- M. Diminished or mottled capillary filling

When evaluating patients who present with inflammatory symptoms, nonspecific causes of inflammation must be taken into account because they can lead to systemic inflammatory response syndrome.

3. Sepsis is defined as the presence of an infection (whether probable or confirmed) along with systemic symptoms of the infection. Organ dysfunction, such as low blood pressure, decreased urine output, intestinal paralysis, reduced circulation, increased creatinine, decreased blood oxygen levels, elevated lactate and elevated bilirubin, abnormal coagulation, or metabolic acidosis, are all symptoms of sepsis.

4. Despite receiving adequate intravascular fluid resuscitation, the patient experiences refractory arterial hypotension or hypoperfusion. Symptoms of hypoperfusion include lactic acidosis, oliguria, and changing.

Causes of Bloodstream Infection:-

The bloodstream can be contaminated by bacteria in many different ways. However, there are distinct causes or routes of entrance into the bloodstream that result in bacteremia for each main type of bacteria (gram negative, gram positive, or anaerobic). Healthcare-associated (acquired while receiving care in a healthcare facility) or community-acquired causes of bacteremia can also be distinguished (acquired outside of a health facility, often prior to hospitalization)

Gram-positive bacteremia:-

Bacteremia is increasingly being caused by gram-positive bacteria.[10] The three most significant and prevalent gram-positive bacterial species that can enter the bloodstream are staphylococcus, streptococcus, and enterococcus. These bacteria are typically found in the gastrointestinal tract or on the skin. In North and South America, *Staphylococcus aureus* is the most frequent cause of healthcare-associated bacteremia and a significant contributor to community-acquired bacteremia. [11] The most significant causes of community-acquired staph aureus bacteremia are skin ulcers or wounds, respiratory tract infections, and IV medication use. The most frequent causes of staph aureus bacteremia in healthcare facilities include intravenous catheters, urinary tract catheters, and surgical operations.

Staphylococcus aureus species come in a wide variety and can all result in bacteremia.[12] Infections of the skin and soft tissues are the usual sources of bacteremia caused by Group A streptococcus (GAS).[13] Neonatal bacteremia is frequently caused by Group B streptococcus and occurs shortly after birth.[14] Species of Viridans streptococci are part of the typical oral bacterial ecology. Viridans strep can result in a brief episode of bacteremia following a meal, brushing, or flossing.[14]

Following dental treatments or in chemotherapy patients, bacteremia can become more serious.[14] and finally, bacteremia in people with colon cancer is frequently brought on by *Streptococcus bovis*[15]. A significant contributor to bacteremia linked to healthcare is enterococci. These bacteria are frequently found in the female vaginal tract and gastrointestinal system. Risk factors for developing bacteremia from enterococcal species include intravenous catheters and surgical wounds[16]. Patients who have previously experienced prolonged hospital stays or frequent antibiotic use may develop bacteremia from resistant enterococcal species.[17]

Gram-negative bacteremia:-

About 24% of all cases of healthcare-associated bacteremia and 45% of all cases of community-acquired bacteremia are caused by gram negative bacterial species [18,19] Gram negative bacteria typically enter the bloodstream as a result of illnesses in the lungs, genitourinary system, digestive system, or hepatobiliary system. Gram-negative bacteremia is more common and is linked to increased morbidity and death in elderly

persons (65 years of age or older)[20]. 75% of cases of community-acquired bacteremia are caused by *E. coli*, making it the most frequent cause[21]. Urinary tract infections are frequently the cause of *E. coli* bacteremia. *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Proteus mirabilis* are additional microorganisms that can result in community-acquired bacteremia[22]. Despite the fact that in the industrialised world, gastroenteritis is typically the only symptom of a salmonella infection.

Gram negative bacteria are a significant contributor to cases of bacteremia in the intensive care unit (ICU) that are related to healthcare[23]. Gram negative bacteria can enter the bloodstream via catheters in the veins, arteries, or urinary tract[13]. Gram negative bacteremia can also result after operations on the digestive, hepatobiliary, or genitourinary systems[13]. The most significant contributors to gram negative bacteremia in the ICU are *Pseudomonas* and *Enterobacter* species.[23]

Risk Factors For Bacteremia:-

The possibility of getting bacteremia from any kind of bacterium is increased by a number of risk factors. [10],[24] These consist of:

- HIV
- Mellitus Diabetes
- Long-term hemodialysis
- Transplant of a solid organ
- Transfer of stem cells
- Administration of glucocorticoids
- Liver problem
- Asplenia[25]

Mechanism Of Bloodstream Infection:-

Bacteremia can move through the bloodstream to far-flung areas of the body and infect those areas (hematogenous spread). The pathogenesis of some infections of the heart (endocarditis), the structures surrounding the brain (meningitis), and the spine (Pott's disease) includes the hematogenous spread of germs. Numerous bone infections are brought on by the hematogenous spread of germs (osteomyelitis)[26].

Artificial heart valves and other prosthetic cardiac implants are particularly susceptible to infection from bacteremia.[27] Prior to the extensive use of immunizations, occult bacteremia was a crucial factor to take into account in feverish infants who otherwise seemed healthy[28]

II. MATERIALS AND METHODS:-

Diagnosis Of Bloodstream Infection:-

The most frequent method for diagnosing bacteremia is blood culture, which involves allowing a sample of blood taken from a vein using a needle to incubate in a medium that supports bacterial growth[29] If there are bacteria in the bloodstream when the sample is taken, they will proliferate and can be seen as a result. Any bacteria that unintentionally enter the culture medium will grow there as well. For instance, if the skin is not well cleaned before to needle insertion, the blood sample may get contaminated with common skin-surface bacteria. [30] Blood cultures must therefore be drawn carefully and according to a sterile procedure

To diagnose bacteremia, two blood cultures taken from different parts of the body are frequently enough. The presence of the same type of bacteria in two out of two cultures typically indicates the presence of a true bacteremia, especially if the organism is not a frequent contaminant. Blood cultures should typically be obtained again after one out of every two positive results to determine whether a contaminant or true bacteremia is present. Before drawing blood, the patient's skin is routinely cleansed with an alcohol-based solution to avoid contamination. Repeat blood cultures may be done periodically to check for persistent bacteremia as opposed to transient bacteremia[30]

A detailed patient history should be obtained before taking blood cultures, paying special attention to any recent invasive operations, a condition of immunosuppression, the presence of recent fevers and chills, and any other focused symptoms of infection, such as those in the skin or soft tissue. All patients with *Staphylococcus aureus* bacteremia should get a cardiac ultrasound to rule out infectious endocarditis.[31]

Treatment Of Bloodstream Infection:-

Antibiotics are virtually usually necessary for the treatment of blood bacteria. This is due to the significant death rates associated with sepsis progression if antibiotics are postponed[23] Empiric antibiotic use should be the first step in treating bacteremia.[20] Any patient who exhibits bacteremia symptoms or has a positive blood culture should begin intravenous antibiotic therapy. The most likely source of illness and the distinctive species that commonly cause that infection dictate which antibiotic should be used. The severity of the patient's current symptoms, the patient's past usage

of antibiotics, and any antibiotic sensitivities are additional crucial factors to take into account[32]. Once the blood culture shows that a specific bacteria has been isolated, empiric antibiotics should be restricted, ideally to a single drug.[32]

Gram-Positive Bacteremia

Uncomplicated methicillin-resistant staph aureus (MRSA) bacteremia is advised to be treated with a 14-day intravenous vancomycin course, according to the Infectious [33]Disease Society of America (IDSA). Uncomplicated bacteremia is defined as having positive blood cultures for MRSA but lacking endocarditis symptoms, having no prostheses implanted, having negative blood cultures after 2-4 days of treatment, and exhibiting clinical improvement after 72 hours[33].For streptococcal and enterococcal infections, different antibiotics are preferred depending on the species. To better treat infections brought on by resistant organisms, it is crucial to examine the blood culture's data on antibiotic resistance patterns for each species.[10]

Gram-Negative Bacteremia

The causative organism plays a significant role in the management of gram-negative bacteremia. The most likely cause of the illness and the patient's prior exposure to healthcare facilities should serve as the basis for empiric antibiotic therapy[34] Particularly, a recent history of exposure to a medical environment may call for the use of antibiotics with extensive coverage for resistant organisms or pseudomonas aeruginosa coverage. Gram negative bacteremia is typically treated with extended generation cephalosporins like ceftriaxone or beta lactam/beta lactamase inhibitor medicines like piperacillin-tazobactam.[34]

Catheter-Associated Infection

The IDSA has issued instructions for catheter removal for intravenous catheter-related bacteremia connected with healthcare. In the event that bacteremia is brought on by any gram-negative bacteria, staph aureus, enterococci, or mycobacteria, short-term catheters (placed for less than 14 days), should be withdrawn. If a patient is showing signs or symptoms of sepsis, endocarditis, or if blood cultures stay positive for more than 72 hours, long-term catheters (>14 days) should be removed [35]

Drugs Used In Bloodstream Infections:-

1. Beta-lactam antibiotics: Ampicillin, Amoxicillin, Cefazolin, Ceftriaxone, Piperacillin-tazobactam
2. Fluoroquinolones: Ciprofloxacin, Levofloxacin, Moxifloxacin
3. Aminoglycosides: Gentamicin, Tobramycin, Amikacin
4. Macrolides: Azithromycin, Clarithromycin
5. Vancomycin
6. Metronidazole

III. RESULT AND DISCUSSION :-

In North and South America, Staphylococcus aureus is the most frequent cause of healthcare-associated bacteremia and a significant contributor to community-acquired bacteremia. The most significant causes of community-acquired staph aureus bacteremia are skin ulcers or wounds, respiratory tract infections, and IV medication use. Patients who have previously experienced prolonged hospital stays or frequent antibiotic use may develop bacteremia from resistant enterococcal species. About 24% of all cases of healthcare-associated bacteremia and 45% of all cases of community-acquired bacteremia are caused by gram negative bacterial species. To better treat infections brought on by resistant organisms, it is crucial to examine the blood culture's data on antibiotic resistance patterns for each species. The causative organism plays a significant role in the management of gram-negative bacteremia.

IV. CONCLUSION :-

Bloodstream infection remains a major challenge in healthcare, leading to increased morbidity, mortality and higher infections. Improved surveillance, early diagnosis and treatment, and better infection control measures are essential to reduce the burden of bloodstream infections in the healthcare setting. Furthermore, improved education and awareness of healthcare workers about the risk factors, signs and symptoms, and management of bloodstream infections is also necessary. Ultimately, the goal is to reduce the incidence of bloodstream infections and improve patient outcomes.

REFERENCES :-

- [1]. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871637/>
- [2]. Libman E. Weitere Mitteilungen über die Streptokokken-enteritis bei Säuglingen. Zentralbl Bakteriol 1897; XXII: 376.

- [3]. Libman E. On some experiences with blood-cultures in the study of bacterial infections. *Johns Hopkins Hosp Bull* 1906; 17: 215–28.
- [4]. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. 1988. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 16:128–140.
- [5]. <https://www.mrmed.in/health-library/haematology/blood-infections-types>
- [6]. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. 1995. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 273:117–123.
- [7]. Cawcutt KA, Peters SG. 2014. Severe sepsis and septic shock: clinical overview and update on management 1. *Mayo Clin Proc* 89:1572–1578.
- [8]. Angus DC, van der Poll T. 2013. Severe sepsis and septic shock. *N Engl J Med* 369:840–851.
- [9]. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. 2013. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 39:165–228.
- [10]. Cervera, Carlos; Almela, Manel; Martínez-Martínez, José A.; Moreno, Asunción; Miró, José M. (200901-01). "Risk factors and management of Gram-positive bacteraemia". *International Journal of Antimicrobial Agents*. 34 Suppl 4: S26–30. doi:10.1016/S0924-8579(09)70562-X. ISSN 18727913. PMID 19931813.
- [11]. Biedenbach, Douglas J.; Moet, Gary J.; Jones, Ronald N. (2004-09-01). "Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002)". *Diagnostic Microbiology and Infectious Disease*. 50 (1): 59–69. doi:10.1016/j.diagmicrobio.2004.05.003. ISSN 0732-8893. PMID 15380279.
- [12]. Lowy, Franklin D. (1998-08-20). "Staphylococcus aureus Infections". *New England Journal of Medicine*. 339 (8): 520–532. doi:10.1056/NEJM199808203390806. ISSN 0028-4793. PMID 9709046.
- [13]. Schwartz, Brian (2016). *Current Medical Diagnosis and Treatment 2017*. New York: McGraw Hill. pp. Chapter 33. ISBN 978-1-25-958511-1.
- [14]. Cohen-Paradosu, Ronit (2015). *Harrison's Principles of Internal Medicine 19th Edition*. New York: McGraw Hill. pp. Chapter 201. ISBN 978-0-07-180215-4.
- [15]. Mayer, Robert (2015). *Harrison's Principles of Internal Medicine 19th Edition*. New York: McGraw Hill. pp. Chapter 110. ISBN 978-0-07-180215-4.
- [16]. Arias, Cesar (2015). *Harrison's Principles of Internal Medicine 19th Edition*. New York: McGraw Hill. pp. Chapter 174. ISBN 978-0-07-180215-4.
- [17]. Kasper, Dennis (2015). *Harrison's Manual of Medicine*. New York: McGraw Hill. pp. Chapter 87. ISBN 978-0-07-182852-9.
- [18]. Gaynes, Robert; Edwards, Jonathan R.; National Nosocomial Infections Surveillance System (2005-09-15). "Overview of nosocomial infections caused by gram-negative bacilli". *Clinical Infectious Diseases*. 41 (6): 848–854. doi:10.1086/432803. ISSN 1537-6591. PMID 16107985.
- [19]. Diekema, D. J.; Beekmann, S. E.; Chapin, K. C.; Morel, K. A.; Munson, E.; Doern, G. V. (2003-08-01). "Epidemiology and outcome of nosocomial and community-onset bloodstream infection". *Journal of Clinical Microbiology*. 41 (8): 3655–3660. doi:10.1128/JCM.41.8.3655-3660.2003. ISSN 0095-1137. PMC 179863. PMID 12904371.
- [20]. High, Kevin (2017). *Geriatric Medicine and Gerontology 7th Edition*. New York: McGraw Hill. pp. Chapter 125. ISBN 978-0-07-183345-5.
- [21]. Luzzaro, F.; Viganò, E. F.; Fossati, D.; Grossi, A.; Sala, A.; Sturla, C.; Saudelli, M.; Toniolo, A.; AMCLI Lombardia Hospital Infectious Study Group (2002-12-01). "Prevalence and drug susceptibility of pathogens causing bloodstream infections in northern Italy: a two-year study in 16 hospitals". *European Journal of Clinical Microbiology & Infectious Diseases*. 21 (12): 849–855. doi:10.1007/s10096-002-0837-7. ISSN 0934-9723. PMID 12525919. S2CID 13043807.
- [22]. Deen, Jacqueline; von Seidlein, Lorenz; Andersen, Finn; Elle, Nelson; White, Nicholas J.; Lubell, Yoel (2012-06-01). "Community-acquired bacterial bloodstream infections in developing countries in south and southeast Asia: a systematic

- review". *The Lancet. Infectious Diseases*. 12 (6): 480–487. doi:10.1016/S1473-3099(12)70028-2. ISSN 1474-4457. PMID 22632186.
- [23]. Peleg, Anton Y.; Hooper, David C. (2010-05-13). "Hospital-Acquired Infections Due to Gram-Negative Bacteria". *The New England Journal of Medicine*. 362 (19): 1804–1813. doi:10.1056/NEJMra0904124. ISSN 0028-4793. PMC 3107499. PMID 20463340
- [24]. Graff, Larissa R.; Franklin, Kristal K.; Witt, Lana; Cohen, Neal; Jacobs, Richard A.; Tompkins, Lucy; Guglielmo, B. Joseph (2002-02-15). "Antimicrobial therapy of gram-negative bacteremia at two university-affiliated medical centers". *The American Journal of Medicine*. 112 (3): 204–211. doi:10.1016/s0002-9343(01)01092-0. ISSN 0002-9343. PMID 11893347.
- [25]. Brigden, M. L. (2001-02-01). "Detection, education and management of the asplenic or hyposplenic patient". *American Family Physician*. 63 (3): 499–506, 508. ISSN 0002-838X. PMID 11272299.
- [26]. Agarwal, Anil; Aggarwal, Aditya N. (2016-08-01). "Bone and Joint Infections in Children: Acute Hematogenous Osteomyelitis". *Indian Journal of Pediatrics*. 83 (8): 817–824. doi:10.1007/s12098-015-1806-3. ISSN 0973-7693. PMID 26096866. S2CID 1561868.
- [27]. Guay, David R. (2012-02-01). "Antimicrobial prophylaxis in noncardiac prosthetic device recipients". *Hospital Practice*. 40 (1): 44–74. doi:10.3810/hp.2012.02.947. ISSN 2154-8331. PMID 22406882. S2CID 10854052.
- [28]. "UpToDate". www.uptodate.com
- [29]. Coburn, Bryan; Morris, Andrew M.; Tomlinson, George; Detsky, Allan S. (2012-08-01). "Does This Adult Patient With Suspected Bacteremia Require Blood Cultures?". *JAMA*. 308 (5): 502–511. doi:10.1001/jama.2012.8262. ISSN 0098-7484. PMID 22851117.
- [30]. Hall, Keri K.; Lyman, Jason A. (2016-12-16). "Updated Review of Blood Culture Contamination". *Clinical Microbiology Reviews*. 19 (4): 788–802. doi:10.1128/CMR.00062-05. ISSN 0893-8512. PMC 1592696. PMID 17041144.
- [31]. Holland, TL; Arnold, C; Fowler VG, Jr (1 October 2014). "Clinical management of *Staphylococcus aureus* bacteremia: a review". *JAMA*. 312 (13): 1330–41. doi:10.1001/jama.2014.9743. PMC 4263314. PMID 25268440.
- [32]. Hooper, David (2016). *Harrison's Principles of Internal Medicine 19th Edition*. New York: McGraw Hill. pp. Chapter 170. ISBN 978-0-07-180215-4.
- [33]. Liu, Catherine; Bayer, Arnold; Cosgrove, Sara E.; Daum, Robert S.; Fridkin, Scott K.; Gorwitz, Rachel J.; Kaplan, Sheldon L.; Karchmer, Adolf W.; Levine, Donald P. (2011-02-01). "Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children". *Clinical Infectious Diseases*. 52 (3): e18–55. doi:10.1093/cid/ciq146. ISSN 1537-6591. PMID 21208910.
- [34]. Russo, Thomas (2016). *Harrison's Principles of Internal Medicine 19th Edition*. New York: McGraw Hill. pp. Chapter 186. ISBN 978-0-07-180215-4.
- [35]. Mermel, Leonard A.; Allon, Michael; Bouza, Emilio; Craven, Donald E.; Flynn, Patricia; O'Grady, Naomi P.; Raad, Issam I.; Rijnders, Bart J. A.; Sherertz, Robert J. (2009-07-01). "Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America". *Clinical Infectious Diseases*. 49 (1): 1–45. doi:10.1086/599376. ISSN 1537-6591. PMC 4039170. PMID 19489710.