Endokarditis Infektif pada Laki-laki Berusia 60 Tahun di RSUP Dr. Kariadi Semarang

Infective Endocarditis in 60 Years Old Man at Dr. Kariadi Hospital

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Abstrak

Endokarditis infektif merupakan infeksi pada lapisan jantung, terutama pada puncak dari katup jantung yang ditandai oleh demam dan bising jantung, dengan ataupun tanpa rasa lelah. Secara klinis dapat dibagi menjadi infeksi tahap awal, fase embolik, dan komplikasi lanjut akibat sepsis dan inflamasi. Gambaran kasus seorang laki-laki berusia 60 tahun dibawa ke RSUP Dr Kariadi dengan keluhan utama demam yang berlangsung kurang lebih 2 bulan. Demam disertai penurunan berat badan 3 kilogram selama 2 bulan. Dari pemeriksaan fisik didapatkan penampilan tampak sakit sedang. Bising sistolik di area katup triskupidal, sedangkan suara paru normal. Hasil positif koloni Streptococcus β haemolyticus dari kultur darah dari 3 sisi lengan yang berbeda dengan jeda 30 menit setiap tempat dan swab tenggorok. Hasil ASTO, *Echocardiography* dan pemeriksaan fisik menunjukkan tanda endokarditis infektif. Terapi yang diberikan Ceftriaxone 2 gram per hari. Setelah hasil kultur negatif dan ada perbaikan klinis, pasien dirawat jalan dengan program tetap mendapatkan Ceftriaxone 2 gram per hari untuk 4 minggu. Diskusi keputusan pengobatan berdasarkan manifestasi klinik dan pemeriksaan mikrobiologi yang dilakaukan pada saat masuk ke instalasi gawat darurat. Kultur darah menggunakan 3 botol kultur yang diberi jarak 30 menit pada setiap tempat pengambilan merupakan prosedur yang penting untuk endokarditis infektif. Lebih lanjut swab tenggorok juga dilakukan untuk konfirmasi endokarditis. Pada akhirnya kultur menunjukkan tidak ada pertumbuhan setelah hari ke delapan perawatan. Kesimpulan metode kultur darah yang spesifik merupakan hal penting untuk diagnosa endokarditis infekstif dan sangat membantu klinisi dalam manajmen perawatan. Pada akhirnya peran spesialis mikrobiologi klinik tidak hanya membantu diagnosa namun pada pengobatan dalam hal pemilihan antibiotik yang tepat sesuai klinis penderita.

Kata kunci : endokarditis infektif, Streptococcus β haemolyticus, kultur darah, pemakaian antibiotik yang tepat

ABSTRACT

Infective endocarditis is an infection of the lining of the heart, particularly the cusps of valves characterized by fever and heart murmur, with or without malaise and fatigue. Clinical features can be divided into early manifestations of infection, embolic events, and late complications of sepsis and inflammation. It was reported that 60 years old man was brought to Kariadi hospital with prolong febris as his chief complaint. Patient has history of high grade fever and accompanied by weight loss, 3 kilograms for about 2 months. From physical examination result, in internal ward, we found he looked moderate ill. Heart systolic bruit at triscupidal valve and lungs were within normal limit. The result of blood culture from 3 different sites and throat swab culture were possitive, lead to the performance Streptococcus β haemolyticus's colonies. From the result of the ASTO, Echocardiography and physical examination show infective endocarditis's sign. The theraphy was Ceftriaxone 2 gram daily. Having obtained the results of negative cultures, and show an improvement of symptoms, finally the patient was getting improvement clinically and then treat as an outpatient. Patient was programmed to get Ceftriaxone 2 gram daily for 4 weeks. The decision of treatment not only from clinical manifestation but also from microbiology examination on the first admission in emergency unit. Blood culture with 3 bottles, interval 30 minutes is important for infective endocarditis. Furthermore, swab of throat area were taken to confirm for endocarditis cultures too. Finally there is no growth in culture until eighth day hospitalizasition. Spesific method on blood culture sampling is important to confirm the diagnostic of infective endocarditis and very useful for the clinicians to do the right clinical management for it. Subsequently, the role of clinical microbiologist in this case not only to support the clinical diagnostic but also the treatment in term of selecting of right antibiotic.

Keyword*: infective endocarditis, Streptococcus β haemolyticus, blood culture, right antibiotic*

CASE REPORT

The case reported 60-years old man hospitalized since July 3th 2012 until July 11th 2012. His main complaint was prolong febris. Since 2 months before hospitalization he was observed fever in general practitioner's clinic and was treated for about 2 weeks in the local hospital hospital, 2 months, the man suffered from fever, high-grade fever, no seizure, no shivering, cough (-), disphagia (-), no discharge from ears, no nose bleeding, no gums bleeding but there was a dental carries at superior left pre molar, no ptechie, no nausea, no vomite, no gastrointestinal and urinary tract complaints. He was got to physician and given some medicine. Two weeks in hospitalization, the man was still fever, given treatment but no improving. After that he refer to Kariadi's hospital. Accompanied by weight loss, 3 kilograms in 2 months. These were loss of appetite, without nausea, and no vomiting. Body image looked underweight. No convulsion and no complaint both in urination and defecation. From

physical examination in emergency room and internal ward, found he looked moderate ill. Heart systolic bruit at triscupidal valve and lungs were within normal limit. The result of throat swab culture was positive with Streptococcus β haemolyticus. So do blood agar cultures from 3 different sites lead to the performance Streptococcus β haemolyticus's colonies. He was hospitalized in internal ward in C3L2.

He lived in urban area in Semarang. There were no data about the same infections in his family and community. He is a manual labour with average income is ± Rp 1.000.000,-/month. Health cost was covered by Jamkesmas. Social economic impression is poor.

From physical examination, a 60-year old man, GCS 15: E4M6V5. The blood pressure was 130/80 mmHg; respiration rate 20 times per minute; pulse rate 100 times per minute, regular and with sufficient pressure; body temperature was 40°C (rectal). Body image looked underweight. Eye with conjungtiva palpebrae not pale; sclera was not icteric. Pupils were equal (Ø 2mm) and reactive to light stimulation. Mouth, there was no stomatitis. No lymph node enlargement at neck regio, normal JVP, no tracheal deviation, no stiff neck. Ear: discharge (-), nose: bleeding (-). Chest: no spider nevi, no muscles atrophy, no gynecomastia, no axillary lymph node enlargement, and no intercostals retraction. Heart systolic bruit at triscupidal valve and lungs were within normal limit. Liver and spleen were unpalpable.

Laboratory examinations during hospitalization were Hb11,2 gr/%l, Ht 33,4%, leucocyte 11.600/ mmk, activated lymphocyte, erythrocyte 4,06jt/ mmk, thrombocyte 117.000/ mmk. Ureum 33 mg/ dl, Creatinine 0,94 mg/dl, albumin 2,7 mg/dl, ASTO positive, CRP 3,21 mg/dl.

Echocardiography found vegetation in triscupidal valve, it suggest an infection track was occured there. In ward patient received nasal oxygen 2 l/minute, RL infusion 30 drops per minute, Ceftriaxone injection 2 grams i.v two times daily, paracetamol 500 mg if necessary, and vitamin B complex three times daily.

There was no change at physical examination, but on July 10th 2012 temperature 37,3°C. Patient was finally went back home on July 11th 2012. He was programmed to get Ceftriaxone 2 grams daily for 4 weeks at outpatient clinic.

DISCUSSION

Etiology

Many bacterias can be etiology of infective endocarditis. *Streptococcus viridians, Enterococcus faecalis, Enterococcus faecium, Enterococcus durans, Staphylococcus aureus, Staphylococcus lugalunensis, Haemopphilus parainfluenza, Haemophilus ophrophilus, Haemophilus paraphrophilus, Haemophilus influenza, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingela kingae, Kingela denitrificans* (HACEK group) (Baddour *et al.,* 2007). In this case, swab staining and blood culture were positive for Streptococcus β haemolyticus and the patient was diagnosed with infective endocarditis.

Pathology of *Streptococcus* β *haemolyticus*

Streptococcus β *haemolyticus* is a member of group A streptococci. Typically appear in purulent lesions or broth cultures as spherical or ovoid cells in chains of short to medium length (4 to 10 cells). On blood agar plates, colonies are usually compact, small, and surrounded by a 2 to 3 mm zone of hemolysis that is easily seen and sharply demarcated hemolysis is caused by either of two hemolysins, streptolysin S and the oxygen labile streptolysin O, both of which are produced by most group A strains. Strains that lack streptolysin S are hemolytic only under anaerobic conditions, because the remaining streptolysin O is not active in the presence of oxygen. This feature is of practical importance, because such strains would be missed if cultures were incubated only aerobically (Ryan, 2004; Forbes *et al.*, 2007; Brooks *et al.,* 2006).

Structure

The cell wall is built on a peptidoglycan matrix that provides rigidity, as in other Gram-positive bacteria. Within this matrix lies the group carbohydrate antigen, which by definition is present in all group A Streptococci. A number of other molecules such as M protein and lipoteichoic acid (LTA) are attached to the cell wall but extend beyond often in association with the hair-like pili. Group A streptococci are divided into more than 80 serotypes based on antigenic differences in the M protein. Some strains have an overlying nonantigenic hyaluronic acid capsule (Forbes *et al.,* 2007; Fischetti and Ryan, 2009).

M Protein

The M protein itself is a fibrillar coiled-coil molecule with structural homology to myosin. Its carboxy terminus is rooted in the peptidoglycan of the cell wall, and the amino-terminal regions extend out from the surface. The specificity of the more than 80 serotypes of M protein is determined by variations in the amino sequence of the aminoterminal portion of the molecule. Because of its location, this part of the M protein is also the most available to immune surveillance. The middle part of the molecule is less variable, and some carboxy terminal regions are conserved across

many M types. There is increasing evidence that some the many known biologic functions of M protein can be assigned to specific domains of the molecule. This includes both antigenicity and the capacity to bind other molecules such as fibrinogen, serum factor H, and immunoglobulins (Fischetti and Ryan, 2009).

Other Surface Molecules

A number of surface proteins have been described on the basis of their similarity with M protein or some unique binding capacity. Of these, a fibronectin binding **protein F** and **LTA** are both exposed on the streptococcal surface and may have a role in pathogenesis.

An IgG binding protein has the capacity to bind the Fc portion of antibodies in much the same way as staphylococcal protein A. In principle, this could interfere with opsonization by creating a covering of antibody molecules on the streptococcal surface that are facing the wrong way. Group A streptococci may have a **hyaluronic acid capsule,** which is a polymer containing repeating units of glucuronic acid and N-acetylglucosamine (Forbes *et al.,* 2007; Fischetti and Ryan, 2009).

Biologically active extracellular products
Streptolysin O

Streptolysin O is a general cytotoxin, lysing leukocytes, tissue cells, and platelets. The toxin inserts directly into the cell membrane of host cells, forming transmembrane pores in a manner similar to complement and staphylococcal toxin. Streptolysin O is antigenic and the quantitation of antibodies against it is the basis of a standard serologic test called antistreptolysin O (ASTO) (Forbes et al., 2007; Fischetti and Ryan, 2009).

In this case, laboratory result ASTO as the sign for **streptolysin O** which positive for Streptococcus β haemolyticus.

Pyrogenic Exotoxins

The manifestations of classical scarlet fever have long been associated with the action of an erythrogenic toxin. This toxin is now included in a family of nine proteins called streptococcal pyrogenic exotoxins (SPEs), one of which is produced by approximately 10% of group A streptococci. The SPEs are identified by letters (eg, A, B, C) and are similar in structure and biological activity to the pyrogenic exotoxins produced by Staphylococcus aureus. They have multiple effects including fever, rash (scarlet fever), T-cell proliferation, B-lymphocyte suppression, and heightened sensitivity to endotoxin. At least some of these actions are due to cytokine release through the superantigen mechanism. SPE-B also has enzymatic activity cleaving elements of the extracellular matrix, including fibronectin and vitronectin (Forbes *et al.*, 2007).

Other Extracellular Products

Most strains of group A streptococci produce a number of other extracellular products including streptokinase, hyaluronidase, nucleases, and a C5a peptidase. The C5a peptidase is an enzyme that degrades complement component C5a, the main factor that attracts phagocytes to sites of complement deposition. The enzymatic actions of the others likely play some role in tissue injury or spread, but no specific roles have been defined. Some are antigenic and have been the basis of serologic tests. Streptokinase causes lysis of fibrin clots through conversion of plasminogen in normal plasma to the protease plasmin (Brooks *et al.,* 2006).

Pathology of infective endocarditis

The term endocarditis or Infective endocarditis (IE) describes infection of the lining of the heart, particularly the cusps of valves (Karchmer, 2006). Infective endocarditis (IE) is caused by microorganisms adhising to and multiplying on the innermost aspect of the chamber of the heart and its valves (the endocardium). Infections often involve an abnormal heart valve such as one previously damaged by rheumatic fever, athisosclerotic plaques, or a prosthetic (artificial) valve. Less frequently, infection occurs at the site of congenital cardiac abnormalities such as a septal defect or an arteriovenous shunt. It is very important to remember that infection can occur on a normal heart valve (Table 1) (Gould *et al.,* 2012).

Table 1. Important predisposing factors for infective endocarditis

Congenital heart disease
• Previous rheumatic heart disease
• Athisosclerotic aortic valve disease
• Prosthetic valve heart surgery
• Severe mitral valve prolapse
• Intravenous drug use

In this case, it's not clear about presdisposing factor, but could be from dental carries. Although many species of bacteria and fungi cause sporadic episodes of endocarditis, only a few bacterial species cause the majority of cases (Table 2) (Limited, 2008).

Clinical Presentation

Clinical features can be divided into early manifestations of infection; embolic events; and late complications of sepsis and inflammation. The earliest features are usually fever and heart murmur, with or

Table 2. Organisms Causing Major Clinical Forms of Endocarditis

Organism	Percent of cases							
	Native valve endocarditis		Prosthetic valve endocarditis at indicated time of onset (months) after valve surgery			Endocarditis in injection drug users		
	Community-Acquired *(n=683)*	Helath Care - Associated *(n=128)*	<2 *(n=144)*	2-12 *(n=31)*	>12 *(n=194)*	Right-Sided *(n=346)*	Left-Sided *(n=204)*	Total *(n=675)*[a]
Streptococci[b]	32	8	1	9	31	5	15	12
Pneumococci	1	-	-	-	-	-	-	-
Enterococci	8	16	8	12	11	2	24	9
Staphylococcus aureus	35	44[c]	22	12	18	77	23	57
Coagulase-negative staphylococci	4	15	33	32	11	-	-	-
Fastidious gram-negative coccobacilli (HACEK group)[d]	3	-	-	-	6	-	-	-
Gram-negative bacilli	3	5	13	3	6	5	13	7
Candida spp.	1	6	8	12	1	-	12	4
Polymicrobial/ miscellaneous	6	1	3	6	5	8	10	7
Diphtheroids	-	-	6	-	3	-	-	0.1
Culture-negative	5	5	5	6	8	3	3	3

[a] **The total number of cases is larger than the sum of right-and-left-sided cases because the location of infection was not specified in some cases**

[b] **Includes viridans streptococci; *Streptococcus bovis*; other non-group A, groupable streptococci; and *Abiotrophia* spp. (nutritionally variant, pyridoxal-requiring streptococci).**

[c] **Methicillin resistance is common among these S.aureus strains.**

[d] **Includes *Haemophilus* spp., *Anggregatibacter (Actinobacillus) actinomycetemcomitans, Cardiobacterium hominis, Eikenella* spp., *and Kingella* spp.**

Note: Data are compiled from multiple studies.

without malaise and fatigue. Features of embolization appear after days or weeks. Early emboli are seen in more aggressive endocarditis. The long-term effects of endocarditis, now rarely seen, are immunologically mediated. Immunological effects include splenomegaly, nephritis, vasculitic rahes or lesions of the eyes and skin (Table 3) (Karchmer, 2010).

In this case, clinically this patient showed symptoms of endocarditis infectious. ASTO, culture, echocardiography and physical examination show it. Based on a careful history taking, it can be concluded that prolonge febris was caused by endocarditis.

Treatment

Theraphy suggestion from clinical microbiology is Ampicillin sulbactam but social indication not permitted for this drug to give because Ampicillin sulbactam must be given 3 grams four times daily. Ceftriaxone become an alternative because it's dosage can be given 2 grams once daily.

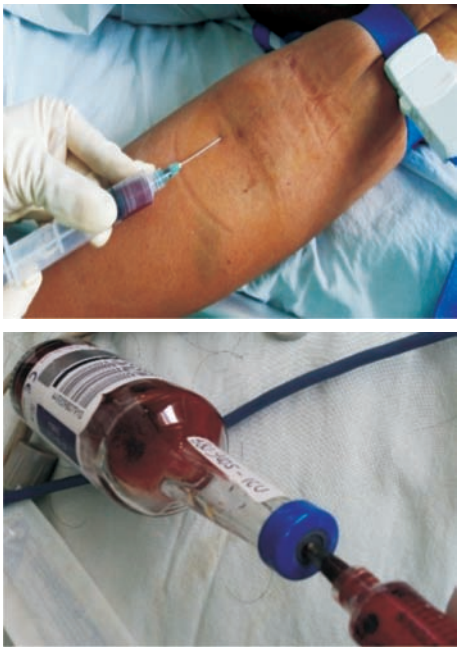

Figure 1. Special handling specimen of blood in endocarditis case

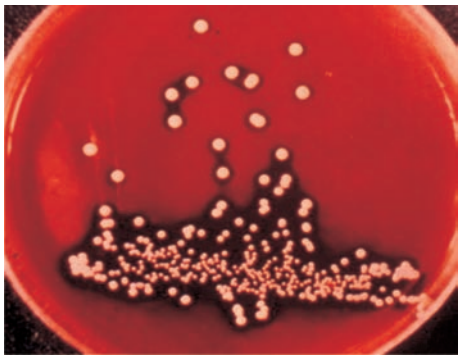

Figure 2. Blood Agar Culture show Streptococcus β haemolyticus

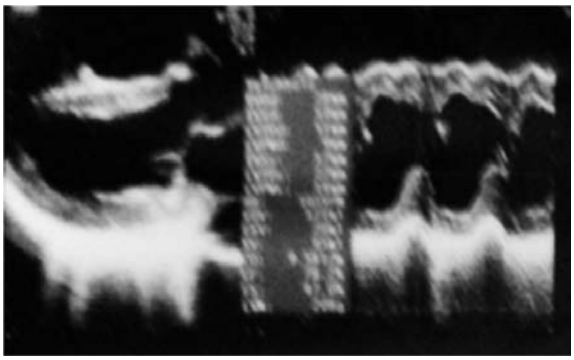

Figure 3. Echocardiography found vegetation in triscupidal valve

Table 3. The duke criteria for the clinical diagnosis of infective endocarditis

Major Criteria
1. Positive blood culture Typical microorganism for infective endocarditis from two separate blood cultures Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus, or* Community-acquired enterococci in the absence of a primary focus, or Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from : Blood cultures drawn > 12 h apart; or All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 h apart Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800
2. Evidence Of Endocardial Involvement Positive Echocardiogram[a] Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or* Abscess, *or* New partial dehiscence of prosthetic valve, *or* New valvular regurgitation (increase or change in preexisting murmur not sufficient)
Minor Criteria
1. Predisposition: predisposing heart condition or injection drug use
2. Fever > 38.0°C (>100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously[b] *or* serologic evidence of active infection with organism consistent with infective endocarditis

CONCLUSION

Right microbiology culture is important to confirm the diagnostic of endocarditis and very useful for the clinicians to do the right clinical management. Subsequently, the role of clinical microbiologist in this case not only to support the clinical diagnostic but also the treatment in term of selecting of right antibiotic based on clinical presentation and laboratory result.

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