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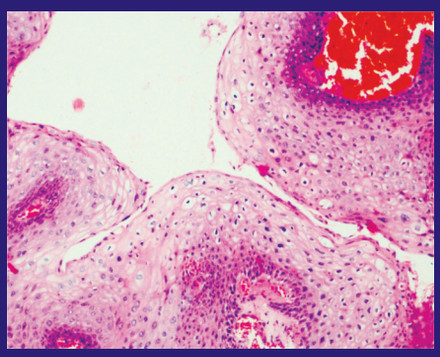

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Research Report

THE ANTI-TB DRUG SENSITIVITY OF *Mycobacterium tuberculosis* FROM CEREBROSPINAL FLUID AND BONE TISSUE BIOPSY SPECIMENS OF PATIENTS SUSPECTED TUBERCULOUS MENINGITIS AND SPINAL TB IN Dr SOETOMO HOSPITAL INDONESIA

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ABSTRACT

Tuberculous meningitis (TBM) is an infection of meningens which potentially life threatening with significant morbidity and mortality. Spinal TB has the same problem with TBM, infection in bone and joint, the delayed diagnosis worsens the prognosis. The rapid and accurate diagnosis plus promt adequate treatment is essential for the good outcome. The aim of this research is to study the first line drug sensitivity of Mycobacterium tuberculosis isolated from specimens of cerebrospinal fluid from suspected tuberculous meningitis patients and bone tissue biopsy from suspected spinal TB patients. The method of this research is TB Laboratory examination in Department of Clinical Microbiology – Dr. Soetomo General Hospital, Indonesia, using the gold standard liquid culture method MGIT 960 System (Becton Dickinson) and solid culture method with Lowenstein-Jensen medium. The specimens CSF from 50 TBM patients at January 2013 until May 2014. Positive isolate detection of Mycobacterium tuberculosis complex were 11 isolates (22%), which sensitivity 100% (11/11 isolates) to Rifampin (R), Pyrazinamide (Z), Ethambutol (E), and Streptomycin (S); one isolate resistant to Isoniazid, sensitivity to Isoniazid 90,90% (10/11); and received 21 specimens of bone tissue biopsy which positive 5 isolates (23%), all isolates sensitive 100% (5/5 isolates) to Rifampin and Pyrazinamide, and 1 isolates resistant to Isoniazid, Ethambutol, and Streptomycin, in which sensitivity 80% (4/5 isolates) to Isoniazid, Ethambutol, and Streptomycin. The conclusion of this research is positivity detection 22% of CSF specimens, and 23% of bone tissue biopsy were low. All isolates sensitive 100% to Rifampin and Pyrazinamide, and 80-90% sensitive to Isoniazid.

Key words: first line anti-TB drug sensitivity, Mycobacterium tuberculosis, tuberculous meningitis, spinal tuberculosis, cerebrospinal fluid

ABSTRAK

Meningitis tuberculosis (TBM) merupakan infeksi selaput otak/meningens, berpotensi mengancam kehidupan pasien dengan morbiditas dan mortalitas tinggi. Spinal TB juga memiliki masalah yang sama dengan TBM, yaitu infeksi pada jaringan tulang dan sendi serta kelambatan diagnosis yang memperburuk prognosis. Diagnosis akurat dan cepat, disertai segera pengobatan adekuat menentukan kesembuhan pasien. Tujuan penelitian ialah studi kepekaan obat anti-TB lini I di antara Mycobacterium tuberculosis complex isolat specimen cairan otak dari pasien diduga meningitis TB, dan biopsi jaringan tulang dari pasien diduga spinal TB. Metode penelitian ini ialah pemeriksaan laboratorium TB di Departemen Mikrobiologi Klinik/ RSUD Dr Soetomo, Indonesia, menggunakan metode gold standard metode kultur pada media cair MGIT 960 System (Becton Dickinson) dan metode kultur pada media padat Lowenstein-Jensen. Hasil penelitian ini ialah pada bulan januari 2014 sampai dengan mei 2014 diperoleh specimen cairan otak dari 50 pasien meningitis TB, terdeteksi 11 Mycobacterium tuberculosis complex (22%), sensitivitas 100% terhadap Rifampin (R), Pyrazinamide (Z), Ethambutol (E), dan Streptomycin (S) (11/ 11 isolat); satu isolat resisten terhadap Isoniazid, sensitivitas sebesar 90,90% (10/11) terhadap Isoniazid; pada 21 spesimen biopsi jaringan tulang ditemukan 5 isolat (23%), semua isolat 100% sensitif

Rifampin dan Pyrazinamide, 1 isolat resisten terhadap Isoniazid, Ethambutol, dan Streptomycin, dengan sensitivitas sebesar 80% (4/5 isolat). Kesimpulan dalam penelitian ini ialah sensitivitas deteksi 22% dari spesimen cairan otak, dan 23% biopsi jaringan tulang, rendah, semua isolat sensitif 100% terhadap Rifampin dan Pyraziamide, 80-90% sensitif Isoniazid.

Kata kunci: *obat anti-TB lini I, Mycobacterium tuberculosis, meningitis TB, spinal TB, cairan otak*

INTRODUCTION

Tuberculosis meningitis (TBM) is a common form of central nervous system infection in developing countries with high endemic TB. Delayed diagnosis and therapy are major factors in determining outcome, death or severe disabilities. Determining diagnosis of TBM based on the complementary standard examination of clinical manifestation, MRI/ cranial CT, cerebrospinal fluid (CSF) laboratory examination i.e. lymphocytes, glucose, protein, and microbes.[1]

The definitive diagnosis of TBM based on isolation and identification of *Mycobacterium tuberculosis* from cerebrospinal fluid (CSF). Isolation and identification of *Mycobacterium tuberculosis* based on the clinical microbiology examination using the gold standard method as follow: culture method and PCR.[1,2,3]

Developed early diagnosis of TBM such as PCR, GenXpert MTB/RIF, interferon-gamma release assay (IGRAs), tuberculostearic acid, and adenosine deaminase in CSF. Delayed diagnosis worsens the prognosis and increases morbidity. The microbiological diagnosis is crucial, despite surgical treatment always necessary anti-TB drugs (Merino *et al.,* 2012).[4]

METHOD

The 75 specimens or samples were CSF from suspected TBM and 21 bone tissue biopsy from suspected spinal TB patients received in TB laboratory of Department/ Instalation of Clinical Microbiology-Dr Soetomo General Hospital, Surabaya, Indonesia at January 2013 until Juny 2014.

Laboratory examination of clinical microbiology using the gold standard: liquid culture method MGIT 960 System (Becton Dickinson) and solid culture method with Lowenstein-Jensen medium; accurate specimens were centrifuged deposit of CSF or processed tissue to microbiologic examination.[5,6,7]

RESULT & DISCUSSION

In TB laboratory of Department of Clinical Microbiology Dr Soetomo Hospital received 75 specimens CSF at January 2013 until Juny 2014. Positive isolate detection of *Mycobacterium tuberculosis complex* were 11 isolates (11/75 = 14,67%), which sensitivity 100% (11/11 isolates) to Rifampin (R), Pyrazinamide (Pza), Ethambutol (E), and Streptomycin (S); one isolate resistant to Isoniazid. Sensitivity to Isoniazid 91% (10/11) (Table 1).

Table 1. Positivity detection & first line anti-TB drug sensitivity of *Mycobacterium tuberculosis complex* isolate from CSF specimens of the suspect TB meningitis patients in Dr. Soetomo Hospital Indonesia, at January 2013-Juny 2014

N	Specimen	Positive (%)	Sensitivity				
			R	I	Pza	E	S
75	Liquor/ CSF	11 (11/ 75= 14,67%)	11 (100%)	10 (91%)	11 (100%)	11 (100%)	11 (100%)

R = Rifampin, I = Isoniazid, E = Ethambutol, S = Streptomycin, Pza = Pyrazinamide

At January 2013 until March 2014, TB laboratory-Department Clinical Microbiology - Dr. Soetomo Hospital received 21 specimens of bone tissue biopsy which positive 5 isolates (5/ 21 = 23.80%), all isolates sensitive 100% (5/ 5 isolates) to Rifampin and Pyrazinamide (Pza), and 1 isolates resistant to Isoniazid, Ethambutol, and Streptomycin. One isolate resistant to Isoniazid, Ethambutol, and Streptomycin, in which sensitivity 80% (4/5 isolates) to Isoniazid, Ethambutol, and Streptomycin (Table 2).

Positivity detection in this study is very low 11/ 75 CSF specimens (14,67%) positive isolate *Mycobacterium tuberculosis complex,* and 5/21 bone tissue biopsy (23,80%) positive.

Many factors could influence the positivity detection of *Mycobacterium tuberculosis complex,* i.e. decided the appopriate criteria of clinical diagnosis for suspected TBM or for suspected Spinal TB; the accurate specimen for suspected TBM or for suspected Spinal TB related to paucy bacilli in locally tissue specimens; and specimen handling.

The sensitivity of *Mycobacterium tuberculosis complex* in this study revealed all isolates 11 from CSF and 5 from

Table 2. Positivity detection & first line anti-TB drug sensitivity of *Mycobacterium tuberculosis complex* isolate from bone tissue biopsy specimens of the patients suspected Spinal TB in Dr. Soetomo Hospital, Indonesia, at January 2013 - March 2014

N	Specimen	Positive (%)	Sensitivity				
			R	I	Pza	E	S
21	Bone tissue biopsy	5 (5/21=23, 80%)	5 (100%)	4 (80%)	5 (100%)	4 (80%)	4 (80%)

R = Rifampin, I = Isoniazid, E = Ethambutol, S = Streptomycin, Pza = Pyrazinamide

bone tissue biopsy 100% still sensitive to Rifampin and Pyrazinamide, and the other advantage were sensivity 80-91% to isoniazid of isolates from CSF or bone tissue biopsy; isolates from CSF 100% sensitiv Rifampin, Pyrazinamide, Ethambutol, and Streptomycin; isolates from bone tissue biopsy 80% still sensitive to Ethambutol and Streptomycin, otherwise the number of isolate samples were very small that could be not significant to reveal the conclusion on the sensitivity, need the valid research with multy centre study.

Accurate definitive diagnosis for TBM or spinal TB start with the essential step i.e. to determine the appropriate criteria standard for suspected clinically diagnosis, accurate specimen collection and handling, accurate standard method on laboratory examination for isolation and identification of etiologic *Mycobacterium tuberculosis.*

Accurate specimens for examination of Mycobacteria from suspected TBM patients: aseptic collection of 2–3 specimens of CSF with each volume 5–10 ml, because of paucy bacilli in CSF specimens.[2]

Accurate specimens for determine etiologic Mycobacteria from suspected spinal TB is bone and joint tissue biopsy durante operation or percutaneous biopsy guided by CT or MRI to obtain optimal tissues of destructive lesions, caseating granuloma or granulomatous inflammation or abscess in vertebral segments, 2 or more sites, on active cases could added blood aspirate around lesion with volume around 10 ml or more.[8,9]

CONCLUSION

Determining tuberculous meningitis and spinal tuberculosis based on the gold standard that included the complementary of examination on clinical manifestation with the standard laboratory of the CNS characteristic figure on MRI/ CT; chronic inflammation or granulomatous or caseousus necotic on histo pathology; iflammatory reaction markers in blood, protein and glucose concentration, biochemical and pathological features in CSF on clinical pathology; and isolation and identification of etiologic bacilli *Mycobacterium tuberculosis* as definitive diagnosis.

Definitive Diagnosis based on isolation and identification *Mycobacterium tuberculosis* included the sensitivity to the first line anti-TB drug.

The gold standard method for isolation, identification, and sensitivity tests of *Mycobacterium tuberculosis* using the combined examination of standard culture method (solid and liquid medium) plus standardized PCR.

Positivity detection 14,67% of CSF specimens, and 23% of bone tissue biopsy were very low. All isolates 100% sensitive to Rifampin and Pyrazinamide, and 80% sensitive to Isoniazid, Ethambutol, and Streptomycin, with considered in very small isolate samples.

The important strategy need for better outcome in management TBM or spinal TB could be starded by the research that included multy centre study to decide the standardized procedure on diagnosis, therapy, prevention and promotion.

Early accurate diagnosis and rapid appropriate therapy could be reached the better outcome, to ovoid disability sequele or mortality.

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Literature Review

MANIFESTATION OF AIDS WITH DIARRHEA

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ABSTRACT

Infectious diseases HIV/AIDS is a global health problem. According to WHO (2000) reported that 58 million people in the world are infected with HIV, within the 22 million people died from AIDS or 7000 people die every day. HIV Infection caused decrease and disorder of humoral and cellular immunity. Intestinal mucosal normally shows a physiologic inflamation that account for intestinal mucosal integrity. Diarhhea in HIV infection due to immune deficiency can caused by pathogen and non pathogen. Acute and chronic diarrhea usually found in HIV infection patient, the latter is more frequent. HIV enteropathy cause chronic diarrhea without pathogen infection because intestinal mucous damage by HIV direct infection. Treatment is characterized as causative supportive and symptomatic treatment causal, supportive and Symptomatic. Immunonutrient is very important within management patient HIV/AIDS.

Key words: *HIV/AIDS, diarrhea, HIV infection, immunonutrient, symptomatic*

ABSTRAK

Penyakit infeksiun HIV/AIDS hingga kini merupakan masalah kesehatan dunia. Berdasarkan WHO (2000) melaporkan bahAsa 58 juta jiwa di dunia terinfeksi HIV, dengan 22 juta jiwa meninggal karena AIDS atau 7000 jiwa meninggal setiap tahunnya. Infeksi HIV disebabkan penurunan dan kelainan kekebalan sel dan humoral. Mukosa usus normal menunjukkan suatu inflamasi fisiologis yang berperanan dalam menjaga dan memelihara integritas dari mukosa. Diare pada infeksi HIV dikarenakan penurunan imun dapat disebabkan oleh patogen dan non patogen. Diare akut dan kronis biasanya ditemukan pada penderita HIV, akhir-akhir ini lebih sering. Enteropati HIV menyebabkan diare kronis tanpa patogen infeksius karena mukosa usus rusak akibat infeksi HIV. Pengobatan ini bertujuan untuk mengetahui penyebab, suportif dan simptomatik. Nutrisi untuk kekebalan tubuh sangat penting dalam manajemen pasien HIV/AIDS.

Kata kunci: *HIV/AIDS, diare, Infeksi HIV, nutrisi untuk kekebalan tubuh, simptomatik*

INTRODUCTION

Infectious diseases HIV/AIDS until now is a global health problem. According to WHO (2000) reported that 58 million people in the world are infected with HIV, within the 22 million people died from AIDS or 7000 people die every day.[1] In the United States until January 2000 found 724,000 cases of AIDS in adults, 425 of them died.[2] In Indonesia (1997) recorded in the MOH are 555 cases, 423 cases of HIV and 132 AIDS cases. From a number of such cases 66 % of men, 30% women and 4% of indeterminate sex.[3]

Although many advances have been achieved in the field of medicine and has been implemented Secondary prevention efforts but nonetheless progression of HIV infection to AIDS with manifestation of diarrhea are found, of which more than 50% of AIDS cases with manifestations of diarrhea.[2] Factors driving the emergence of diarrhea in AIDS patients is a direct effect of HIV infection and the manifestation of secondary infection. Most of the secondary infections that cause diarrhea are protozoa and cytomegalovirus infection.[2]

Manifestations of diarrhea in AIDS patients need to get serious attention, because it is often fatal even encourage death.[4,5] Based on these various circumstances discussed AIDS with manifestation of diarrhea.

PATHOPHYSIOLOGY

HIV infection causes a decrease and disruption of the function of the immune system, especially mobile. Cellular immune system disorder characterized by a decrease in CD4 T-lymphocyte count to less than 1,000/ul. The mechanism of CD4 T-lymphocyte decline is not fully known. Some theories suggest that the direct cause of the cytopathic effect (virulence) gp 41 on the outside of the HIV virion. While indirectly occur through the process of cell apoptosis, cell destruction caused by an autoimmune response, cell maturation barriers, destruction of CD4 memory T-lymphocytes.

Decreased function of other immune system includes barriers CD4 T- lymphocyte interactions with MHC II, resulting in decreased fungal antigen presenting cells (APCs). Besides a decline in the function of macrophages and Natural Killer (NK) cells. As a result of a decrease in interferon-gamma, increased production of cytokines from T lymphocytes cells, resulting in cell proliferation and differentiation of B lymphocytes also decreased resulting in disruption humoral immune response.[6,7]

Disease course of HIV infection is divided into stages based on clinical circumstances and the number of CD4 T lymphocytes that includes.[3,6]

1. ***Primary Infection*;** HIV is an acute phase that lasts 6-12 weeks after HIV enters the body. CD4 T Limfositl decreased and then returned close to normal, the symptoms include fever, malaise, myalgia, arthralgia, enlarged lymph nodes and meningoencephalitis
2. ***Early Immune Deficiency*** (CD4 > 500/ul); Asymptomatic phase that lasts about 5 years, often no symptoms but can be Guillain-Barre syndrome symptoms, Demielinating chronic neuropathy, idiopathic thrombocytopenia, Reiter's syndrome, Bell's palsy.
3. ***Intermediate Immune Deficiency*** (CD4 200–500/ul); A replication phase that lasts between 5–10 years. In this phase, resulting in lysis of CD4 T-lymphocytes, are susceptible to secondary infections zooster herpes, tuberculosis, sarcoma and lymphoma nonhodgkins Kapposi's. Clinical symptoms arise usually progressive weight loss, fever without apparent cause and diarrhea.
4. ***Advanced Immune Deficiency*** (CD4 < 200/ul); Is the last phase (AIDS), which took place 10–13 years after infection. In this phase of severe immune deficiency causing opportunistic infections and cancers.

Intestinal immunity consists of phagocytic cells, humoral and cell mediated. Each component makes a specific contribution to the individual to an infection or inflammation of the intestine. Normal intestinal mucosa showed a physiological inflammation in the lamina propria, with the number of neutrophils, macrophages, plasma cells, and lymphocytes, which play a role in protecting and maintaining the integrity of the mucosa. Neutrophils are important in immunity, impaired neutrophil function when the defense mechanisms in the gut also disrupted so prone to infection of the gastrointestinal tract.[5]

PATHOPHYSIOLOGY DIARRHEA IN HIV INFECTION BY:

Dirrect toxic effects of HIV

This direct toxic effect of happens due to the influence of gp 41 on the outer surface of HIV virions to the mucosa, epithelial, nervous system, causing intestinal disturbances in intestinal motility and secretion. This occurs through a process:[8]

- Expression of gp 41 at the membrane and budding of virus particles can cause an increase in membrane permeability, calcium influx toxic or osmotic lysis of infected cells.
- Membrane of infected CD4 T lymphocyte virus fusing with other cells that are not infected by gp 120 causes the formation of multiple multinucleated giant cells or syncitia. This process is lethal to the infected cells and uninfected.
- Viral replication can interfere with the synthesis and expression of cellular proteins that result in cell death.
- Binding of gp 120 to CD4 + T-lymphocytes induces gp 41 that have toxic effects.

This situation is known as AIDS enteropathy is due to the interaction of the HIV virus to the gastrointestinal tract. Histological picture of the patient's small bowel mucosal atrophy are lowgrade, with a decrease in the mitotic process that will lead to hyporegenerative state. Expression of p24 antigen in the intestinal mucosa will cause the inflammatory process.[7] This will lead to the opening of tight junctions between epithelial cells on cytokine stimulation of HIV causing diarrhea with leak flux mechanism.[9] The condition is often associated with chronic diarrhea mechanism, due to the morphological changes of the intestinal mucosa, causing malabsorption and decreased intestinal absorption overall.[10]

The reaction is caused by the HIV hipersensitifiti slow type which results in increased permeability of the intestinal mucosa, causing disruption to absorption and increased secretion of the intestinal wall which will cause inflammatory diarrhea.[11]

Due to Pathogen Infection

a. Infection from Intraluminal Intestinal

Intestinal microflora is a normal flora is very important role in the defense in the intestine. Normal flora in the gut is important as a saprophyte which act to resist the colonization of pathogenic bacteria. Because in HIV infection is immunodeficiency, it will change to the normal flora of pathogens that would induce the secretion of chemical mediators, cytokines and inflammation in the intestinal mucosa occurs that would cause an increase in intestinal secretion and absorption disorders.

The decline in the immune system in people with HIV/AIDS led to the growth of other pathogenic bacteria in the gastrointestinal tract, such as bacterial infections, viruses, protozoa and fungi. Classically pathogens in HIV/AIDS is cryptosporidia, Isospora belli, Mycrosporidia, cytomegalovirus and Mycobacterium avium - intraceluler (MAI) which will give the manifestation in the form of chronic diarrhea.[12]

b. Secondary Infection Extraluminal
Systemic diseases can give gastrointestinal manifestations such as nausea, vomiting and diarrhea, as in pneumocistis carinii pneumonia and sepsis caused by the release of endotoxins and toxins released by microbes. Endotoxin shock is usually caused by bacterial products in sepsis can occur when there is excessive cytokines production. Production of cytokines will stimulate the release of mediators such as bradykinin, prostaglandins and leukotrine that will increase motility and increased secretion of water and electrolytes from the intestinal wall.[8,10]

Etiology of Diarrhea in Patients with HIV/AIDS

HIV patients with diarrhea were not found in the intestinal pathogens found about 15–46% and the rest is caused by a pathogen invasion.[11]

Diarrhea due to Infection

All pathogens can cause diarrhea, HIV/AIDS patients. Classically pathogens in the gut in people with HIV/AIDS is Cryptosporidia, *Isospora belli,* and *Mycobacterium avium*-Mycrosporidia intraceluler (MAI)[13]

Bacteria: Pathogenic bacteria found in people with HIV/AIDS is as a opportunistic infection such as:

- *Mycobacterium avium complex* (MAC) that gives non inflammatory manifestations include diarrhea, weight loss, night sweats and hot and usually occurs in patients with CD4 + T-lymphocytes < 50 U/l. MAC bacteria are very distinctive with an overview granular nodules with a diameter of about 1-4 mm erythematous surface. Complications arising from the MAC infection is intestinal obstruction, perforation, fistula and gastrointestinal bleeding.[5]
- Other pathogenic bacteria that are often found include Salmonella, E. coli, Campylobacter and Shigella.[11,13]

Parasit: Intestinal opportunistic parasitic in infectious HIV patients which often cause diarrhea are *Cryptosporidi*, 20% *Microsporidia,* 4,9% *Giardia lamblia,* 2,6% *Entamoeba histolitica* and *approximately* 1,5% *Isoposa beli. Cryptosporidium* infection has secretoric diarrhea as an effect and mostly assumed that it is correlated with malabsorption. *Microsporidial* is often correlated with atrophy villus, hipper, increasing lymphocyte intraepithelial and D-xylose malabsorption.[14]

Virus: Citomegalovirus (CMV) is common and its effect on a very serious intestinal infections in people with HIV/AIDS. Symptoms of cytomegalovirus infection in gastrointestinal disease causing intermittent and persistent diarrhea and cause abdominal pain, tenesmus, heat and weight loss. Cytomegalovirus infection is more frequent cause of infection in the colon with a picture of a diffuse erythematous mucosa and submucosa that fibrils with hemorrhagic and ulcerated mucosa. Viral pathogens are also frequently found in people with HIV/AIDS, among others, the herpes simplex virus and adenovirus.[5]

Fungi: Histoplasma capsulatum and Candida albicans is a two fungal pathogen that often cause colitis in patients with HIV/AIDS. Candidiasis is a specimen that causes watery diarrhea and abdominal pain as well as the implications colonic ulcers.[5]

Table 1. Etiology agent of diarrhea in HIV infection based on the location in the intestine[5]

Smal intestine	*Large intestine*
Cryptosporidia	*Cytomegalovirus*
Microsporidia	*Cryptosporidia*
Isospora belli	*Mycobacterium avium complex*
Mycobacterium avium complex	*Shigella sonnei*
Salmonella species	*Clostridium difficille*
Campylobacter species	*Campylobacter jejuni*
Giardia lamblia	*Histoplasma capsulatum*
	Adenovirus
	Herpessimplex
	Pneumocytis carinii

Diarrhea caused by Non Infectious

Movement of non-infectious diarrhea in patients with HIV/AIDS need to be considered because of a neoplastic intestinal, drug reactions, lactose intolerance and pancreatic insuffisiensi secondary to pentamidine or didanosine therapy and therefore malabsorption and steatorrhea.[9]

DIAGNOSIS APPROACH OF HIV WITH DIARRHEA

Approach to the diagnosis of HIV/AIDS patients with diarrhea, an important consideration is to detect movement with a degree of immune deficiency and clinical symptoms.[11] There is a term that is often used is the AIDS -related complex (ARC). ARC is diagnosed when there are symptoms/signs of constitutional AIDS without opportunistic infections or tumors. This concept uses for the benefit of the clinic, the alleged progression to AIDS and for prognosis.[15]

Table 2. Criteria ARC: There are 2 or more of the clinical symptoms that have lasted 3 months or more plus 2 or more laboratory abnormalities.[15]

Clinical Symptoms	Laboratory Abnormalities
– Fever 38° C	– Limfopeni/lekopeni
– BB decrease > 10%	– Trombositopeni
– Enlarged lymph nodes	– Anemi
– Diare intermitten/ continuou	– Ratio CD4/CD8 decrease
– Weak, Physical activity decrease	– CD4 decrease
– Night sweats	– decreasing blastogenesis,
	– Increasing globulin

Determination movement diarrhea Noteworthy food history, history of medicine penggunaan, travel history and symptoms along with diarrhea (nausea, vomiting, fever, other systemic symptoms) and diet (lactose) which can give clues to the cause of diarrhea. Furthermore, the determination of the degree of immune deficiency, decreased CD4 count and opportunistic infection is an indication of the decline of the immune system. Evaluation of the degree of immune deficiency useful in determining the movement of diarrhea.[5,9,11]

Examination Support[5,9,14,16]

Microscopic examination of feces, microbiological and culture is very important in determining the movement of the symptoms of diarrhea if the infection is still a suspect. Examination is generally performed three times due to the growth of microorganisms in episodic. Examination of stool culture can detect pathogens Campylobacter, cytomegalovirus, adenovirus, mycobacterium avium complex and salmonella.

Acid Fast Staining Bacil (AFB) of the stool can detect pathogens mycoobacterium avium complex. Antigen test to detect pathogens Giardia and Cryptosporidium are more sensitive than microscopic examination.

Endoscopic examination with biopsy be an option if you find a bloody diarrhea, tenesmus. By doing endoscopy can determine the specific location of pathogens in the gut. Diagnosis of HIV enteropathy with histopathologic examination and abnormal function of the gut with no found any pathogens or malignancy.

MANAGEMENT

HIV patients with diarrhea therapy intended to treat HIV infection and diarrhea. Treatment of diarrhea in patients with HIV is essentially connected with a state of decreased immunity, opportunistic infections and HIV enteropathy. Strategic treatment aimed at specific and general therapy to reduce complaints and general state of repair.[8,13]

Specific Therapy

Specific therapy aimed at the treatment of HIV infection (antiretroviral therapy), provision of anti- microbial, fluid rehydration and correction of electrolyte disturbances. Provision of anti-retroviral therapy is not promptly given to patients suspected. For AIDS patients (stage III and IV disease) is recommended immediately given antiretroviral therapy irrespective of CD4 cell count or total lymphocyte count. Recommendation also be given to patients with stage II and III with number of CD4 < 200 cells/mm^3.[17]

Table 3. Antiretroviral therapy[17]

If examination cd4 can be performed:
– Clinic stadium IV, without taking the number of CD4
– Clinic stadium I,II or III with CD4 < 200/mm^3
If examination cd4 can not be performed:
– Clinic stadium IV, without taking the number of lymphocyte
– Clinic stadium II or with the number of lymphocyte Ý 1200/mm^3

Antiretroviral drugs recommended by WHO (2002)[17]

Nucleosida reverse transcriptase inhibitors (NsRTI)	Non nukleoside reverse trancriptase inhibitor (NNRTI)	Protease inhibitors
Abacavir; Tablet 300 mg, Syrup 100 mg/5 ml	Efavirens; Kapsul 50 mg, 100 mg, 200 mg	Indinavir; Kapsul 100 mg, 200 mg, 333 mg, 400 mg
Didanosin; Tablet 5 mg, 100mg, 150 mg, 200 mg	Nevirapine; Tablet 200 mg, Syrup 50 mg/5 mg	Ritonavir; Kapsul 100 mg, Syrup 400 mg/5 ml
Lamivudin; Tablet 150 mg, Syrup 50 mg/5 ml		Lopinavir + ritonavir; Kapsul 133,3 mg + 33 mg, Syrup 400 mg/5 ml + 100 mg/5 ml
Stavudin; Kapsul 15 mg, 20 mg, 30 mg, 40 mg, Syrup 5 mg/5 ml		Nelfinavir; Tablet 50 mg, Powder 50 mg/g
Zidovudin ; Kapsul 100 mg, 250 mg, 300 mg		Saquinavir; Kapsul 200 mg

Therapeutic response sometimes is a tool in establishing a diagnosis of diarrhea caused by an infection. If the stool examination found no pathogenic organisms empirical therapy trial with a quinolone (ciprofloxacin) and metronidazole can be given for 1-2 weeks prior to the examination endoskofi. Standard treatment regimens for movement of infection in HIV/AIDS patients with diarrhea.[14,16]

Cryptosporidiosis were paromycin 500 mg every 8 hours for 14 days, azitromycin, and Letrazuril. Isosporiasis were trimethoprin – sulfamethosaxole 160/800 mg every 6 hours for 10 days, then thrice a day for 21 days, metronidazole, and pyrimethamin. Microsporidiosis was albendazole 400 mg every 12 hours for 14 days. Salmonella, shigella, enterocolitis were ciprofloxacin 500 mg every 12 hours for 14 days, cefotaxime, ceftriaxone, and chloramphenicol. Campylobacter colitis was erytromycin 500 mg every 6 hours. Mycobacterium Avium Complex was rifabutin 300 mg every days added ethambutol 400 mg every 12 hours dan claritromycin 500 mg every 12 hours. Cytomegalovirus was ganciclovir 5 mg/KgBB every 12 hours for 14 days. Candida Albicans, Histoplasma capsulatum were nystatin oral, amphotericin B, intraconazole, fluconazole used systematically in severe cases.

Lack of fluids and electrolytes cause serious problems in a patient with severe diarrhea. Monitoring immediate fluid replacement especially for severe diarrhea so that the volume of fluid lost should be measured and the amount of fluid and electrolyte replacement should be done immediately.[5] Oral rehydration with fluids containing glucose, Na, K, Cl and bicarbonate is effective in patients with mild dehydration. Parenteral fluid administration (Ringer's lactate) is given in the acute state of severe dehydration.[12]

General Therapy

Therapy aimed at the general supportive and symptomatic treatment, nutritional support and counseling to people with HIV/AIDS. Symptomatic treatment is very important for all patients with diarrhea in the case to prevent fluid loss and improve disturbance and functional status of patients. Symptomatic therapy, among others:[18]

- Luminal anti diarrhea such as Bismuth subsalicylate or aluminum antacids, cholesttyramine, recommended especially in mild cases
- Antimotility agents including loperamide 2–4 mg given four times a day or diphenoxylate 2 tablets given four times daily.
- Octreotide 100–500 mcg administered subcutaneous or intravenously every 8 hours, especially given the severe cases that do not respond to oral medications.

In HIV-infected patients often have impaired nutrient intake caused a decline in the body's biological functions. Immunonutrient important to consider in the management of patients with HIV/AIDS, which contains a variety of materials that can meet the needs of patients who have an infection. Immunonutrient contains the components necessary to meet basic metabolic needs are carbohydrates, proteins, fats and also contains 3 main imunonutrient namely arginine, gluthamin and fish oil that have a positive impact on the immunological function of the body. The supplement should also contain a variety of vitamins (vitamin C and vitamin E) and minerals (Mn, Cu, Se and Zn) that has the ability of anti -oxidants as well as exogenous triggers endogenous anti-oxidant potential and has anti-apoptotic effects.[19,20]

Nutrition given orally if the patient is still able to eat. Oral nutritional supplements should be given in the form of a convenient and easily absorbed nutrient dense. Enteral nutrition orally given if insufficient or limited by the presence of lesions in the mouth and esophagus until the patient is able to maintain sufficient oral intake. Parenteral nutrition and oral performed when enteral nutrition can not be tolerated in considerable amounts. Parenteral nutrition is given on a case by forceful vomiting and prolonged and severe diarrhea.[21]

SUMMARY

HIV Infection caused decrease and disorder of humoral and cellular immunity. Intestinal mucosal normally shows a physiologic inflamation that account for intestinal mucosal integrity. Diarhhea in HIV infection due to immune deficiency can caused by pathogen and non pathogen. Acute and chronic diarrhea ussually found in HIV infection patient, the latter is more frequent. HIV enteropathi cause chronic diarrhea without pathogen infection because intestinal mucous damage by HIV direct infection. Treatment is aimed to causal, supportive and symptomatic. Immunonutrient very important within management patient HIV/AIDS.

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Literature Review

BACTERIA CAUSED SEPSIS BIOMARKERS

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ABSTRACT

Sepsis is a clinical condition of patients with serious infections that show a systemic inflammatory response, with or without a positive blood culture. sepsis is one of the most frequent causes of death in patients in intensive care units. We are at urgent need for biomarkers and reliable measurements that can be applied to risk stratification of septic patients and that would easily identify those patients at the highest risk of a poor outcome. Such markers would be of fundamental importance to decision making for early intervention therapy. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF- α), interleukins-1,-6,-8 (IL-1, IL-6, IL-8) are postulated to play a major role in the pathogenesis of the syndrome. C-reactive protein (CRP) and procalcitonin (PCT) are among a few biomarkers that incorporated into clinical practice although their precise role in the pathopysiology of sepsis and organ dysfunction still unclear.

Key words: Sepsis, biomarker, inflammatory, C-reactive protein (CRP), procalcitonin (PCT)

ABSTRAK

Sepsis adalah suatu kondisi klinis penderita dengan infeksi serius yang memperlihatkan respons inflamasi sistemik, dengan atau tanpa kultur darah yang positif. Sepsis merupakan salah satu penyebab kematian yang paling sering pada penderita di unit perawatan intensif.. Kita berada pada kebutuhan mendesak akan biomarker dan pengukuran yang handal yang dapat diaplikasikan untuk risiko stratifikasi pada pasien septik dan akan diidentifikasi dengan mudah pada pasien dengan risiko tertinggi pada hasil. Penanda akan menjadi kepentingan mendasar dalam pengambilan keputusan untuk therapy. Pro-inflammatory sitokin seperti nekrosis tumor faktor-α (TNF- α), interleukins-1,-6,-8 (IL-1, IL-6, IL-8) merupakan acuan dasar yang berperan penting dalam sindrom patogenesis. C-reactive protein (CRP) dan procalcitonin (PCT) adalah beberapa biomarker yang dimasukkan ke dalam kegiatan klinis meskipun mereka berperan patifisiologi sepsis dan disfungsi organ masih tak jelas.

Kata kunci: *Sepsis, biomarker, inflamasi, C-reactive protein (CRP), procalcitonin (PCT)*

INTRODUCTION

Sepsis is a clinical condition of patients with serious infections that show a systemic inflammatory response, with or without a positive blood culture.[1] The diagnosis of sepsis was referring to the consensus criteria in 1991. These criteria are inviting a lot of dissatisfaction, so that a better approach might be to the stratification system. The new system is based on the PIRO characterize sepsis predisposition, basic infection, response and organ dysfunction. However this system works well, is very important to identify biomarkers of response profiles that can identify patients at risk of developing into an organ dysfunction.[2]

Sepsis is one of the most frequent causes of death in patients in intensive care units. In America, there are approximately 700,000 patients each year and 210,000 of them died. Despite new therapies that support and more potent antibiotics, sepsis remains often causes death in 30–70% of patients with severe sepsis and significantly lowers the quality of life for patients who survived.[2]

Generally, sepsis is a spectrum disorder that is caused by infection by bacteria, viruses, fungi or parasites or toxic products. The spectrum of disorders of sepsis is the result of microbial invasion of the bloodstream or intoxication with early signs of circulatory compromise include tachycardia, tachypnea, peripheral vasodilation and fever

(or hypothermia) to circulatory collapse with multiple organ dysfunction and death.

Several different bioactive molecules have been proposed as a biomarker to assess the degree of patients with sepsis. Among them are bacterial products such as endotoxin and bacterial DNA, acute phase proteins (protein C, procalcitonin), coagulation factors (fibrin degradation products, anti- thrombin III, D-dimer), cellular processes (apoptosis), hormones (cortisol, ACTH) and cytokines (TNF-α, IL-1, IL-6, IL-8, IL-10). Unfortunately, only a few biomarkers that can be used in clinical practice.[2] In this literature review will discuss some of the biomarkers are often used in studies.

Phatophysiology of Sepsis

The body's defense mechanism against bacterial infection is influenced by the structure and bacterial pathogenicity. Depending on the structure of the cell walls, the microbes are classified in the class of Gram-positive bacteria, Gram-negative, and *spirokaeta mycobacteria*. There are several general overview of the immune response to microbes, namely: Defense against microbial-mediated effector mechanisms of innate immunity and acquired immunity, non-specific immune response against microbes play an important role in determining the specific immune response that will take place, The immune system is able to specialize and respond differently to the types of microbes, Survival and microbial pathogenicity is strongly influenced by the ability of microbes to evade the host immune system, tissue damage and disease as a consequence of infection is generally caused by the host response to microbes and their products.[3]

Innate defense system of the body is the first line of defense against infection and can be activated when pathogen via natural defense barrier. The body's defense system includes the humoral elements (the alternative pathway and mannan-binding lectin of the complement system, acute phase proteins and cytokines) and cellular elements (monocytes, macrophages, neutrophils and dendritic cells natural killer cells).[4]

Detection of invading microorganisms mediated by receptors expressed on the surface of innate immune cells. These receptors can recognize structures that are usually found in microbial pathogens.[4]

Lipopolysaccharide (LPS) bacteria are the main targets of immune recognition. Macromolecules is only found in the outer lipid bilayer that surrounds the walls of Gram-negative bacteria. There are two proteins that recognize humoral LPS is LPS-binding protein and soluble CD14.[5]

Parslow, 2001. CD14/LPS complex then interacts with toll-like receptor-4 (TLR4). TLR4 activation causes the transcription of a number of inflammatory genes and the immune response through the mediation mechanism of nuclear factor-αB (NF-αB).[4]

Gram-positive organisms can also cause sepsis least through two mechanisms: through the production of exotoxins that act as superantigens and through the cell wall components that stimulate the immune cells. Superantigens are molecules that are bound to MHC class II molecules on antigen presenting cell and T cell receptor Vβ chain to produce large amounts of proinflammatory cytokines. Staphylococcus enterotoxin, toxic shock syndrome toxin-1 and *streptococcal* pyrogenic eksotosin are examples of bacterial superantigens. Toll-like receptor 2 (TLR2) mediates cellular responses to kill Gram-positive bacteria and the structure of the cell wall (peptidoglycan, lipoproteins, lipoteichoic acid and phenol- soluble modulin).[4]

Innate immune defense is another important group of serum proteins called complement pathway. Complement can be activated via three routes, all via the C3 complement activation: the classical pathway, the alternative pathway and the lectin pathway.[5]

With the exception of C3, almost all soluble mediators of innate immunity found in small amounts in normal conditions. This concentration can be increased to 1000 times during a serious infection, which is part of the protective reaction called the acute phase response. In these circumstances, the liver increases the synthesis of more than 30 different serum proteins, called acute phase proteins. Some of them are complement factors C3 and B, MBL (mannan-binding lectin), LBP (LPS-binding protein), C-reactive protein and amyloid P protein and other coagulation factors such as fibrinogen include, granulocyte colony-stimulating factor anti -oxidants and serum protein -binding metal. Acute phase response occurs when hepatocytes associated with cytokines, especially interleukin-6 (IL-6), interleukin-1 (IL-1) or tumor necrosis factor-α (TNF-α) are released locally or into the bloodstream by other cells.[5]

Excessive stimulation by proinflammatory cytokines or other mediators may cause systemic damage and endothelial cell dysfunction. Endothelial cell activation leads to increased expression of nitric oxyde synthase which causes nitric oxyde and intra- cell adhesion molecules excessive, stimulates neutrophil chemotaxis and the interaction of endothelial cells.[6]

Bone et al., 1997. Split pathophysiology of sepsis into 5 stages:[1,7]

Stage 1: Enforcement infection. When the infectious organisms will begin to proliferate produced inflammatory molecules such as lekotrien, complement components, cytokines and antigen-antibody complexes, attract neutrophils to areas of infection, followed by monocytes. Stacking leukocytes at sites of inflammation is facilitated by IL-8, endothelial cell selectins and cellular adhesion molecules. Leukocytes recognize and phagocytize bacteria and fungi teropsonisasi. This process is due to local release of cytokines from macrophages (monocyte tissue). Proinflammatory cytokines and other mediators including TNF-α, IL-1, IL-2, IL-6, interferon-γ, platelet-activating factor (PAF) and others. The release of these mediators will be balanced by compensating anti-inflammatory response

of IL- 4, IL-10, IL-11, IL-13, soluble TNF receptor-α, IL-1ra, TGF-β and other substances.

Stage 2: early systemic response. In a state of severe infection, proinflammatory cytokines would result in systemic symptoms. The emergence of clinical symptoms shows microenvironment unable to control the infection. Proinflammatory cytokines in this process is TNF-α, IL-1, IL-6 and interferon-γ. The reaction of the body heat produced by the release of IL-1 that reach the hypothalamus. Prostaglandin E2 may also be produced locally in the hypothalamus and increases the set point temperature.

Stage 3: systemic response. Endothelial cell dysfunction is a cause of pathophysiological changes at this stage. As a result of the activity of TNF-α, IL-1 and other cytokines, endothelial cell phenotype shift toward prothrombotik stage. Inflammatory cells and platelets move towards endothelial injury. Disturbances in endothelial cell physiology will affect the ability of the endothelium to regulate blood flow. Consequently there is an increase in microvascular permeability, fluid transudation, organ dysfunction and shock.

Stage 4: The reaction of anti-inflammatory compensation. Normally, a cascade of proinflammatory mediators followed by a counter-regulatory cytokine that rapidly regulate the secretion of proinflammatory cytokines and clinical manifestations of sepsis. This regulatory cytokines in principle is IL-4, IL-10, transforming growth factor-β (TGF-β) and other anti-inflammatory molecules.

Stage 5: The failure of the immune system. This is the final stage, which is seen in some patients. This stage is characterized by the inability of monocytes to respond physiologically, increasing the risk of developing an infection, organ failure and death.

Biomarker Detection

Biomarkers are any characteristic that can be objectively measured and evaluated as an indicator of biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention.

Measurement of existing biomarkers using ELISA method, measured by immunoluminometric procalcitonin assay is similar in principle to the ELISA.[8]

Protein molecules associated with sepsis is very broad, including cytokines, chemokines, adhesion mediator, soluble receptors and acute phase proteins. Protein biomarker research is currently focused primarily on procalcitonin and interleukin some magic bullet as diagnostic biomarkers for infection. The standard method for assessing the use of this diagnostic is Characteristic Receiver Operator Curve (ROC) by determining the cut point (cut-off) in order to obtain true-positive diagnoses (sensitivity) and false-positive diagnosis.[8]

Tumor necrosis factor-α (TNF α)

TNF-α is a 17-kd polypeptide is expressed in the form bound to the membrane and form secretion. Activated macrophages and monocytes, T cells and NK synthesize TNF-α. TNF-α is secreted bound to the cell surface receptors: type I (55 to kd) or type II (75-kd). Stimulation of type I receptor causes activation of NF-$\kappa\beta$, induction of IL-6, the expression of tissue factor (TF), regulate thrombomodulin (TM) and TM increases catabolism, activation of fibrinolysis, regulation of endothelial cells, induction of nitric acid synthase, neutrophil activation and biological effects other. Receptor type II facilitates TNF-α binding to type I receptors and signal transduction.[1]

TNF-α is an early factor in the activation of the body's response and a series of cytokines released during infection, where the concentration is increased 24 times (828 ng/L) compared to the concentration before infection at 2 h after LPS interacts with endotoxin in vivo during the study. However, the use of TNF-α as a diagnostic tool is not good, in terms of differentiating inflammation and infection. Analysis of the ROC curve shows the sensitivity and specificity were weak. Difficulty TNF-α as a diagnostic tool of sepsis due to an increase in the concentration of bacteria associated with rapid and short half-life of about 17 minutes.[8]

Interleukin-1 (IL-1)

Other proinflammatory cytokines associated with sepsis is the IL-1 which include IL- 1α IL-1β and IL-1 receptor antagonist (IL-1ra) in which excessive amounts of IL-1β during sepsis.[1,8]

IL-1β interests to provide diagnostic disagreement, between the increase and decrease, so does the same thing has been reported in neonates. Instead concentration of IL-1ra showed a consistent increase in patients with sepsis with a concentration of 2–31 mg/L (concentration in normal individuals is not detected). ROC analysis showed sensitivity of 93% and a specificity of 92% at the time of the diagnosis. But it should be noted that high concentrations have also been reported in patients who underwent thoraco-abdominal aneurysm repair.[8]

IL-1 is the best along with IL-8 in terms of predicting the output. This means that the predictive value of these cytokines is better than the prototype clinical prognostic scores were used in the intensive care unit, the Acute Physiology and Chronic Health Evaluation Score (APACHE II).[2]

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a glycoprotein 21-30-kd widely produced by the cells, including monocytes and macrophages, T cells, endothelial cells, fibroblasts and keratinocytes. This molecule is the biggest cause of the acute phase response, causing the growth and differentiation of T cells, NK cell activity and promote the maturation of megakaryocytes. IL-6 can inhibit endotoxin -induced TNF-α and IL-1 and increase the degree of soluble TNF-α receptor type I and IL-1ra.[1]

IL-6 is a cytokine with important prognostic value in sepsis. Although the role of IL-6 in this syndrome remains controversial, IL-6 cytokine proposed as an important

biomarker in sepsis due to the slow kinetic plasma, stable and easily detected in blood samples and correlated well with the intensity of the inflammatory response. Persistent increases in levels of IL-6 associated with organ failure and death.[2,6]

Such as TNF-α, IL-6 plays a role in the immune response at the beginning. Value for adults in sepsis reported to range from 300–2700 ng/L, above 100 ng/L for SIRS. However, there are reports that say that no significant difference between the concentrations in SIRS and sepsis, and between sepsis and trauma patients. This contradiction has been confirmed by the lack of sensitivity and specificity based on ROC analysis.[8,9]

Interleukin-8 (IL-8)

Interleukin-8 (IL-8) is a chemokine, an agency that recruits inflammatory cells to the site of injury. IL-8 is synthesized by monocytes, macrophages, neutrophils and endothelial cells. TNF-α, IL-1β and IL-2 stimulates the release of IL-8. Following stimulation of IL-8, also stimulated neutrophil function, promote chemotaxis, adhesion molecule expression and regulation of activity of respiration changes and degranulation.[1]

Among other biomarkers associated with sepsis, IL-8 were higher in adult studies, although the main focus is the diagnosis of IL-8 in neonatal research. Concentrations of IL-8 in septic neonates was 94–4335 ng/L compared with 2–42 ng/L in healthy neonates. Although in one study said that is not useful for the diagnosis, the majority of studies reported a consistent increase of the concentration of IL-8. ROC analysis mentioned sensitivity 92 % and specificity of 70%.[8]

The degree of IL-8 correlated with lactic acid, the presence of DIC, severe hypoxemia and mortality in patients with severe infection or septic shock (Balk, 2004). IL-8 together with IL-1 cytokines are the best in terms of prediction output.[2]

***C-reactive protein* (CRP)**

C-reactive protein is a member of the pentraxin family of proteins decomposed during acute inflammation, causing the immune response to the antigen, activates the complement and enhance the production of monocyte tissue factor. C-reactive protein binds phosphoryl kholin on the surface of bacteria, acts as opsonin for gram-positive bacteria and play a role in the body's defenses. C-reactive protein also binds low density lipoprotein cholesterol (LDL-C) in vitro, suggesting a direct interaction with atherogenic lipids.[9]

CRP is often used as a marker of bacterial infection, however CRP may also be released because of non bacterial stimuli such as state after surgery, autoimmune diseases and rheumatic even on myocardial infarction and malignancy.[10]

CRP is an acute -phase proteins, which are in a state of acute phase plasma levels were varied. CRP is an additional biomarker in the diagnosis of sepsis. CRP has a plasma half-life that is constant in almost all circumstances. Levels in the plasma is determined by the speed of synthesis, which reflects the presence and spread of disease activity. Induction of CRP requires a minimum of 12–18 hours and CRP increased late during sepsis also decline takes several days. CRP is not useful to distinguish the evolution of sepsis in severe sepsis and septic shock and septic complications in patients with trauma, the slow period after the trauma of high CRP values. Patients with SIRS also have elevated levels of CRP. Opinions on the usefulness of CRP as a diagnostic tool varies, on the one hand claim to have high value and low on the other side. Concentrations were reported in patients with sepsis is between 12–159 mg/L, showing overlap with SIRS patients who are between 13–119 mg/L. ROC analysis showed low sensitivity and specificity.[8,11,12]

Procalcitonin

Procalcitonin (PCT) is a peptide with 116 amino acids with a sequence that is identical to the prohormone of calcitonin, but PCT itself has no activity as a hormone. In normal metabolic conditions, PCT only in thyroid gland C cells. In bacterial infection and sepsis, intact PCT is found in the blood and more importantly PCT levels associated with severe sepsis.[12]

During severe systemic infection, procalcitonin allegedly generated by the extra thyroid tissue. Patients who previously underwent total thyroidectomy procalcitonin still produce at a high level during severe sepsis. Procalcitonin for sepsis pathophysiology is unclear.[10]

In normal physiology PCT is a precursor of calcitonin. Calcitonin is known to regulate the function of bone and calcium metabolism and inhibits osteoclast resorption. Regulation of the release of calcitonin was first influenced by the concentration of ionized calcium in plasma. Whether this can be attributed to a condition with hypocalcemia in patients with sepsis, remains unclear.[13]

Serum procalcitonin levels increased during bacterial infections, parasites or fungi with systemic manifestations. In severe viral infections or inflammatory reactions of non-infectious cases, procalcitonin levels are not increased or only a modest increase. In patients without the presence of infection is very low procalcitonin levels (< 0.1 ng/L) or very high (6–53 ng/L) in severe infections. Resolution of infection with antibiotic therapy reduce levels of procalcitonin. Local bacterial infection and viral infection causes only mild and moderate increase (0,3–1,5 ng/L). That's why the proposed procalcitonin as an indicator of severe infection or sepsis.[12,14]

For the record, procalcitonin levels may be elevated in the first days of life in the absence of infection. Patients with C-cell carcinoma of the thyroid gland may also be there is an increase in the level of procalcitonin in the absence of underlying infection.[14]

In vivo studies showed increased LPS stimulation after a period of 2–6 hours after injection, with a plateau curve from 8–24 hours. PCT as a biomarker measurement is

preferred because it has a half-life 22–29 hours and this increase will be long during sepsis. Positive and gram negative organisms causing an increase in the concentration of PCT in the absence of a significant difference.[8]

Procalcitonin levels increased with increasing degree of inflammatory response in response to infection. When patients were categorized into SIRS, sepsis, severe sepsis and septic shock, particularly increased procalcitonin levels in patients with severe sepsis and septic shock. In a recent study, the levels of TNF-α, IL-6, C-reactive protein and procalcitonin were followed for 14 days after the diagnosis of sepsis. Procalcitonin levels were consistently lower in patients compared to survivors who did not over a period of 14 days. While TNF-α and IL-6 are not consistent and not significantly increased in patients who can not be saved, possibly because of a too high variability from day to day. C-reactive protein is increased in both, patients who survived and did not survive. Procalcitonin levels associated with the severity of the inflammatory response to infection, efficient therapy may be adjusted by a decrease in the levels of procalcitonin. Instead procalcitonin levels indicated poor prognosis. So, procalcitonin can be used as an important indicator for the severity of infection and prognosis of infection and can determine the wisdom of therapy efficacy measurements.[10]

Castelli et al, reported differences in CRP and PCT picture. CRP concentrations increased immediately during severe organ dysfunction and systemic inflammation, but the value is not increased during stage organ dysfunction gain weight. While increased levels of PCT, especially in patients with organ dysfunction, severe sepsis and septic shock.[11]

SUMMARY

Sepsis has been diagnosed according to the consensus guidelines established in 1991 as an infection in addition to the symptoms of systemic inflammatory response syndrome. It is frequently fatal infectious condition. The incidence continues to increase despite the use of specific antibiotics. We are at urgent need for biomarkers and reliable measurements that can be applied to risk stratification of septic patients and that would easily identify those patients at the highest risk of a poor outcome. Such markers would be of fundamental importance to decision making for early intervention therapy. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukins-1, -6, -8 (IL-1, IL-6, IL-8) are postulated to play a major role in the pathogenesis of the syndrome. C-reactive protein (CRP) and procalcitonin (PCT) are among a few biomarkers that incorporated into clinical practice although their precise role in the pathopysiology of sepsis and organ dysfunction still unclear.

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Literature Review

A PATIENT DENGUE HEMORRHAGIC FEVER WITH SPASMS

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ABSTRACT

Indonesia is one of the countries with the high endemic of Dengue viral infection followed by Thailand, Myanmar, India and Srilanka. For more 10-15 years, Dengue Viral Infection/DHF has become a cause of patient who should be hospitalized and was the first cause of death children in south easthern Asia.[1,2] Batavia was the first city of Indonesia found Dengue Viral infection which had been written in journal by David Bylon in the 1779. Encephalopathy of dengue (ED) is one unusually complication of dengue viral infection which had been characterized by aberration the arrangement of nerves central (CNS). This paper want to describe of a young teenage with suffer from DHF and seizure. Beside it, pleural effusion and cerebral edema had been found. Seizure most likely due to dengue encephalopathy associated with cerebral edema and was supported by positive IgG and IgM anti dengue. Corticosteroid was given to improve cerebral edema. By good management as long as admission, she was discharged from hospital with a good condition.

Key words: dengue viral infection, encephalopathy endemic, pleural effusion, IgM anti dengue test, IgG anti dengue test

ABSTRAK

Tercatat negara-negara endemis tinggi kasus DD/DBD adalah Indonesia diikuti oleh Thailand dan Myanmar, endemis sedang adalah India dan Sri Lanka. Selama lebih 10-15 tahun terakhir, DD/DBD telah menjadi penyebab terbanyak indikasi opname dan menduduki peringkat pertama penyebab kematian anak-anak di Asia tenggara.[1,2] Di Indonesia, demam dengue endemik dilaporkan pertama kali di Batavia oleh David Bylon pada tahun 1779. Ensefalopati dengue (ED) adalah salah satu komplikasi tidak lazim dari infeksi viral dengue yang ditandai dengan kelainan susunan saraf pusat (SSP). Dilaporkan seorang anak remaja dengan DBD tingkat I dan kejang. Bukti yang mendukung kebocoran plasma sebagai ciri dari DBD adalah efusi pleura dan edema logis. Kejang diduga akibat dari demam berdarah ensefalopati berkaitan dengan edema otak dan diperkuat oleh IgG positif dan IgM anti demam berdarah, Kortikosteroid diberikan untuk meningkatkan edema otak. Dengan manajemen yang selama masuk, maka akan keluar dengan keadaan baik.

Kata kunci : infeksi viral dengue, endemik encepalopati, efusi pleura, uji anti dengue IgM, uji anti dengue IgG

INTRODUCTION

Today, dengue viral infection has been the main health problems. An estimated 2.5 billion people than 100 countries at risk exposed infection. Reported a 10 million cases dengue fever and 500,000 dengue hemorrhagic fever was dengue shock syndrome with mortality 5% occurring every year. Indonesia is one of the high endemic countries followed by Thailand and Myanmar, India and Srilanka. For more 10-15 years, dengue fever/dengue hemorrhagic fever has become a cause most indication hospitalized and was the first rank cause of death children in southeastern Asia.[1,2]

Batavia was the first city of Indonesia found Dengue Viral Infection which had been written in journal by David Babylon on 1779. On the next years, on 1968, DHF had been found in Surabaya and followed by other city such as Jakarta, Medan, and so on. In Indonesia adult cases trend to increase, since the 1993-1998 mostly of DHF case (60%) occurring at age group 5-14 years, then in 1997 and 1998 shift to age more than 15 years.[3,4]

Encephalopathy of dengue (ED) is one of unusual complication dengue viral infection which had been characterized by aberration the arrangement of nerves central (CNS). Diagnosis encephalopathy had been identified after marker of diagnosis DHF with accompanied manifestation CNS had been found. Actually ED is a rare but more recently increased every year. At the intensive care child hospital - Ho Chi Minh had reported that rate of occurrence ED about 0.5% of the DHF by mortality of 22%; while at the child devision of RS Cipto Mangunkusumo - Jakarta obtained incident ED of 6.2% of the DHF that had been hospitalized. With encephalopathy, these cases were unusually occurred as a complication of prolonged shock with bleeding, but can also be occurred in DHF not be accompanied by shock.[5,6] This paper would like to show on experience of a doctor which had found a DHF patient with spasms manifestation, and had been predicted as that this one had releated with primer disease, of DHF.

CASE

A patient Nn R, 15 years old, address Balon-Cepu came to IRD RSUD Dr. Soetomo with firstly complain of spasms.

The history of this case as followed: A patient got spasms since in Cepu Hospital or 5 hours before hospitalized. When she showed spasms attach she did not conscious two eyes of her foamed an appearance with hand and feet get stiff, no frothy mouth or bitten tongue, spasms occured about 5 minutes, then the patient conscious, She was bought to Surabaya by ambulance. She showed a clinical manifest of spasms

On the 7th day of fever she showed a better temperature than the days before especially on the first day of fever suddenly showed a high temperature, headache, nausea, painful muscle and joints. The temperature was becoming decrease after get a medicine but the temperature showed increase again especially on the 5th day, then she send to Cepu hospital and was hospitalized for 2 days with diagnoses DHF with low trombosit. There was no nose bleeding, gum bleeding or manifestation of other bleeding. When there was no abnormality of intestine moving. On the last disease history there was no spasms history when the patient had been suffered from DHF in 2 years old and hospitalized in Cepu hospital until recovered and discharged in better health condition.

The physical examination of this case as followed: The patient was in good conscious (GCS 4-5-6) with tension 110/70, pulse 108×/minutes (low), breath 22×/minutes, and temperature 37,4°C. There was no anemia, icteric, cyanosis or dyspneu. Did not found enlargement of the heart, normal heart sound and there is no murmur. Vesikular breath sound, there was no ronchie and wheezing. Move equipment in normal limit with result of Rumpel Leede test showed a positive.

The laboratory examination showed: Laboratory result: Hb 11,6 g%, leukocytes 5.100 l/mm^3, trombosit 83.000/mm^3, PCV 33%, GDA 90 mg/dl, SGOT 87 U/L, BUN 5 mg/dl, SC 0,53 mg/dl, K 3,78 meq/L, Na 145 meq/L. Thorax x-ray showed a minimal right pleura effusion. Result of head CT- scan showed cerebral edema.

The division of the lung xrays showed a minimal right pleura effusion cause DHF process due to extravasasion. Result of neurology division concludedas a focal of secondary generalized seizure which might be caused by metabolic ensefalopaty (anoxiq of the brain can cause cerebral edema).

There for the conclusion of the assesment she suffer from DHF with brain edema. Diagnosis planning showed DL series (total trombosit evaluation), IgM and IgG anti dengue, pleura fluid analisys (if trombosit > 100.000). The treatment had been done by given infus ringer acetat 2000 cc/24 hours, diet TKTP 1900 calori, paracetamol 3 × 500 mg, ranitidine 2 × 1 ampoule, multivitamin 2 × 1 tablet, methylprednisolon injection 3 × 125 mg, and diazepam 1 ampoule dan fenitoin bolus 300 mg if spasms and dosis maintenance 3 × 100 mg.

On the next period, the doctor in charge observed the clinical manifestation as followed: On the second day in Dr. Soetomo hospital there was no fever (in the 8th day) and the complaint of headache was decrease, painful of muscle and joint got better. Nausea and vomit were still exist. There was no manifestation of bleeding and didn't show a spasms. Tension 110/50 mmHg, pulse 92×/minutes, RR 20×/minutes, and temperature 37°C. Examination of head, neck, breast, abdomen, and member's motion in normal limit. Laboratory: Hb 12.2 g%, leukocytes 4.200/mm^3, Diff count - / - / 3 / 55 / 39 / 3 , PCV 35.8% , Trombosit 33.000/mm3, albumin 3.4 mg/dl, total protein 6.2 mg/dl, SGOT 67 U/L, SGPT 72 U/L, and also Ig M and IgG anti dengue showed positive result. Physiologic coagulasion showed that PPT 12,1(C=13,9), KPPT 25,7. Assesment showed DHF with brain edema. Therapy: Infus ringer acetat 2000 cc and HES 500 cc/ 24 hours, methylprednisolon 3 × 125 mg (the 2nd day), Fenitoin maintenance 3 × 100 mg.

On the third day in Dr. Soetomo hospital the clinical manifestation of this case as following: There was no fever found and complaining of chemical manifestation was becoming decrease. There was no spasms and bleeding. Tension 110/70 mmHg, pulse 88×/minutes, RR 20×/minutes, temperature 37°C. Laboratory result showed Hb 12.6 g%, Leukocytes 5.500/mm^3, trombosit 149.000/mm^3, PCV 36.9%, LED 15-30/jam. The assesment showed as a case of DHF with brain edema. The treatment was to continue given methylprednisolon 3 × 125 mg until 3 days and together with other drug

On the fourth day in Dr. Soetomo hospital hospital the clinical manifestation of this case as following: The patient could not defaecates for 3 days, but no fever, bleeding, or spasms. Tension 110/70 mmHg, pulse 64×/mnt, RR 18×/mnt, temperature 36,8°C. Meteorism occured with

normal noisy intestine. Laboratory showed Hb 11,7 g%, luekocytes 10.800/mm^3, trombosit 201.000/mm3, PCV 36.7%. Assesment showed constant and antasida 3 ×1 tablespoon, ranitidine 2 × 1 ampoule, multivitamin 2 ×1 tablet had been given, the condition of care more better.

On the fifth day in Dr. Soetomo hospital the clinical manifestation of this case as following: There was no complain. General condition is good. Stabil sign vital. Hb 12 g%, leukocytes 8.720.000/mm^3, trombosit 317.000/mm^3. Repeated breast x-ray showed no pleura effusion and the patient permitted to go home after the doctor control and the result better health.

DISCUSSION

Dengue viral is infection a single stranded RNA that was the family of flaviviridae and consists of 4 serotipe (den-1, den-2, den-3, den-4).This viral rod-shaped, spatially termolabil, sensitive to inactivasion by dietileter and sodium dioksikolat, stable at a temperature of 70°C. Fourth serotipe the viral has been found on patients in Indonesia where den-3 serotipe is the dominant and has to do with cases heavy when this incredible happenings or outbrench of dengue viral infection.[3,4,6]

The length of the genome of dengue viral about the planning. The virions mature have three protein structure (core, associated membrane, envelope), and 7 (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). Principal biological function of these viruses associated with the envelope. It said that these proteins to bind with a receptor on a cell host and allowing the past. The envelope this is also related with the hemaglutinasion to erythrocytes, inducing an antibody netralising and who were protective immune response.

Principal of dengue vector in Indonesia is the Aedes aegypti, and Aedes albopictus, aedes albopictus. The nest of vector is found in clearly water and as in the bathtube, drum chicken collectors water, canned the former, etc. The data DHF have been found in every province in indonesia and 200 city has been reported outbreak of Dengue Viral Infection.[6]

There are many clinical spectrum of Dengue Infection forms. The differences of degree severity of clinical manifestation of DHF case it might be due to underlying pathophysiology of disease.[6,7]

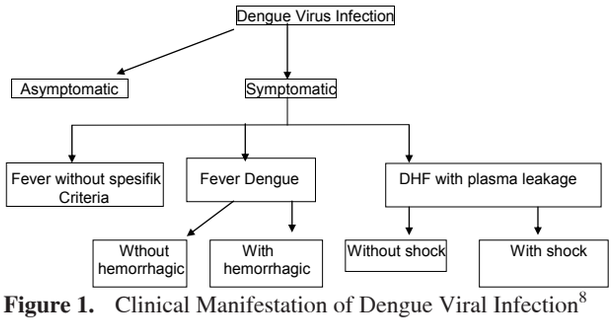

Figure 1. Clinical Manifestation of Dengue Viral Infection[8]

Clinical Criteria:
1. Fever (suddenly high temperature for 2–7 days)
2. Manifestation of bleeding (Tourniquet test which is positive, petekie, purpura, ekimosis, epistaksis, gum bleeding, hematemesis or melena, hematuria)
3. Enlargement of liver
4. Shock, with high pulse and low and decrease tension, hypotension, foot and hand moist skin, with restless case.

Laboratory Criteria
1. Trombocytopenia (total trombosit 100.000/mm^3 or less)
2. Hemoconcentration (decrease hematokrit 20% or more)

The diagnosis of DHF in this case based on the two clinical criteria and supported by thrombocytopenia and hemoconcentration. The presence an effusion of pleura and or hipoalbuminemia can strengthen the diagnosis.[6] DHF diagnosis should be identified by laboratory test of IgM and IgG anti dengue or ELISA method of dengue based on the severity of dengue viral infection.[8]

Table 1. The Severity of Dengue Viral Infection[8]

Grade	Symptoms
Grade I (lighter)	Suddenly fever (2-7 days) Non specific constitunal symptoms Bleeding manifestation on only if positive in tourniquet test
Grade II (medium)	Same as level I Spontan bleeding
Grade III	Circulation failed/sign of early schock (pulse fast and low, tension decrease (20 mmHg or less), hypotension, cyanosis around mouth, skin cold and moist
Grade IV	Shock (tension and pulse can not feel)

This patient showed symptoms of muscular pains and manifestation bleeding form of a positive Rumple Leede, and obtained thrombocytopenia (83.000/mm^3). The right lung of pleural effusion was improving of plasma leakage, so the diagnosed was DHF. It said that besides serotipe and virulence viral; other factors that influence the clinical manifestation DHF was age, sex, immune status and the background host. Guzman *et al* said that a severity hospitalized cases DHF/DSS the highest were found in group of babies and elderly, if these cases got secondary infection due serotipe den-2 it could cause a risk of mortality 15 times in children than adults. DHF had been reported more severity of women malnutrition

Retrospective Research of 152 DHT cases that hospitalized in RSCM-Jakarta. Acquired image clinical most prominent form of hyperpyrexia, change of consciousness and convulsions. Examination laboratory showed, there were increased serum transaminase, hiponatremia and hypoxia. A neurological disorder in form of hemiparese, tetraparese and atrophy nervus the second.[9] This event were followed by Malaysia, reported the manifestation symptoms of weakness instrument motion and decline sensory on either side and bleeding the brain. There were also manifestation neurological form as stiff of the neck and seizure general in children supposedly caused by increased pressure intrakranial. The act of lumbar puncture (LP) have been done to exclusion possibility meningitis or ensephalitis. The result showed the all of the cases recovered perfect and leave no bad symptoms occured.[10]

In Singapore ever reported a sufferers dengue virus infection with a complication CNS disorder with manifestation of amnesia; obtained the result PCR and serologis a positive and results MRI brain disorder showing the hippocampus.[11]

In Thailand reported incidents encephalopathy related DHF about 34 the case of 1.465 cases DHF that hospitalized at the pediatrics RS Petchabun for 3 years (2.3%). Acquired 30 cases fall into encephalopathy during the shock 4 in while in the healing. Factors the risk for the encephalopathy among other: shock conflict, bleeding gastroduodenal that profuse, impaired function severe heart and granting liquid excessive.[12]

In south Vietnam the studies against 378 sufferers suspected infection exposed to the CNS; infection acquired incident CNS just because dengue viral as many as 4.2%. Of the ED the 7 people exposed infection primary and 13 people exposed secondary infection. Acquired isolation virus (PCR positive) on 10 sufferers while 3 patients of indicates the presence of antibodies in liquid his mind. Manifestation main CNS disorder of patients was in form of impairment of consciousness and convulsions.[13]

Research of case-control and prospective study on the intensive pediatrics hospital in Ho Chi Minh showed that the patients ED got an increase a liver enzyme and bilirubin with a significant result and one case produce PCR-RNA virus DEN-3 from a liquid the brain, 14 cases showed a positive result of IgM anti DHF and the majority MRI showed edema of the brain.[5]

Patient with manifestation CNS disorder in form of spasm. She does not obtain bleeding gastroduodenal, disorder electrolyte, shock and granting liquid glasses. Results CT-scan of head showed an barin edema.

Immunopathogenesis DHF and DSS still controversial. The first theory which was professed was hypothesis secondary of heterologous infection or antibody-dependent enhancement.[14] It said that if someone sinus infection for the second time with divergent (heterologous) serotipe dengue viral, it will happen cross reaction between antibodies serotipe viral from infection with the viral formerly without neutralization through the process so that the viral could enter the monocytes. The number of monocytes and t-cell infected was increase, it was describing increasing of antigens, frequency dengue viral - t cells and activation and proliferation t memory. T cells also produces sitokins as IFN-γ, IL-2 dan TNFα and also lysis of monocytes that infected dengue viral. The complement will be enabled by complex antigen-antibody by sitokins so that the discharge occurs c3a and c5a, which directly affect the permeability vascular. The synergistic effect of IFN-γ, TNF-α and complement who switched to would cause the occurrence of plasma leakage from the endothelial cells.[6,7,15]

Dengue hemorrhagic fever can be stimulated a transcription and to secretions RANTES and IL-8, the establishment of an antibody hemorrhagic fever and the establishment of the complement non-lysis complex. Dengue viral infection in endothelial cells in vitro can cause the occurrence of pothogenesis. It has been said that the complement, who switched to chemokin and mediate apoptosis causing the occurrence of leakage plasma membrane.[16]

A second hypothesis that the dengue virus could change genetic as resulting from pressure during a replication of the viral in human body and mosquitoes. A phenotype in a genome is a replication of the viral and could cause the viremia, increase and it is potential to cause virulence of the plague. It says that there the manifestations, and the DSS is probably caused by a variant of dengue viral that has a different degree virulence. The epidemic in southeast Asia support this hypothesis. It was reported that the risks may - in Thailand DSS regarding the DEN-2. Philippine DEN-3 role in the outbreak in Indonesia den-3 a type virus existing related with severe cases presently occurring outbrench of dengue virus infection.[6,15]

Typical patofisiologi of dengue fever is the leakage of plasma and disorder hemostasis. The data prove the existence of a leak plasma namely the increase in the hematokrit, an effusion of the pleural and ascites, hipoproteinemia and decrease in volume plasma. Lost plasma that weight can cause the occurrence of shock hypovolemia and death. Hemostasis an abnormality that occurs because by 3 the main factor of change namely: vascular, thrombocytopenia, and coagulopati. Dissaminated intravascular coagulation (DIC) can happen and cause bleeding great.[7,17]

Pathogenesis the occurrence of encephalopathy hemorrhagic fever was still not clear. Some research in Indonesia Thailand and other Asian countries get that an abnormality of the CNS occurs in DHF prolonged with or without the occurrence of shock. The hemorrhage brain is not caused directly by a virus that may be pierced Blood Brain Barrier (BBB). Gathered evidence in the form of the virus den-3 isolation from a liquid the brain on 4 cases, from 6 the remaining positive result PCR.[18]

Imbert et al, 1994. stated that dengue viral which have the ability to infect broad neurons mice in vitro, viruses like has a specific receptor on the surface of neurons.[19] Chaturvedi et al found BBB damaged during infection dengue (den-2) so happen leakage protein to the brain.

Gubler et al suspected the genetic variation or due to changes in biological virus and also strains some viral.[18]

Lum LC et al, 1996 reported that many factors who caused the encephalopathy among other: impaired function heart, disorder electrolyte, edema cerebri (caused by changes permeability vascular so extravasation a liquid); hipoperfusi (resulting from disruption circulation) and encephalitis week.[20] In some patients encephalitis this obtained isolation virus from a liquid the brain.[21]

Abnormality CNS on DF/DHF formerly thought due to nodular that causes penetrated BBB. The cognitive deficit is more because encephalopathy than encephalitis. Although the MRI by contrast show bbb who was whole, but partly expert confident that encephalitis caused by invasion virus directly to the brain through BBB, while other writers postulates that due to the occurrence of encephalitis process imunopatologis.[11]

Due to an immune response that rises rapidly, difficult to get the isolation virus den a positive on blood sufferers. All the case indicating the presence of antibodies with titer high when examined. So clinical manifestation sufferers and the levels hi antibodies against flavivius, IgM anti dengue a positive and neutralization a positive test had been considered that the virus as a cause.[21]Based on patient who was 2 years old had gotten DHF, so it was really possible as the secondary heterologous infection. The ultimate principle management DBD aims to replace the liquid plasma during a period of leakage active in 24-48 the first hour because at that period would cause the occurrence of shock, anoxia, acidosis, and death. Antipyretic can be given during phase of heat, avoid the use of aspirin. The critical period happen when a transition from phase of heat into free heat that can be started on the third day. A liquid used as a substitute for plasma shall spatially isotonic having the content of the electrolyte similar to plasma.[3,6,17]

On ED consciousness patient decreased to become on somnolen, it could accompanied by seizure. ED can happen to DBD/SSD. When patients shock,it will be found impairment of consciousness, and to ensure the ED shock to be overcome first. The act of lumbar punction (LP) done when shock has handled awareness but still declining (careful when platelets <50,000). On ED could be found elevated levels of transaminase (SGOT/SGPT), PPT & KPTT elongated, their blood sugar decline alkalosis on analysis gas blood, and hiponatremia.[6]

ED is one of complication DHF, its treatment more complicated. Several points that should undertaken in management ED[3]:

1. Replacement no liquid given in doses full, but fairly given 4/3 to 4 5/dose to prevent or make it worse edema brain during phase recovery shock
2. Wearing a liquid crystalloids ringer acetic to avoid metabolism lactate in liver, when accompanied by impaired liver
3. A corticosteroid administered to reduce edema the brain, but is contra indication on DSS with hemorrhage massive.

On encephalopathy likely edema the brain and alkalosis, therefore when shock has handled, liquid replaced with a liquid containing no hco3- and the amount of fluid must be reduced. Prevent increased pressure an extern cranial by reducing the amount of fluid (when necessary with a diuretic), correction asidois and disorders electrolytes. Try not giving drugs that not needed to reduce the burden detoxification medicine in heart. Transfusion of blood fresh or components can be given over indications proper.[6]

Main therapy with this replacement liquid to crystalloid and had given colloidal. Ringer acetat was chosen because obtained increase transaminase, given 2 quarts in and colloidal (HES) 500 cc within 24 hours. methyl prednisolon 3 × 125 mg was given for 3 days, associated with edema cerebri. There was no shock; disorder diuresis, disorder electrolyte and lengthening faal hemostasis.

A patient DBD could be discharged after to meet the criteria of clinical improvement, no fever for 24 hours), (without antipyretic cannot be found distress the breath (because effusion of the pleura or acidosis), hematocrit stable, the number of platelets tending to rise (> 50.000), three days after shock handled, and has been improving appetite.[6] The patient was discharged after fulfill the criteria of those mentioned above. When a repeat photograph thoracic legs already does not obtain again an image of an effusion of plura.

SUMMARY

It has been reported a young teenage with DHF followed by seizure. Evidences that supporting plasma leakage as hallmark of DHF are pleural effusion and cerebral edema. Seizure most likely due to dengue encephalopathy associated with cerebral edema and strengthen by positive IgG and IgM anti dengue. Corticosteroid was given to improve cerebral edema. By good management as long as admission, she was discharged from hospital with good condition.

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Research Report

UPDATE MANAGEMENT CONCURRENT INFECTION BETWEEN DENGUE VIRAL AND SALMONELLA

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ABSTRACT

Since Januari 2013, Soerya Hospital has found many cases with positive result of IgM Salmonella along with NS1 or IgM & IgG Dengue. The clinical manifestations mostly are high fever, headache, vomiting, malaise and plasma leakage. Some of them with convulsion and unconsciousness. Therefore in order to get well of care management, this clinical phenomena should be studied carefully. The aim of this research is to get update management concurent Dengue Viral and Salmonella infection. Observational study had been done, since Januari 2013 until Juli 2013. Purposive sampling in 30 case of concurent Dengue Viral and Salmonella infection compared with 30 case of Dengue Viral infection alone. Diagnosis has published based on WHO 2011 criteria. By using anti vomiting drug, anti pyretic, anti convulsion and antibiotic for Salmonella infection and rehidration using Ringer Acetate, combining Ringer Asetat and Dextrose 5% or combining Ringer Asetat Saline 0,225% or solution of Dextrose 5% and Saline 0,45 during 4–5 days hospitalization. The result show that all cases were recovered and got well. There is no significant different between concurent Dengue Viral and Salmonella infection compared with Dengue Viral infection alone. Some cases showed that length time to stay in hospital become 1–2 days longer. It was due to delayed getting antibiotic for Salmonella infection. All cases had got first drugs accurately in a clinical manifestation that has been daily showed. It was as a problem solving for saving all the cases.

Key words: concurrent infection, dengue viral infection, Salmonella infection, care, NS1

ABSTRAK

Sejak Januari 2013, Rumah Sakit Soerya menemukan banyak kasus pasien positif IgM Salmonella dengan NS1 atau IgM & IgG Dengue. Manifestasi klinis yang tampak ialah demam tinggi, pusing, mual, tidak enak badan, dan pecahnya plasma. Beberapa di antara mereka ada yang mengalami gangguan hebat dan ada yang tidak. Oleh karena itu untuk mendapatkan perawatan yang baik maka fenomena ini perlu dipelajari dengan teliti. Tujuan dari penelitian ini ialah untuk mendapatkan pembaharuan manajemen virus dengue dan infeksi Salmonella. Observasi telah dilakukan sejak Januari 2013 hingga Juli 2013. Sampel purposive pada 30 kasus virus Dengue dan infeksi Salmonella yang dibandingkan dengan 30 kasus infeksi virus dengue saja. Diagnosa telah dipublikasikan oleh criteria WHO tahun 2011. Menggunakan obat anti mual, anti penurun suhu tubuh, anti konvulsi (tidak enak badan), dan antibiotic untuk infeksi salmonella dan rehidrasi menggunakan Ringer Asetat Saline 0,225% atau larutan Dextrose 5% dan Saline 0,45 selama 4–5 hari di rumah sakit. Hasil penelitian menunjukkan bahwa semua kasus akan dipulihkan dan sembuh. Tidak ada perbedaan yang signifikan antara virus dengue dan infeksi salmonella yang dibandingkan dengan infeksi virus dengue saja. Beberapa kasus menunjukkan bahwa waktu untuk di rumah sakit menjadi 1–2 hari lebih lama. Hal itu akan tertunda jika mengkonsumsi antibiotic untuk infeksi salmonella. Semua kasus telah mendapatkan obat pertama pada manifestasi klinik yang mana ditunjukkan sehari-hari. Hal tersebut merupakan solusi untuk semua kasus.

Kata kunci: *infeksi konkuren, infeksi viral dengue, infeksi Salmonella, perawatan, NS1*

INTRODUCTION

On 2013 there are many cases dengue viral concurrent with Salmonella infection. Some of them showed a duration of clinical manifestation more longer than usual (see Fig. 2 and 3).

Why this event occur, it might be due to late coming as the second infection occur. Before discussing this event, we want to discussed a natural cause of Dengue Viral Infection and Salmonella infection.

Dengue Viral Infection are usually shown a clinical manifestation of fever as saddle back phenomena and followed by vomiting attack and headache.[1,2,3,4]

Salmonella infection as usually shown the duration of infection need more time until four weeks, if the patient don't get early antibiotic for bacterial of Salmonella, patient showed clinical manifestation of gastritis, abdominal pain and concurrent with vomiting.

In the past one decade, coincident cases rare to be concern by pediatrics, but in 2013 at Soerya Hospital has found more than 100 cases in 1 year. We thought why these case could happen and getting many more, these are the global changes season and population changes. In early rainy season, we found that DVI cases was increased in order to summer season. When the rainy season prolonged, it could cause many problem in environment such as worsening hygiene individu and environment, it could cause increased salmonella infection cases. That's why many cases coincident DVI and Salmonella infection.

MATERIALS AND METHODS

Observational study had been done, since Januari 2013 until Juli 2013. Purposive sampling in 30 case of concurent Dengue Viral and Salmonella infection compared with 30 case of Dengue Viral infection alone. Diagnosis has published based on WHO 2011 criteria.

THE RESULT

Clinical manifestation of DVI patients including:[1,2,3,4,5]

a. Fever: acute onset, high and continuous, lasting 2–7 days in most cases
b. Any of the following haemorrhagic manifestations including a positive tourniquet test (the most common), petechiae, purpura (at venepuncture sites), ecchymosis, epistaxis, gum bleeding and haematemesis and or melena
c. Enlargement of the liver (hepatomegaly) is observed at some stage of the illness in 90–98%
d. Shock, manifested by tachycardia, poor tissue perfusion with weak pulse and narrowed pulse pressure (20 mmHg or less) or hypotension with the presence of cold, clammy skin and or restlessness.

Clinical manifestation of Concurrent DVI with Salmonella infection patients including:

a. Fever
b. Nausea
c. Vomitting
d. Diarrhea and abdominal pain
e. Epistaksis

These are clinical manifestations from 30 patients that we were observed in Soerya Hospital and 30 patients concurrent DVI with Salmonella infection.

Table 1. Clinical Manifestation DVI patients and Concurrent DVI with Salmonella infection.

SYMPTOMS	DVI patients	**DVI + Salmonella infection**
Fever	100%	100%
Nausea	62%	83%
Vomitting	40%	63%
Diarrhea	6%	20%
Abdominal pain	36%	73%
Epistaksis	2%	-

By using anti vomiting drug, anti pyretic, anti convulsion and antibiotic for Salmonella infection and rehidration using Ringer Acetate, combining Ringer Asetat and Dextrose 5% or combining Ringer Asetat Saline 0,225% or solution of Dextrose 5% and Saline 0,45 during 4-5 days hospitalization. The result show that all cases were recovered and got well. There is no significant different between concurent Dengue Viral and Salmonella infection compared with Dengue Viral infection alone. Some cases showed that length time to stay in hospital become 1–2 days longer. It was due to delayed getting antibiotic for Salmonella infection.

DISCUSSION

Concurrent infection of Dengue Viral Infection (DVI) and Salmonella in children. It is 2 kind of diseases that infect a child in a same time. How to know that these cases were caused by 2 agents (viral and bacteria), is we did anamnese, examined these patients and we used laboratory test (NS1 and IgM Salmonella) to support our diagnosa.

It is very difficult for us to know whether DVI or salmonella infection that first infect to these children. We might try to study by identifying the agents that correlate with symptoms.

We had analysed that concurrent DVI and Salmonella infections patients may stay longer in the hospital, than patient with single infection, especially if they came late to the hospital.

There are the figure of length of stay patients with Dengue Viral Infection (DVI) compared with concurrent DVI and Salmonella infection.

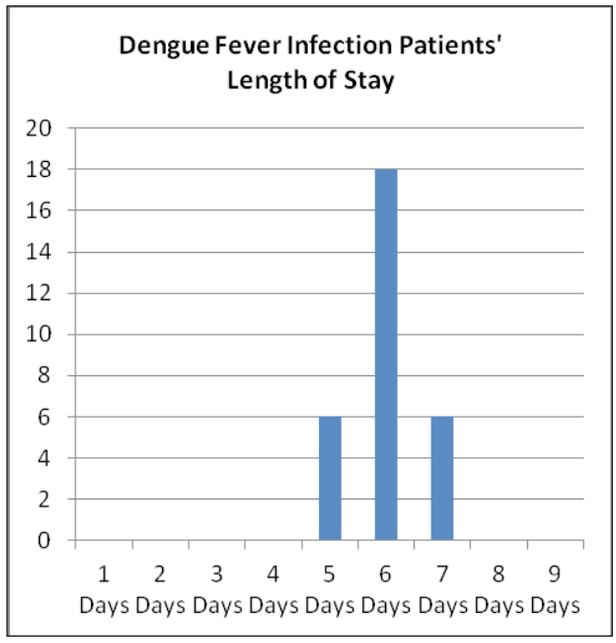

Figure 1. Length of Stay DVI Patients.

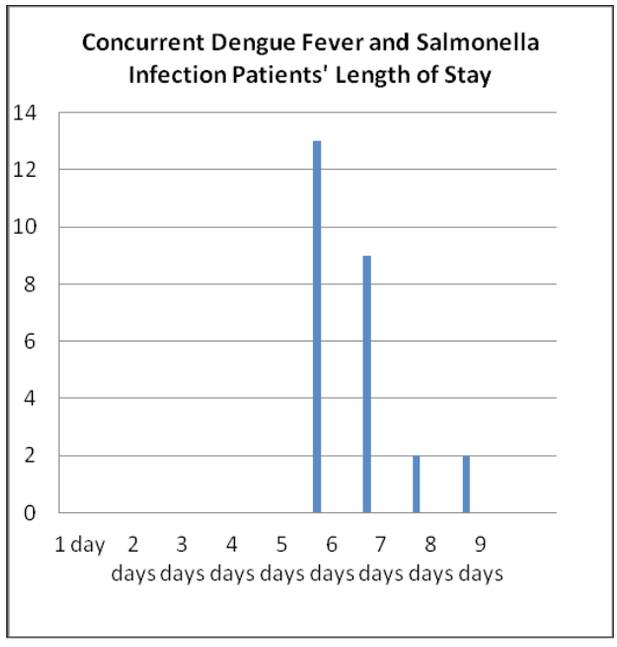

Figure 2. Length of Stay Concurrent DVI and Salmonella Infection Patients.

From the figure 1 and 2 we know that patients with NS1 positive, stayed 5–6 days in the hospital. But the patients with concurrent DVI and Salmonella infection might stay longer (7–9 days) in the hospital. But in average they stayed for about 6 days in the hospital because we could diagnose the disease early and give therapy to them.

PROBLEM SOLVING

We try to study which one disease come first by doing observational study about clinical manifestation and symptom that occur,[5,6,7] these are:

1. High fever (high fever curve)
   From the curve, we know that there was a different fever pattern of DVI patient and Concurrent Infection patients. DVI patients had a high fever in early day they admitted in the hospital, and then slowly go down in couple days.[7] Concurrent DVI and Salmonella infection had an irregular fever pattern.
2. Vomitting
3. Nausea
4. Abdominal pain
5. Diarrhea
6. Epistaksis

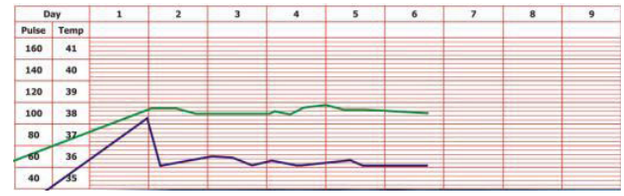

Figure 3. Body's temperature of DVI patients (purple line) and heart rate (green line).

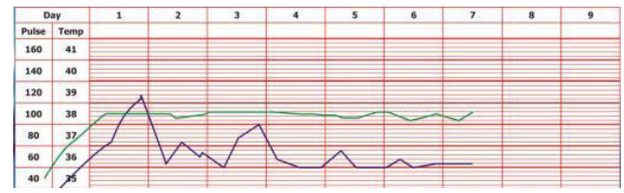

Figure 4. Body's temperature of concurrent DVI and Salmonella infection patients (purple line) and heart rate (green line).

TREATMENT

We use some drugs to these patients, such as:

1. Crystalloid fluid
   We had use Ringer Acetate as a resuscitation fluid, because of its metabolism in muscle, not in liver so that it will not aggravate liver function.[8]
2. Metoclopramide or Ondansentron
   To solved the clinical manifestation of vomiting due to gastritis that can be given by oral or intravenous.

Based on the problem that had been ocur in concurent infection dengue virus and salmonella. The patient should be care in the hospital by giving infusion base on the age and body weight of cases, such as:

1. Anti pyretic drop, per drop dossage 4-8 hours for high fever.

2. Anti convulsing drop such as dilantin, dossage is 5 mg/kgBB/24 hours giving per drip.
3. Some cases who showed frequently vomiting try to give anti vomiting by drip per infussion such as ondancetron.

Beside this event, many cases showed plasma leakaged with could be identified by increasing hematocrit and decreasing trombocyte. The patient look pale of the face, foot and hands feel cold, high rate pulse of hand.[5,6] For this case should be using cristaloid solution. Such ringer acetat, phisiology sollution in 1–2 hours. If the condition of case still worse, give colloid solution. If the patient show bleeding such epistaxis, haematemesis or melena, please give blood transfusion from their own blood family transfusion.[5,6,7,8]

Please awarness using ringer lactat could cause liver damage, so please choose ringer acetate, because ringer lactat metabolism in liver can make trouble of liver physiology and induce DIC. But if we use ringer acetat that metabolism in muscle.

CONCLUSION

All cases had got first drugs accurately in a clinical manifestation that has been daily showed. It was as a problem solving for saving all the cases.

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