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Editor’s note

YI Kasjmir

Discoveries concerning the pathogenesis of osteoarthritis (OA) have changed our understanding of this disease. Several proinflammatory cytokines, the most important of which are tumor necrosis factor α and interleukin (IL)-1β, have been known to play an important role in the pathogenesis of OA. Studies have also found the presence of these cytokines in synovial tissue and joint cartilage of OA patients.1 Previously, treatment of OA has been purely symptomatic, with the use of analgesics and nonsteroidal anti-inflammatory drugs,2 or surgical therapy in advanced stages of the disease. The discovery of the role of inflammation in OA opens new possibilities in the approach for treatment of OA, such as the use of anti-interleukin agents. More direct target at the inflammation process means that drugs that belong to this class have symptoms-modifying properties.2 Based on this, Kasjmir et al3 (see page 15) attempted to study the correlation of diacerein, an anti–IL-1β, with pain intensity and functional status of knee OA patients. This study found that diacerein was significantly correlated with reduced pain and disability in knee OA patients in Cipto Mangunkusumo General Hospital. The result of this study is similar to previous studies4,5 which found the effectiveness of diacerein in reducing pain and improving the functional status of OA patients.

The proven efficacy of anti-interleukin agents also raise a question on how to optimize the benefit of this drug in OA patients. One of this is related to the characteristics of inflammation and the distribution of proinflammatory cytokines, particularly IL-1β, in OA. The mechanism of IL-1β production and distribution in OA is different from rheumatoid arthritis; while in rheumatoid arthritis IL-1β is present both in the synovial tissue and the peripheral blood, in OA patients IL-1β is only found in synovial tissue.6 Based on this fact, one may consider the possibility of intra-articular administration of this drug as a method that may potentially bring more benefit to the patients, particularly because of less adverse effects of this route of administration.

REFERENCES

Diagnosis and management of osteomyelitis

Gunawan,1 B Setiyohadi2

ABSTRACT
Osteomyelitis is an infection of the bone that causes bone destruction and formation of new bone as the result of the inflammatory process. Proper diagnosis in osteomyelitis is important since it determines the decision-making in the management of the disease: whether to perform aggressive treatments or administration of long-term antibiotic treatment. Imaging techniques play an important role in the diagnosis of osteomyelitis, but their results should be interpreted with care as they have a wide range of sensitivity and specificity. A combination of imaging techniques could improve their sensitivity and specificity. Conventional radiography is an affordable and widely available technique, and has been proven to be useful in diagnosing and excluding the differential diagnoses of osteomyelitis. Surgical intervention to remove necrotic tissues and administration of antibiotics to eradicate pathogens are necessary in the management of osteomyelitis. Several antibiotics such as quinolones, rifampin, and clindamycin have been proven to have good penetration into bone.

Osteomyelitis is an infection of the bone that causes bone destruction and formation of new bone as the result of the inflammatory process. The first report about osteomyelitis was written circa 400 BC by Hippocrates, who described it as “a boil of the bone marrow”. Terms such as “abcessus in medulla” or “necrosis” were also used to describe the condition until Nelaton introduced the term “osteomyelitis” in 1844. In the last 40 years there has been much development in the definition, pathogenesis, diagnosis, and treatment of osteomyelitis.1,2

Osteomyelitis management has always been a challenge. Before the use of antibiotics in the 1940s, the treatment of choice for osteomyelitis was surgical therapy, with wide incision to remove all of the necrotic bone. This procedure had a high mortality rate, which could reach 33%. After the discovery of more potent antibiotics, complications of osteomyelitis such as sinus formation, sequestration, and sepsis are now rarely encountered. Besides, the aim of therapy has also changed from merely palliative to curative.2

New diagnostic techniques, aggressive surgical methods with the use of prostheses, and the availability of safe broad spectrum antibiotics help the management of osteomyelitis in outpatient settings. However, the increasing number of immunocompromised patients (particularly those with human immunodeficiency virus/acquired immunodeficiency syndrome or receiving immunosuppressive treatment) adds to the prevalence of osteomyelitis and antibiotic resistance, which present major challenges in the management of osteomyelitis.

DEFINITION
Osteomyelitis is defined as infection affecting bones, causing destruction and formation of new bone. There are several mechanisms of infection that may cause osteomyelitis: (a) contiguous focus of infection (e.g. after trauma, surgery, or insertion of prosthetic joint); (b) vascular insufficiency (e.g. in diabetes mellitus or peripheral vascular disorder); and (c) hematogenous spread of infection (e.g. in vertebral osteomyelitis in children). Based on the duration of disease, osteomyelitis is divided into acute and chronic osteomyelitis (Lee and Waldgovel classification).3,4 Acute osteomyelitis will usually resolve in several days to weeks, although it may also progress to chronic osteomyelitis. There is no precise definition for when osteomyelitis becomes chronic but it is defined as such if the infection persists for weeks or years.2

PATHOGENESIS
Normally, bone tissue is resistant to infection. Osteomyelitis occurs when there is inoculation of a large number of microorganisms, preceeding trauma, or presence of foreign material in the bone. The pathogenesis of osteomyelitis is multifactorial and has yet to be fully understood. Some important factors in the pathogenesis are pathogenic virulence; coexisting disease and host immunity; and bone type, location, and vascularization.

The pathogenic determinants of osteomyelitis are bacterial adherence, activity of proteolytic enzymes produced by the pathogen, and resistance to host immunity. Bacterial adherence plays a role in osteomyelitis and arthritis caused by *Staphylococcus aureus*. This bacteria has the ability to adhere to some bone matrix components, such as fibrinogen, fibronectin, laminin, collagen, sialoglycoprotein, and factor A.5–9 The adherence process is mediated by specific adhesin expressed by *S. aureus*, called microbial surface components recognizing adhesive matrix molecules (MSCRAMM).5–10

Proteolytic activity can be found under normal conditions in a joint without inflammation. In the
presence of infection, the inhibition of proteolytic activity is diminished. In an in vitro study by Williams et al that inoculated \textit{S. aureus} into mature chondrocytes, there was a decrease in protein matrix synthesis and release of collagenases and gelatinases.\textsuperscript{11}

Resistance to host immune responses at the cellular level as well as in the extracellular matrix also complicates the management of osteomyelitis. \textit{S. aureus} has been found to be present inside the cultured osteoblasts. Production of arachidonic acid metabolites such as prostaglandin E2, which is a potent agonist of osteoclasts, reduces the number of bacteria needed for the infection to occur. Protein A expressed by \textit{S. aureus} on the cell wall peptidoglycan binds with Fc components of polymorphonuclear cells and thus disrupts the opsonization and phagocytosis against \textit{S. aureus}. Furthermore, secretion of exotoxin and toxic shock syndrome toxin-1 (TSST-1) suppresses plasma cell differentiation and causes an increase in cytokine production such as interleukin-1, interferon $\gamma$ (IFN$\gamma$), and tumor necrosis factor $\alpha$ (TNF$\alpha$).\textsuperscript{15,16}

**PATHOPHYSIOLOGY**

As stated above, osteomyelitis could be caused by direct pathogen inoculation following trauma of surgery, contiguous spread from adjacent soft tissue or joint, or hematogenous spread from a focus of infection. Hematogenous osteomyelitis is usually monomicrobial, while the other types are polymicrobial.

In the long bones, osteomyelitis usually affects the metaphyseal area since the main vascularization enters the bone in its middle part, runs on both sides of the bone through its length, and forms loops before reaching the epiphyseal plate. The decrease in blood flow and the absence of basal membrane in the metaphysis predispose this area to infection.

In the presence of infection, inflammatory exudates cause increases in intramedullary pressure and extension of the exudates into the cortex, with subsequent rupture through the periosteum. These will disrupt the blood supply to the periosteum and cause necrosis of the bone, with fragments of necrotic bone (sequestra) detectable on radiographs. There is also formation of new bone (involution) around the damaged periosteum.

In acute osteomyelitis, infection occurs before the development of sequestra. In some forms of infection, development of sequestra is relatively slow (such as vertebral osteomyelitis), while in others the development of sequestra occurs relatively rapidly (such as osteomyelitis in the setting of prosthetic devices). In vertebral osteomyelitis, infection may involve two adjacent vertebrae simultaneously, since their vascularization is supplied by a single artery.

**CLASSIFICATION**

There are two classification systems commonly used in osteomyelitis: Lee-Waldvogel and Cierny-Mader classification.\textsuperscript{1,4}

Lee and Waldvogel classified osteomyelitis according to the duration of disease (acute vs. chronic) and the mechanism of infection (hematogenous vs. secondary to contiguous focus of infection). This classification is based on etiology and is not used for choosing specific treatments.

Cierny and Mader classified osteomyelitis based on the part of the bone involved, host physiological status, and local environment (table 1). This system could be used as a guidance for the management of osteomyelitis: stage 1 can be sufficiently treated with antibiotics, while stages 2 to 4 usually require more aggressive treatment such as debridement or orthopedic reconstruction, if necessary.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cierny and Mader classification of osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomic type</strong></td>
<td><strong>Stage 1: Medullary osteomyelitis</strong></td>
</tr>
<tr>
<td></td>
<td>Infection only involves intramedullary surface of bone, e.g. in hematogenous infection and bone marrow infection.</td>
</tr>
<tr>
<td></td>
<td><strong>Stage 2: Superficial osteomyelitis</strong></td>
</tr>
<tr>
<td></td>
<td>True osteomyelitis, caused by direct inoculation or contiguous focus of infection after exposure of necrotic bone surface under damaged soft tissue.</td>
</tr>
<tr>
<td></td>
<td><strong>Stage 3: Localized osteomyelitis</strong></td>
</tr>
<tr>
<td></td>
<td>Marked by presence of thick sequestra on bone cortex; this could be removed surgically without disturbing bone stability.</td>
</tr>
<tr>
<td></td>
<td><strong>Stage 4: Diffuse osteomyelitis</strong></td>
</tr>
<tr>
<td></td>
<td>At this stage, bone resection is usually required to stop the infection; bone may lose its stability before or after the debridement.</td>
</tr>
</tbody>
</table>

**DIAGNOSIS**

Symptoms of acute osteomyelitis usually develop over several days. Patients will complain of dull pain in the involved bone, accompanied with local symptoms such as tenderness, redness, swelling, warmth, and systemic symptoms such as fever, shivering, and malaise. In some cases affecting hip, vertebrae, or pelvis, pain may be the only symptom. Acute osteomyelitis may also coexist with septic arthritis, because infection from metaphysis could extend to joint following cortex destruction caused by intramedullary inflammation. Clinical manifestations of chronic osteomyelitis are pain, erythema, edema, and occasionally formation of cutaneous sinus; the latter is pathognomonic for osteomyelitis.

Diagnosis of osteomyelitis may be more difficult in the presence of prosthesis, extensive ulcer, or vascular insufficiency.\textsuperscript{17} In general, osteomyelitis should be taken into consideration when there is persistent wound or ulcer on the skin despite adequate treatments. Diabetic patients who have ulcer and chronic osteomyelitis may give noncharacteristic clinical feature, e.g. osteomyelitis may occur before the

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exposure of underlying bone through the skin ulcer. In that case, the possibility of osteomyelitis is even greater if the bone is clearly exposed. In the presence of ulcer larger than 2 × 2 cm, or if the underlying bone is palpable, diagnosis of osteomyelitis is so likely that further noninvasive evaluation is unnecessary.17,18

Proper diagnosis in osteomyelitis is important because it determines the decision-making in the management of the disease: whether to perform aggressive treatments or administration of long-term antibiotic treatment. The diagnostic standards for osteomyelitis are isolation of pathogens from bone biopsy and histopathologic presence of inflammation and osteonecrosis.19

Diagnostic tests, particularly imaging techniques, play important roles in diagnosing osteomyelitis. However, results of diagnostic imaging procedures should be interpreted with care as they have a wide range of sensitivity and specificity. Conventional radiography is both affordable and widely available, and has been proven to be useful in diagnosing and excluding the differential diagnoses of osteomyelitis. Imaging findings in chronic osteomyelitis include cortical erosion, periosteal reaction, and mixed lucency and sclerosis.19,20 Figure 1 shows an example of imaging result of chronic osteomyelitis.

![Figure 1](image)

Figure 1  (A) Sagittal fluid-sensitive short-tau inversion recovery (STIR) image demonstrates high signal fluid collection along the plantar surface of the calcaneous (white arrow); (B) Sagittal postcontrast T1-weighted image with fat saturation demonstrates the peripherally enhancing fluid collection (white arrow); (C) Sagittal T1-weighted precontrast image demonstrates some cortical interruption (white arrow); (D) Lateral radiograph demonstrates soft tissue loss overlying the plantar aspect of the calcaneous (white arrow). Osseous remodeling and periosteal reaction about the posterior calcaneous (asterisk) reflect changes associated with longstanding chronic osteomyelitis. (Adapted from Horwich, 2010)21

In a meta-analysis22 of studies comparing imaging techniques with histological analysis, findings on culture, and clinical follow-up of more than six months, conventional radiography has sensitivity and specificity of 54% and 68%, respectively. To improve sensitivity, conventional radiography can be combined with other imaging techniques. Bone scintigraphy has better sensitivity (81%) but limited specificity (28%). In contrast, leukocyte scintigraphy has better specificity (68%) although it has lower (74%) sensitivity compared with bone scintigraphy. Combination of bone and leukocyte scintigraphy could improve their sensitivity and specificity. The comparison of sensitivity and specificity of several imaging techniques are shown in table 2.

### Table 2 Sensitivity and specificity of several imaging techniques in osteomyelitis

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe to bone/exposed</td>
<td>0.60 (0.46–0.73)</td>
<td>0.91 (0.86–0.94)</td>
</tr>
<tr>
<td>Conventional radiography</td>
<td>0.54 (0.44–0.63)</td>
<td>0.68 (0.53–0.80)</td>
</tr>
<tr>
<td>MRI</td>
<td>0.90 (0.82–0.95)</td>
<td>0.79 (0.62–0.91)</td>
</tr>
<tr>
<td>Bone scintigraphy</td>
<td>0.81 (0.73–0.87)</td>
<td>0.28 (0.17–0.42)</td>
</tr>
<tr>
<td>Leukocyte scintigraphy</td>
<td>0.74 (0.67–0.80)</td>
<td>0.68 (0.57–0.76)</td>
</tr>
</tbody>
</table>

Computed tomography (CT) scan and magnetic resonance imaging (MRI) are the more popular techniques in the diagnosis of osteomyelitis. To date, MRI is the best technique to acquire anatomical images of bone marrow involvement and inflammation. MRI is also reliable in diagnosing pedal (in diabetic patients) and vertebral osteomyelitis (detailed visualization of spinal nerves and neighboring structures).23,24 Gadolinium contrast is used to obtain better visualization of sinuses, fistulas, and abscesses. MRI has a high negative predictive value; therefore the possibility of osteomyelitis can be excluded if the symptoms have been present for 1 week. Edema visualized in MRI is not specific for infection: contusion, fractures, or history of surgery may yield similar findings; thus interpretation of bone marrow edema on MRI should be guided by clinical findings and other diagnostic tests.25,26 CT scan is the technique of choice when MRI could not be performed. It is useful in evaluating cortical and trabecular integrity, periosteal reaction, intraosseous gas, and the extent of sinus tracts.27–29

One of the drawbacks of imaging techniques is their limited ability to differentiate osteomyelitis from noninfectious lesions, such as trauma, surgery, recently healed osteomyelitis, septic arthritis, degenerative joint diseases, bone tumors, Paget’s disease, and other noninflammatory bone diseases.30,31 Currently there is no specific laboratory test for diagnosing osteomyelitis. There may be leukocytosis, particularly in the acute phase of infection, and increase in erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP).32,33 Blood culture is positive in 50% cases and is more common in cases with hematogenous spread.

**MANAGEMENT**

In the management of osteomyelitis, both surgical intervention to remove necrotic tissues and administration of antibiotics to eradicate pathogens are necessary. Antibiotic treatment should be given in accordance with culture and sensitivity results. If culture results have not arrived, empirical antibiotic treatment should be started immediately. Some recent antibiotic regimens
for the management of osteomyelitis are shown in table 3. Osteomyelitis caused by Gram-negative microorganisms is best treated with quinolones (after confirmation by sensitivity test) because their good penetration into bone, even with oral administration. Several in vitro studies showed that rifampin, clindamycin, and quinolones also penetrate well into bone. Use of prostheses may increase antibiotic resistance by formation of biofilms. Some experts suggest combination of rifampin with other antibiotics since there are high rates of resistance when it is used alone.

Antibiotics is usually given in long-term because there is persistence of S. aureus in osteoblasts, as has been shown by several animal studies. In some patients, penetration of antibiotics can be disrupted if there is vascular disorder or post-traumatic scar tissue. There has not been any consensus upon the duration of antibiotic administration, but it is a common practice among experts to administer antibiotics for 6 weeks after the last debridement. Serial measurement of inflammation markers such as ESR and CRP should also be performed to monitor treatment response.

**CONCLUSIONS**

Proper diagnosis in osteomyelitis is important since it determines the decision-making in the management of the disease. The clinical diagnosis of osteomyelitis may be complicated by several conditions, such as the presence of prosthesis, extensive ulcer, vascular insufficiency, or diabetes mellitus. Imaging techniques play an important role in the diagnosis of osteomyelitis, but their results should be interpreted with care as they have a wide range of sensitivity and specificity. Conventional radiography, an affordable and widely available technique, has been proven to be useful in diagnosing and excluding the differential diagnoses of osteomyelitis. Surgical intervention to remove necrotic tissues and administration of antibiotics to eradicate pathogens are necessary in the management of osteomyelitis. Quinolones, rifampin, and clindamycin are some antibiotics that have been proven to have good penetration into bone.

**Table 3** Recommendations of antibiotic treatment for osteomyelitis

<table>
<thead>
<tr>
<th>Onset</th>
<th>Pathogen</th>
<th>Intravenous treatment of choice</th>
<th>Alternative intravenous treatment</th>
<th>Oral treatment or i.v.-to-p.o. switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (initial therapy as in MSSA; treatment given according to culture results)</td>
<td><em>S. aureus</em> (MRSA)</td>
<td>Linezolid 600 mg (i.v.) every 12 hours for 4–6 weeks</td>
<td>Clindamycin 300 mg (p.o.) every 8 hours for 4–6 weeks</td>
<td>Quinolones (moxifloxacin 500 mg, levofloxacin 500 mg, or gatifloxacin 400 mg) every 24 hours for 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Quinupristin/dalfopristin 7.5 mg/kgBB (i.v.) every 8 hours for 4–6 weeks</td>
<td>or Cephalaxine 1 g (p.o.) every 6 hours for 4–6 weeks</td>
<td>or Quinolones (ciprofloxacin 500 mg, levofloxacin 750 mg, moxifloxacin 400 mg) every 24 hours for 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Minocyclin 100 mg (i.v.) every 12 hours for 4–6 weeks</td>
<td>or Cefotaxime 2 g (i.v.) every 8 hours for 4–6 weeks</td>
<td>or Quinolones (moxifloxacin 500 mg, levofloxacin 400 mg, or gatifloxacin 400 mg) every 24 hours for 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Vancomycin 2 g every 12 hours for 4–6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em> (MSSA)</td>
<td>Ceftriaxone 1 g every 24 hours for 4–6 weeks</td>
<td>Cefotaxime 2 g (i.v.) every 6 hours for 4–6 weeks</td>
<td>Clindamycin 300 mg (p.o.) every 8 hours for 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Meropenem 1 g (i.v.) every 8 hours for 4–6 weeks</td>
<td>or Cefotaxime 2 g (i.v.) every 8 hours for 4–6 weeks</td>
<td>or Cephalaxine 1 g (p.o.) every 6 hours for 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
<td>Ceftriaxone 1 g (i.v.) every 24 hours for 4–6 weeks</td>
<td>Cefotaxime 2 g (i.v.) every 6 hours for 4–6 weeks</td>
<td>or Quinolones (moxifloxacin 400 mg, levofloxacin 500 mg, or gatifloxacin 400 mg) every 24 hours for 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Quinolones (ciprofloxacin 400 mg, levofloxacin 750 mg, gatifloxacin 400 mg, or moxifloxacin 400 mg) every 24 hours for 4–6 weeks</td>
<td>or Cefotaxime 2 g (i.v.) every 8 hours for 4–6 weeks</td>
<td></td>
</tr>
<tr>
<td>Chronic (diabetes mellitus)</td>
<td>Group A or B streptococcus, <em>S. aureus</em> (MSSA), <em>E. coli</em>, <em>P. mirabilis</em>, <em>K. pneumoniae</em>, <em>B. fragilis</em>, <em>S. aureus</em> (MRSA)</td>
<td>Meropenem 1 g (i.v.) every 8 hours* or Piperacillin/tazobactam 3.375 mg (i.v.) every 6 hours* or Ertapenem 1 g (i.v.) every 8 hours* or combination therapy Ceftriaxone 1 g (i.v.) every 24 hours* with metronidazole 1 g (i.v.) every 24 hours*</td>
<td>Moxifloxacin 400 mg (i.v.) every 24 hours* or Cefotaxime 2 g (i.v.) every 8 hours* or Ampicillin/sulbactam 3 g (i.v.) every 6 hours* or combination therapy Clindamycin 600 mg (i.v.) every 8 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours with quinolones (i.v.) every 24 hours</td>
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<tr>
<td></td>
<td></td>
<td>or Ceftriaxone 1 g (i.v.)* with moxifloxacin (i.v.)* or monotherapy Moxifloxacin 400 mg (p.o.) every 24 hours*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic (peripheral vascular disease, non-diabetic)</td>
<td><em>S. aureus</em>, group A or B streptococcus, Enterobacteriaceae</td>
<td>Ceftriaxone 1 g (i.v.) every 24 hours for 2–4 weeks or Cefotaxime 2 g (i.v.) every 8 hours for 2–4 weeks</td>
<td>Clindamycin 600 mg (i.v.) every 8 hours for 2–4 weeks with quinolones (i.v.) every 24 hours for 2–4 weeks</td>
<td>Clindamycin 300 mg (p.o.) every 8 hours for 2–4 weeks with quinolones (p.o.) every 24 hours for 2–4 weeks</td>
</tr>
<tr>
<td>Tuberculous osteomyelitis</td>
<td><em>M. tuberculosis</em></td>
<td>Treatment as in pulmonary tuberculosis for 6–9 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*usually administered for 1 week after debridement or surgery.

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; i.v., intravenous; p.o., per oral.
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Tuberculous arthritis: an overview

L Hamijoyo

ABSTRACT
Tuberculous arthritis is a part of tuberculosis infection. Although the number of this disease is very small compared to the other causes of musculoskeletal infection, it can cause joint damage and eventually disability to the patient. Tuberculous arthritis should always be considered as one of the differential diagnosis in cases with insidiously developed monoarticular arthritis of the large weight-bearing joints, especially in developing countries where there is a high prevalence of tuberculosis. Early recognition and treatment with antituberculosis drugs provide better outcome for the patient; however, surgery due to unresponsiveness to medical treatment or presence of large abscess, arthroplasty, and arthrodesis may be necessary.

Tuberculous (TB) arthritis is a chronic septic arthritis caused by Mycobacterium tuberculosis. This disease should always be taken into consideration as one of the causes of chronic arthritis, especially in the developing countries where there is a high prevalence of tuberculosis.

The diagnosis of osteoarticular TB is usually delayed because the possibility of tuberculosis is often overlooked in the differential diagnosis of joint disease. Early symptoms are often minimal, and the delay could sometimes stretch to months or even years, until disease progression and disability prompt more aggressive diagnostic investigation. The mean duration from the onset of initial symptoms to the confirmation of diagnosis is 19.5 months (ranging from 12 to 36 months). In one report it takes even longer, about 6.5–7 years.

EPIDEMIOLOGY
Tuberculosis continues to ravage the populations of developing countries, with 9.4 million new cases in 2009 and 1.7 million deaths. About one third of the world’s population is infected with tuberculosis, providing a reservoir that will continue to complicate its global control. Five to ten percent of people who are infected with TB bacilli will eventually become sick or infectious at some time during their life. 

M. tuberculosis is ranked third globally after India and China, with the prevalence of 660.000 and incidence of 430.000 or 189 per 100.000 population in 2009.

Musculoskeletal TB accounts for about 5% of cases of tuberculosis, with estimated percentages ranging from about 2% of all TB cases in United States to more than 6% in developing countries.

Tuberculous arthritis is the second most common form of musculoskeletal TB, following vertebral TB. Involvement of the osteoarticular system is most commonly found in the elderly in developed countries; however, in developing countries it could be found at any age, mostly in children and young adults. There has been reported an increased prevalence of tuberculous arthritis among HIV-infected individuals and those who received antitumor necrosis factor (anti-TNF) therapy.

PATHOPHYSIOLOGY
Arthritis is generally secondary to hematogenous seeding (at the time of initial infection or during reactivation), but it can also occur as a consequence of lymphatic dissemination or direct spread from a contiguous lesion, such as adjacent osteomyelitis. However, characteristic pulmonary or extrapulmonary findings are not always present.

In long bones, hematogenous spread commonly affects the synovium, causing erosive deforming arthritis. Initially the synovium develops an inflammatory reaction followed by formation of granulation tissue, which lead to development of pannus. The margins and surface of the joints can be eroded by the pannus. As the effusion develops, fibrin may precipitate, forming “rice bodies” in synovial fluid, bursae and tendon sheath. However, the “rice bodies” are not typical for tuberculosis; they can also be found in patients with rheumatoid arthritis (RA). The granulation tissue erodes and eventually destroys the cartilage, leading to demineralization of the bone and caseation necrosis. Because M. tuberculosis does not produce collagenases, and because this proteolytic enzymes are absent from the tuberous exudates, joint destruction is more insidious than in septic arthritis due to pyogenic organisms. The infection then spreads to the upper metaphysis and epiphysis on either side of the joint through the periarticular vasculature. In advanced and later stage of disease, para-osseous cold abscesses develop around the joints. Spontaneous drainage of the cold abscesses results in sinus tract formation and may develop into cutaneous fistulae. M. tuberculosis is rarely isolated from these sinuses tracts because of frequent pyogenic contamination.

Tuberculosis related to anti-TNF inhibitors may be due to the inhibition of a TNF-dependent
chemokine gradient disrupting the cellular migration necessary to maintain the integrity of granulomas. The pro-inflammatory cytokines, such as interleukin (IL)-1, IL-2, IL-6, IL-12, interferon γ (IFNγ), and TNFα, play a key role in protection against tuberculosis and also in granuloma formation. TNFα recruit macrophages, leading to granuloma maintenance and formation (Ghon’s lesion), which is very important to contain and kill Mycobacterium microorganisms and are indicators of an effective immune response.

CLINICAL MANIFESTATIONS
Constitutional symptoms such as fever, night sweats, and weight loss are typically subtle or absent in patients with TB arthritis. The classic presentation is that of monoarthritis with pain (with or without movement), stiffness, and gradual loss of function over weeks to months. The peripheral joints most frequently affected are the large weight-bearing joints such as the hip and knee. Other joints commonly involved include the sacroiliac, shoulder, elbow, ankle, carpal, and tarsal joints. Monoarticular involvement is much more frequent than polyarticular disease. Oligoarticular involvement of both knees was reported more commonly than other joints.

On physical examination, the joint is swollen with or without warmth. Limited motion due to pain and boggy swelling due to synovial hypertrophy and effusion could also be found. Periarticular abscesses and draining sinus tracts are late findings. Prolonged immobility due to pain may eventually lead to deformity.

Clinical features of tuberculous arthritis can mimic other processes such as juvenile RA and gout. The dephosphorylated nuclei may be found. Periarticular abscesses and draining sinuses are late findings. Prolonged immobility due to pain may eventually lead to deformity.

Clinical features of tuberculous arthritis can mimic other processes such as juvenile RA and gout. The dephosphorylated nuclei may be found. Periarticular abscesses and draining sinuses are late findings. Prolonged immobility due to pain may eventually lead to deformity.

There is a type of reactive arthritis called Poncet’s arthritis in patients with active TB infection. It is associated with extrapulmonary TB, usually lymphadenitis TB. This is a separate entity from TB directly affecting joint spaces. The joint fluid analysis does not reveal the presence of M. tuberculosis. It usually manifests itself as polyarticular inflammation of the large joints associated with fever and malaise. Tuberculin test is frequently positive, and the clinical symptoms of Poncet’s resolve with antituberculosis therapy.

DIAGNOSIS
The definitive diagnosis should be made by culture and histopathological analysis of biopsy specimen. However, several diagnostic tools can help in making the diagnosis of tuberculous arthritis, such as radiograph (including chest X-ray), magnetic resonance imaging (MRI), radionuclide, tuberculin skin test (TST), and synovial aspiration and analysis.

Imaging
Radiographic abnormalities may only appear later in the course of disease, although newer imaging techniques have resulted in earlier detection of abnormalities and the distinction of tuberculosis from other infections as well as neoplasm.

 Initially, the infection may be primarily synovial, with radiographic evidence of joint swelling resulting from a combination of synovial hyperthrophy and effusion. The chronic synovitis leads to hyperemia and periarticular osteoporosis. The normally sharp, subarticular cortical outline becomes blurred, smudged, or even invisible. Eventually destruction of articular cartilage leads to narrowing of the joint space. Additional radiographic findings that may be present include soft tissue swelling, subchondral cysts, periostitis, and calcifications. Another typical feature is lack of sclerosis or periostitis in the early stage, except for children, in whom a layered periosteal reaction is seen. The end stage of tuberculous arthritis is characterized by severe joint destruction and eventually sclerosis and fibrous ankylosis when the active infectious stage has slowly extinguished. Bony ankylosis is only occasionally seen, but this sequel is more frequent in pyogenic arthritis.

The Phemister’s triad is the characteristic radiographic findings of tuberculous arthritis, consisting of juxta-articular osteoporosis, marginal erosions, and gradual joint space narrowing. Similar changes can occur in other forms of infection or RA.

Compared with pyogenic joint infections, minimal sclerosis and relative preservation of joint space favor the diagnosis of tuberculous arthritis. By using MRI to evaluate tuberculous arthritis, Sung et al reported that bone erosion was more common in patients with tuberculous arthritis than in those with pyogenic arthritis, while subchondral marrow signal intensity abnormality was seen more frequently in patients with pyogenic arthritis than in those with tuberculous arthritis. Furthermore, tuberculous abscesses have thin and smooth rim enhancement, while most pyogenic abscesses have thick and irregular rims. M. tuberculosis forms tubercles with central caseating necrosis that shows intermediate signal intensity on T2-weighted images of MRI.

In 1988, Martini and Ouahes classified the radiographic findings in tuberculosis of the bone and joint as:

- Stage I : no bony lesions, localized osteoporosis
- Stage II : one or more erosions (or cavities) in the bone, discrete diminution of the joint space
- Stage III : involvement and destruction of the whole joint without gross anatomic disorganization
- Stage IV : gross anatomic disorganization

Radionuclide bone scan is useful in the initial stages to detect the tuberculous arthritis when radiograph do not yet demonstrate characteristic abnormalities, as well as computed tomography (CT) scan. CT scan may demonstrate bony destruction, bony sequestration, and extension of disease to the surrounding soft tissue.
Laboratory
Getting a correct diagnosis requires vigorous pursuit and usually includes synovial biopsy and culture. Initial studies are often misleading and may contribute to delayed diagnosis or misdiagnosis.1 Synovial effusion is often minimal, and the fluid, even if it is obtainable, shows variable, usually turbid and cloudy, and do not distinguish this arthropathy from other inflammatory or septic arthritides.2 Cell counts more often suggest inflammatory rather than septic arthritis and contain a preponderance of neutrophils (approximately 60%), but occasionally of lymphocytes.13,35 Synovial fluid protein is usually elevated but glucose tends to be low and more than 10 mg/dL below fasting serum levels, but nonfasting determinations are often misleading.

The diagnosis may be facilitated if the organism is observed on an acid-fast smear of synovial fluid, but only 20% of cases are positive. In contrast, 80% of synovial fluid cultures are positive.34 Synovial biopsy specimens can reveal the histologic finding of TB in approximately 80% to 90% of patients, although proper selection of tissue is paramount because the histologic picture can vary depending on the site of biopsy.36 The histologic examination alone may be confusing because granulomatous synovitis may also be found in atypical mycobacterial infection, sarcoidosis, erythema nodosum, brucellosis, Crohn’s disease, and foreign body reaction. With the open-biopsy technique, granulomatous histologic features and positive cultures are present in 94% of cases. No data are available for direct amplification tests in mycobacterial arthritis, but their use should be considered in suspected cases to provide earlier diagnosis. One report has suggested that a synovial fluid lymphocyte proliferation assay using tuberculin protein may have diagnostic value.37 Correct diagnosis is highly dependent, in most cases, on demonstration of the infectious agent by microscopic examination and culture of affected tissue. The role of nucleic acid amplification tests in diagnosing these infections is still being defined, and they must be interpreted with caution in extrapulmonary tissue specimens and when the clinical suspicion of infection is low.38-40

Other laboratory test such as elevated erythrocyte sedimentation rate and C-reactive protein level, are nonspecific.10

Tuberculin skin test (TST)
Tuberculin and other skin tests may provide useful clues to etiology, but results are not invariably positive, especially in debilitated or immunosuppressed patients. This test is unable to distinguish latent infection from active disease and may be negative in the face of severe active TB.1 False negative results may occur in patients using corticosteroid 15 mg/day or more, elderly and malnourished patients. Likewise, false positive results may be found in the case of infection with nontuberculous mycobacteria or previous Bacille Calmette-Guérin (BCG) vaccine.1 This test is an important but imperfect screening tool for M. tuberculosis infection.

Interferon γ release assays
This test has been developed due to the limitations of traditional TST. These assays measure the production of IFNγ by whole blood mononuclear cells stimulated by specific M. tuberculosis antigens. It has good sensitivity and specificity for latent TB infection.41

DIFFERENTIAL DIAGNOSES
- Gouty arthritis typically presents as intermittent episodes of (rather than persistent) monoarthritis in a patient with risk factors for hyperuricemia. The radiographic findings of erosions in chronic recurrent gouty arthritis usually overhangs the edge
- Pyogenic arthritis is also monoarticular but has a more rapid progression
- Rheumatoid arthritis is usually polyarticular, and involves mainly the small bones of the hands and feet. Occasionally, it may be monoarticular at the onset or affects only a few medium-size joints, and can simulate other causes of mono- or oligoarthritis including TB arthritis. In some cases, TB can superimpose on an RA joint.
- Osteoarthritis is much less inflammatory affecting weight bearing joints. Radiographic findings include subchondral bony sclerosis and osteophyte formation.

MANAGEMENT
Education
During the acute phase, immobilization and rest are reserved for relief of pain, and followed by early, active mobilization without weight bearing for 4 to 6 weeks.13

Multidrug therapy
Various regimens have been proposed, from the conventional duration of 18 to 24 months to shorter but more intensive multidrug therapy for 6 months (table 1).13 However most recommended regimens for extrapulmonary tuberculosis should last at least 9 to 12 months. The longer courses for musculoskeletal disease were based on poor tissue penetration into osseous tissues and high rates of relapse.1

The daily doses of antituberculosis drugs are isoniazid 5 mg/kg or 300 mg, rifampicin 10 mg/kg or 450 to 600 mg, pyrazinamide 15 to 30 mg/kg, and ethambutol 5 to 15 mg/kg or streptomycin 15 mg/kg or 1 g intramuscularly. Pyridoxine 25 to 50 mg daily, may be added to daily regimens that include isoniazid.10

The overall clinical response to anti-mycobacterial therapy is good. However, allergic reaction can occur to any drug; thus careful attention must be paid to toxicity. Streptomycin can affect the vestibulocochlear nerve, resulting in deafness or vestibular functional derangement. Rifampicin can produce hepatotoxicity; hence the level of aspartate and alanine aminotransferase must be monitored. Ethambutol can produce depressed thyroid function.36

Radiographic features of mycobacterial disease may not change much after 6 months of treatment, and response to treatment is based mainly on clinical features, including reduction in pain, resolution of constitutional symptoms, and improvement in mobility.1
Surgery
Surgical intervention is indicated as a diagnostic tool and when necessary to drain abscesses unresponsive to medical treatment. Articular procedures for tuberculous infection include excisional arthroplasty (hip and elbow) and arthrodesis (knee, shoulder, ankle, and wrist). Individuals requiring total hip or knee replacement for quiescent TB should receive perioperative antituberculosis therapy (isoniazid and rifampicin) 1 to 4 weeks before and 6 to 9 months after surgery to minimize risk of reactivation.13

SUMMARY
The diagnosis of tuberculous arthritis is often delayed because the failure to consider the diagnosis. Condition which should alert physicians to the presence of tuberculous arthritis is an insidious onset of a monoarthritis, especially in the country with high burden of tuberculosis disease. The gold standards of diagnosis are culture and histopathology. Early diagnosis of this disease as well as adherence to chemotherapy are important in order to minimize the risk of deformity and enhance the outcome.

### REFERENCES


### Table 1 Antituberculosis therapy

<table>
<thead>
<tr>
<th>Regimen (month)</th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drugs</td>
<td>Duration (month)</td>
</tr>
<tr>
<td>18–24</td>
<td>INH, RIF ± ETB or STM q.d.</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>INH, RIF q.d.</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>INH, RIF, PZA ± ETB or STM q.d.</td>
<td>2</td>
</tr>
</tbody>
</table>

INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; ETB, ethambutol; STM, streptomycin; q.d., daily; b.i.w, twice weekly.
Role of diacerein in pain intensity and functional status in patients with knee osteoarthritis

YI Kasjmir,1 F Imelda,2 L Erawati,2

ABSTRACT

Background: Inflammation is an important mechanism in the pathogenesis of osteoarthritis (OA). Proinflammatory mediators, especially interleukin-1β (IL-1β), play a significant role in the occurrence of joint inflammation, which lead to pain and limitation of daily activities. As an anti–IL-1β, diacerein is therefore have potency to reduce pain and improve functional status of OA patients.

Objective: To evaluate the role of diacerein in pain intensity and functional status of knee OA patients.

Methods: This is a pre-post study without control group using consecutive sampling conducted at rheumatology outpatient clinic at the Cipto Mangunkusumo General Hospital, Jakarta from January until May 2006. At the first visit, all patients underwent assessment of pain intensity (using visual analog scale (VAS)) and functional status (Lequesne algofunctional index) to obtain baseline data. We also performed knee radiograph examination to evaluate joint damage based on the Kellgren-Lawrence classification. Measurement of IL-1β level in synovial fluid was performed using enzyme-linked immunosorbent assay, with a minimum detectable value of 3.9 pg/mL. Diacerein was administered with a dose of 50 mg, given orally twice a day for 2 months. Follow-ups were done in the first, second, and eighth week after the administration of diacerein. In the eighth week we repeated the measurement of IL-1β level.

Results: Thirty three patients were enrolled in this study, most (78.8%) of them were female. The majority (81.8%) belong to the 50- to 70-year-old age group. More than half of the patients (54.5%) had detectable IL-1β level. The median baseline VAS score was 65.00 (range 25–100) while the median baseline Lequesne score was 11.00 (range 1.5–21.0). The statistical analysis showed a significant decrease in VAS at the first (p = 0.000), second (p = 0.000), and eighth week (p = 0.000). Lequesne index score was also decrease significantly at the first (p = 0.000), second (p = 0.000), and eighth week (p = 0.000) of treatment. We found no significant correlation of IL-1β level with VAS and Lequesne algofunctional index scores.

Conclusions: Among the patients in this study, there were significant decrease in pain intensity and disability after the administration of diacerein.

Osteoarthritis (OA) is one of the musculoskeletal diseases that has become the concern of the World Health Organization because it affects the social and mental function and the quality of life of the patients. It is estimated that 10% of the world population older than 60 years old suffers from OA.1

The concept of inflammation as the pathogenesis of OA, a fact that is supported by many studies, has also become a major concern. Several proinflammatory mediators have been known to be involved in the pathogenesis of OA, the most important of which are tumor necrosis factor α (TNFα) and interleukin (IL)-1β.2 Studies by Martel-Pelletier et al1,3 and Firestein et al4 have found the presence of IL-1β, TNFα, dan IL-1–receptor antagonist (IL-1RA) in the synovial tissue of OA patients. Smith et al5 in his study by using arthroscopy found increase in cell wall thickness, vascularization, infiltration of inflammatory cells, IL-1β, and TNFα in joint cartilage in accordance with the severity of OA. Interleukin-1β and TNFα have the ability to increase their secretion and trigger chondrocytes to secrete IL-8, IL-6, and leukocyte inhibitory factor (LIF), therefore increasing the production of protease and prostaglandin E2. Interleukin-1β also inhibit the synthesis of aggrecan, an important component of joint cartilage matrix.2,3,6

Both the degeneration and inflammation process will eventually disturb joint integrity and cause complaints of pain, limitation in joint range of movement, muscle atrophy, decrease in strength and endurance of muscle, deformity, and joint instability. Diacerein, an anthraquinon derivative, and its metabolite, rhein, shows strong in vitro inhibitory action against cytokines (particularly IL-1β in synovium) and chondrocytes which affect the cartilage degradation. Besides, diacerein has also been shown to decrease the bioactivity of IL-1 receptor in vitro. From studies we know that diacerein have both symptoms-modifying effects and structure-modifying effects.7–9 In this study we aim to investigate the IL-1β level in synovial fluid of OA patients and its correlation with pain intensity, radiographic joint damage, and Lequesne algofunctional index.

METHODS

This study used a pre-post design without control group. Samples were collected using consecutive sampling method at rheumatology outpatient clinic at the Cipto Mangunkusumo General Hospital,
RESULTS
Table 1 shows that the prevalence of OA among the patients was higher in women (80.6%). The majority of patients were in the 50- to 70-years-old age group. There were 7 patients with knee joint effusion and 6 patients with knee deformity. We also found that there were 8 patients who were undergoing rehabilitative therapy in the last 2 months. From 33 patients, 18 (54.5%) had detectable baseline IL-1β level. Twelve patients had their IL-1β level measured at week 8. Among these, only two had detectable baseline IL-1β level (4.917 pg/mL and 16.679 pg/mL), but all had detectable IL-1β level at week 8 and showed increase in IL-1β level compared with their baseline level. Most of the patients (94%) had severe disability according to Lequesne score. Patients with 2nd degree joint damage according to the Kellgren-Lawrence score have the greatest proportion (33.3%), followed by 9 patients (27.3%) who had 1st degree joint damage.

Table 1 Characteristics of patients (N = 33)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (78.8)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>50–70</td>
<td>27 (81.8)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Baseline IL-1β level, pg/mL</td>
<td></td>
</tr>
<tr>
<td>&lt;3.9</td>
<td>15 (45.5)</td>
</tr>
<tr>
<td>≥3.9</td>
<td>18 (54.5)</td>
</tr>
<tr>
<td>Baseline Lequesne algofunctional index score</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>5–7</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>8</td>
<td>31 (94.0)</td>
</tr>
<tr>
<td>Kellgren-Lawrence score</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>I</td>
<td>9 (27.3)</td>
</tr>
<tr>
<td>II</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>III</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Knee joint effusion</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25 (75.8)</td>
</tr>
<tr>
<td>Mild</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (18.2)</td>
</tr>
</tbody>
</table>

Figure 1 shows the VAS and Lequesne algofunctional index scores at baseline and during the follow-ups. There was a trend that these scores were decreasing during the follow-ups, and from analysis (presented in table 2) we found that the decrease was statistically significant.
Table 2  Statistical analysis of visual analog scale (VAS) and Lequesne algofunctional index (Leq) scores at baseline and during the follow-ups

<table>
<thead>
<tr>
<th></th>
<th>VAS week 1</th>
<th>VAS week 2</th>
<th>VAS week 8</th>
<th>Leq week 1</th>
<th>Leq week 2</th>
<th>Leq week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS baseline</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Leq baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as p value.

Table 3  Correlation of interleukin-1β (IL-1β) level with visual analog scale (VAS) and Lequesne algofunctional index (Leq) scores at baseline and at week 8

<table>
<thead>
<tr>
<th></th>
<th>VAS baseline</th>
<th>VAS week 8</th>
<th>Leq baseline</th>
<th>Leq week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β baseline</td>
<td>0.398 (0.102)</td>
<td>0.055 (0.829)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β week 8</td>
<td>0.016 (0.961)</td>
<td>0.160 (0.620)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as r (p value).

We also analyzed the correlation of the IL-1β with the Kellgren-Lawrence score. We found no significant correlation of both the baseline IL-1β level (r = 0.182, p = 0.484) or IL-1β level at week 8 (r = 0.335, p = 0.287) with the Kellgren-Lawrence score.

DISCUSSION

In this study we found that the majority of the patients were women. This is in line with data from World Health Organization (WHO) that shows higher tendency of OA in women (female to male ratio of 2.95:1.71). Estrogen is believed to play a role in this discrepancy. Administration of estrogen to premenopausal women was reported to decrease the production of IL-1β and in a cohort study was shown to slow the progression of OA.

Because the measuring kit we used in this study was only able to detect IL-1β level at 3.9 pg/mL or higher, we could not determine valid mean, median, or standar deviation values of IL-1β level. Previous studies have used different measuring kit with different reference ranges. At the time of this study there has not been data of a normal range of IL-1β in human. Pelletier et al reported a range of 0.3±0.04 pg/mL in healthy dogs. Another study have reported involvement of IL-1β in inflammation process, indicated by increase in its level in synovial fluid, with no reference ranges. It is also important to consider some characteristics of cytokines that may affect the result of IL-1β level measurement in this study. Cytokine has a high affinity to its ligand, is prone to oxydation, and has a dynamic characteristics inside the body; thus estimation of its level would be more accurate if measurement is performed more than once.

From the T-test analysis we found significant decrease in the VAS and Lequesne score during the follow-ups. This is in line with a study by Nguyen et al which had showed effect of diacerein in reducing pain in OA patients. In a 3-year study by Dougados et al, diacerein also had shown an effect in reducing Lequesne algofunctional index of hip OA patients.

Interleukin-1β play a role in causing pain in OA through a cascade involving cyclooxygenase-2 and nitric oxide synthase, which will increase prostaglandin E2 level, a major inflammatory mediator in nociceptor sensitization. From statistical analysis we found no significant correlation of IL-1β level with VAS and Lequesne algofunctional index scores. The result of this study differs from several other studies who investigated the correlation of functional status and inflammatory parameter, such as a study by Kertia et al who found significant correlation of Lequesne algofunctional index with malondialdehyde as well as leucocyte and macrophage count in synovial fluid. Ranitya et al reported increased serum hyaluronic acid level, with significant correlation with Lequesne algofunctional index. Garnero et al in their study found correlation of biochemical marker of synovitis in OA with the Western Ontario and McMaster Universities Arthritis Index and joint damage. The nonsignificant correlation we found in the study may be due to the small sample of detectable baseline IL-1β level or high drop-out rate. It is also important to consider that evaluation of Lequesne algofunctional index consists of other parameter such as joint deformity and this may contribute to the nonsignificant correlation.

We found no significant correlation of the IL-1β level with the Kellgren-Lawrence score. This is in line with the result of a studies by Brenner et al who reported no significant correlation between synovial membrane cytokines level and Kellgren-Lawrence score and Fraenkel et al who reported no significant correlation between cytokine produced by mononuclear cells and the Kellgren-Lawrence score.

CONCLUSIONS

There was a significant decrease of the pain intensity and disability after the administration of diacerein among patients in this study from the first to eighth week of treatment. Concerning correlation of IL-1β level in synovial fluid with the pain intensity and disability, future study with larger sample size and inclusion of a control group is needed in order to draw more definitive conclusions.
REFERENCES


Reliability and validity of European Quality of Life 5 Dimension (EQ-5D) for measuring health-related quality of life in knee osteoarthritis patients at Cipto Mangunkusumo General Hospital

A Pramono,1 Sumariyono,2 H Isbagio2

ABSTRACT

Background: Quality of life is very important to knee osteoarthritis (OA) patients. The term quality of life denotes one that is health-related. One of the questionnaires most frequently used to measure the quality of life is the European Quality of Life 5-Dimension (EQ-5D) questionnaire. At Cipto Mangunkusumo General Hospital, until today there has not been any instrument for measuring the health-related quality of life in knee OA patients that has been tested for its reliability and validity.

Objective: To prove the reliability and validity of EQ-5D as a measurement tool in determining the health-related quality of life in knee OA patients at Cipto Mangunkusumo General Hospital.

Methods: This is a validity study in which all patients were asked to complete both the EQ-5D form and 36-item short form (SF-36) on their first visit. They were subsequently asked again to complete only the EQ-5D form one week after their first visit.

Results: Data were obtained from 86 respondents. The value of the intraclass correlation coefficient of each EQ-5D dimension, EQ-5D index, and visual analogue scale (VAS) was excellent (>0.75). Cronbach’s α value for internal consistency reliability in this study was 0.6772 (<0.7). The external validity of EQ-5D compared to SF-36 was analyzed with the Pearson’s correlation test and revealed a significant correlation (p<0.01) of all EQ-5D dimensions, EQ-5D index, and EQ-5D VAS with total score of SF-36 except for the dimensions of self-care, pain, and anxiety/depression. The construct validity of EQ-5D showed that all of the dimensions were significantly correlated with the EQ-5D index (p<0.01) except for self-care dimension.

Conclusion: EQ-5D is a valid and reliable measurement tool. It is thus recommended for measuring the health-related quality of life in knee OA patients at Cipto Mangunkusumo General Hospital.

Osteoarthritis (OA) is a common joint disease and is one of the causes of disability and pain.1-3 This disease often attacks the weight-supporting joints such as the knee, hip, and backbone.1,3,4 According to a study conducted by Cushnaghan et al,5 41.2% of all the symptomatic osteoarthritis involve the knee. A study conducted in Malang showed that the issues of OA in Indonesia may be greater compared to those in western countries. More than 85% of OA patients in Indonesia have activity impairment, especially during squatting, going up and down the stairs, and walking. Those are crucial activities performed in the daily life of the Indonesian people.6

Health-related quality of life is defined by Cella and Tulsky as the perception of one’s current functional capacity and satisfaction compared to that one expects. Health-related quality of life is an abstract variable. Basically, there are two components of quality of life: subjective expression/perception and objective component.4 The objective data measured is the health status of a person.5,7 The subjective expression is more difficult to measure but could still be measured indirectly by using a questionnaire. The respondent’s answer is then converted into score that could be measured objectively.4

One of the commonly used questionnaires of quality of life is the European Quality of Life 5 Dimension (EQ-5D), which was constructed by the British-based EuroQol Group. EQ-5D is designed such that it could be filled out by the respondent him/herself because it contains easy-to-follow instructions. It could be used for postal questionnaire, self-administered response in the clinic, and direct interview. EQ-5D is simple and only needs a few minutes to fill out. EQ-5D contains two sheets. The first sheet consists of the 5 dimensions of measurement: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of scoring: no problem, some problems, or extreme problems. The second EQ-5D sheet contains the visual analogue scale (VAS) to describe the subject’s perception about his/her quality of life using a particular scale.6

EQ-5D has been translated into various languages and used in various countries. Studies of EQ-5D in OA has previously been done, such as by Brazier et al8 in 1993 in England and by Fransen
et al. in 1999 in Sydney; both confirmed the reliability and validity of EQ-5D. Until today, Indonesia has not performed a study of reliability and validity of EQ-5D as a measurement tool of health-related quality of life in knee osteoarthritis patients.

This study is aimed at proving that EQ-5D is a reliable and valid measurement tool to determine health-related quality of life of knee OA patients at Cipto Mangunkusumo General Hospital.

METHODS
This is a validation study using consecutive method, which involved all OA patients aged above 50 years old who visited the rheumatology clinic at Cipto Mangunkusumo General Hospital, Jakarta from March 2007 until May 2007. The inclusion criteria were knee OA patients who fulfilled the clinical and radiographic criteria based on the American College of Rheumatology (ACR) criteria and have Kellgren-Lawrence score of >2 (mild, moderate, or severe OA) and willing to participate in the study. The exclusion criteria were coexisting dementia, aphasia, and psychosis.

Necessary data were collected by performing anamnesis, physical examination, plain radiograph of the knee (if both knees suffer from OA, assessment was conducted on the more severe one), and completing the EQ-5D and 36-item short form (SF-36) questionnaires. After one week, respondents were again asked to fill the EQ-5D questionnaire. Intraobserver and internal consistency of each EQ-5D dimension for reliability was assessed using intraclass correlation coefficient (ICC) and Cronbach’s $\alpha$ coefficient ($\alpha$). External validity (the average of each EQ-5D and SF-36 component) was assessed using the Pearson’s correlation coefficient. Construct validity was assessed using correlation formula.

RESULTS
Characteristics of the respondents
There were 86 respondents enrolled in the study, consisting of 73 females and 13 males. The mean age of the respondents was 58.22 years old, in which the oldest was 77 years old. Most (51.2%) of the respondents were homemakers, followed by entrepreneurs/small business owners (20.9%). Most (41.9%) had only grade school education, while 29.1% had a high school degree.

Reliability
In this study we used intraobserver test-retest and internal consistency to assess reliability. Intraobserver test-retest is the degree of agreement of the outcome of the study conducted by the same observer during the first visit and the visit one week after. Intraobserver test-retest to assess reliability was measured using ICC. The value ranges between 0 and 1, in which <0.4 means weak correlation, 0.4–0.75 means good correlation, and >0.75 means excellent correlation. The reliability outcome of EQ-5D could be seen in table 1. All the ICC values were >0.75, which indicated that the correlation was excellent and therefore reliability was excellent.

Validity
In the external validity, EQ-5D was compared to SF-36 using the Pearson’s correlation coefficient test to obtain the $r$ value. Table 2 shows the correlation between EQ-5D and SF-36. In table 2, we could see that the EQ-5D index and EQ-5D VAS had significant correlation with SF-36 total score ($p<0.01$). Some scores of each EQ-5D dimension and SF-36 also had significant correlation ($p<0.01$).

<table>
<thead>
<tr>
<th>EQ-5D</th>
<th>Intraclass correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>0.886</td>
</tr>
<tr>
<td>Self-care</td>
<td>0.907</td>
</tr>
<tr>
<td>Usual activity</td>
<td>0.897</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>0.896</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>0.883</td>
</tr>
</tbody>
</table>

Each item of the measurement tool must correlate with each other. This is called internal consistency and is measured using the Cronbach’s $\alpha$ with values ranging from 0 to 1. Internal consistency of EQ-5D for assessing reliability in this study showed Cronbach’s $\alpha$ value of 0.6772, which indicated that EQ-5D had reliability with a low level of confidence.
Table 2  Pearson’s correlation coefficients between European Quality of Life 5 Dimension (EQ-5D) and Short Form-36 (SF-36)

<table>
<thead>
<tr>
<th>EQ-5D</th>
<th>Mobility</th>
<th>Self-care</th>
<th>Usual activity</th>
<th>Pain/discomfort</th>
<th>Anxiety/depression</th>
<th>Index</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>r  −0.163</td>
<td>p  0.134</td>
<td>−0.144</td>
<td>−0.185</td>
<td>−0.076</td>
<td>−0.303**</td>
<td>0.178</td>
</tr>
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<tr>
<td>Role-physical</td>
<td>r  −0.345**</td>
<td>p  0.001</td>
<td>−0.011</td>
<td>−0.559**</td>
<td>−0.182**</td>
<td>−0.294*</td>
<td>0.230*</td>
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<tr>
<td>Bodily pain</td>
<td>r  −0.378**</td>
<td>p  0.000</td>
<td>0.036</td>
<td>−0.461**</td>
<td>−0.238*</td>
<td>−0.089</td>
<td>0.290**</td>
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<tr>
<td>General health</td>
<td>r  −0.19</td>
<td>p  0.079</td>
<td>0.238</td>
<td>0.695</td>
<td>0.078</td>
<td>0.005</td>
<td>0.101</td>
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<tr>
<td>Vitality</td>
<td>r  −0.187</td>
<td>p  0.085</td>
<td>0.023</td>
<td>0.106</td>
<td>−0.082</td>
<td>0.093</td>
<td>0.006</td>
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<tr>
<td>Social functioning</td>
<td>r  −0.152</td>
<td>p  0.163</td>
<td>0.143</td>
<td>−0.365**</td>
<td>−0.08</td>
<td>−0.031</td>
<td>0.152</td>
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<tr>
<td>Role-emotional</td>
<td>r  −0.226*</td>
<td>p  0.036</td>
<td>0.043</td>
<td>0.103</td>
<td>0.173</td>
<td>0.046</td>
<td>0.78</td>
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<tr>
<td>Mental health</td>
<td>r  −0.042</td>
<td>p  0.699</td>
<td>0.092</td>
<td>0.354</td>
<td>0.559</td>
<td>0.577</td>
<td>0.85</td>
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</tr>
<tr>
<td>Total score</td>
<td>r  −0.377**</td>
<td>p  0.000</td>
<td>0.392</td>
<td>0.000</td>
<td>0.041</td>
<td>0.033</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* A significant correlation existed at p<0.05; ** A significant correlation existed at p<0.01.
VAS, visual analogue scale.

Table 3 shows the construct validity of EQ-5D. The EQ-5D dimensions were compared with the scores of EQ-5D index using the Pearson’s correlation test to obtain the r value.

The result showed that the EQ-5D dimensions of mobility, usual activity, pain/discomfort, and anxiety were significantly correlated with EQ-5D index (p<0.01). All the EQ-5D dimensions had negative correlation with EQ-5D index.

Except for the self-care dimension, the EQ-5D dimensions had r (absolute) value of >0.3. Kline11 had determined the r value to be = 0.3 in assessing the validity of the psychometric measurement tool; thus all the EQ-5D dimensions were clinically correlated with the EQ-5D index.

Table 3  Pearson’s correlation coefficients between each European Quality of Life 5 Dimension (EQ-5D) dimension and EQ-5D index

<table>
<thead>
<tr>
<th>EQ-5D dimensions</th>
<th>EQ-5D index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>−0.684 (0.000)</td>
</tr>
<tr>
<td>Self-care</td>
<td>−0.166 (0.126)</td>
</tr>
<tr>
<td>Usual activity</td>
<td>−0.401 (0.000)</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>−0.859 (0.000)</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>−0.631 (0.000)</td>
</tr>
</tbody>
</table>

All values are r (p value).

Health-related quality of life

In this study, we obtained the scores of health-related quality of life of knee OA patients. The details could be seen in table 4.

Table 4  The scores of European Quality of Life 5 Dimension (EQ-5D) index, EQ-5D visual analogue scale (EQ-5D VAS), and total Short Form-36 (SF-36) (N = 86)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SF-36</td>
<td>59.461 (12.506)</td>
<td>34.17–82.50</td>
</tr>
<tr>
<td>EQ-5D index</td>
<td>0.734 (0.162)</td>
<td>0.124–1</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>71.98 (12.206)</td>
<td>60–90</td>
</tr>
</tbody>
</table>
The distribution of respondents according to the EQ-5D index could be seen in figure 3. There were 15.1% of respondents who had EQ-5D index score of 1 (maximum) and 2.3% who had the lowest EQ-5D index score of 0.124.

The outcome of EQ-5D of each dimension is presented in table 5. Most respondents (ranging between 22.1 and 93%) had no problem (score of 1) for the mobility dimension (EQ1), self-care (EQ2), usual activity (EQ3) and anxiety/depression (EQ5). Most (75.6%) respondents experienced moderate pain/discomfort (score 2) for the pain/discomfort dimension (EQ4).

The total score in the assessment of quality of life using SF-36 was 59.461 of the possible scores between 34.17 and 82.50. The dimension with the highest score (72.093) was the social functioning dimension while the bodily pain dimension had the lowest score (42.78). The physical component summary was the mean of the physical functioning, role limitations due to physical health problems (role-physical), bodily pain, general health, and social functioning with a value of 54.9093 (SD 13.8065). The mental component summary was the mean of the general health, social functioning, role limitations due to physical health problems (role-physical), bodily pain, general health, and social functioning with a value of 67.373 (SD 11.7586). Further details could be seen in table 6.

### Table 5: The score of each European Quality of Life 5 Dimension (N = 86)

<table>
<thead>
<tr>
<th>EQ1, mobility</th>
<th>EQ2, self-care</th>
<th>EQ3, usual activity</th>
<th>EQ4, pain/discomfort</th>
<th>EQ5, anxiety/depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 1, no problem</td>
<td>43 (50)</td>
<td>80 (83)</td>
<td>48 (57)</td>
<td>19 (22.1)</td>
</tr>
<tr>
<td>Score 2, some problems</td>
<td>43 (50)</td>
<td>6 (7)</td>
<td>37 (43)</td>
<td>65 (75.6)</td>
</tr>
<tr>
<td>Score 3, extreme problems</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2.3)</td>
</tr>
</tbody>
</table>

All values are n (%).

### DISCUSSION

This is a validity study with respondents consisting of knee OA patients whose ages ranged from 50 to 77 years old and had educational background ranging from grade school to associate degree. There was a variety of occupations. Female patients outnumbered male patients. The above distribution of respondents could represent the heterogeneity of the study population. We did not find any other chronic diseases, such as diabetes mellitus, hypertension, or asthma during this study.

Reliability was assessed using intrarater test-retest and internal consistency. There has not yet any study conducted to assess the reliability of EQ-5D using ICC and Cronbach’s α of knee OA patients. Studies that had been conducted so far was the evaluation of ICC in rheumatoid arthritis, stroke, the elderly, and general population. Fransen et al compared the reliability and validity of the EuroQol (EQ-5D) in knee OA patients with Western Ontario and McMaster Universities (WOMAC) index, OA index, and SF-36 and found reliability and construct validity of EQ-5D with an ICC value of 0.70 with a confidence interval (95% CI) of 0.58–0.80 and test-retest analysis of each EQ-5D dimension with a correlation between 0.28 (p = 0.008) for mobility and 0.60 (p = 0.001) for anxiety/depression. The study revealed that the ICC value was 0.70; however, internal consistency using Cronbach’s α was not evaluated.

As a comparison, the following are studies using ICC to determine the reliability of EQ-5D. A study conducted in Zimbabwe with respondents from the general population using EQ-5D in the local Shona language showed an ICC value of >0.75 in the dimensions of mobility and usual activity and between 0.4 and 0.75 for the dimension of self-care, pain/discomfort and anxiety/depression. A study of EQ-5D in stroke patients conducted by Dorman et al found that the ICC for mobility dimension and EQ-5D index was >0.75 while in other dimensions it was between 0.4 and 0.75. Hurst et al conducted a study of EQ-5D in rheumatoid arthritis patients and found that the ICC of EQ-5D index and EQ-5D VAS was >0.75. The three studies found that EQ-5D had good to excellent intraobserver reliability and there was no bad ICC value (<0.4). Harmaini found that the ICC value ranged from 0.611 to 0.936 with the highest ICC value for mobility and the lowest value for anxiety/depression while the Cronbach’s α was in the elderly population.

We conducted an intraobserver test-retest instead of the interobserver test because the assessment and the measurement tool were performed by the respondents. The interobserver test is performed if the measurement tool that will be tested needs the evaluation from the researcher, for example in measuring the blood pressure using a manometer, reading plain chest X-ray, or reading plain radiograph of the knee. If
the interobserver test had been conducted in this study, the outcome would have been different from the intraobserver test because of the cognitive differences between those of the respondents and those of the observers.

The Cronbach’s $\alpha$ value of the internal consistency reliability of this study was 0.6772. The use of internal consistency to evaluate the EQ-5D reliability is still debatable. Some authors state that it is not needed but others, such as Velarde-Jurado et al., stated that EQ-5D internal consistency could be performed although he did not report the Cronbach’s $\alpha$ value in his article. The Cronbach’s $\alpha$ value obtained in this study was <0.7, indicating that EQ-5D in knee OA patients had a low level of confidence.21–23

The low level of confidence of Cronbach’s $\alpha$ value in this study was caused by various factors: the anxiety/depression dimension was not always present in knee OA respondents, and self-care and pain dimension did not affect the daily activities of the knee OA patients. Because of the various factors above, a low Cronbach’s $\alpha$ value did not indicate that EQ-5D had a low reliability. By passing two reliability tests—ICC value of EQ-5D was from good to excellent and Cronbach’s $\alpha$ value was of low confidence level—we can say that the Indonesian version of EQ-5D had reliability to measure the health-related quality of life in knee OA patients with ICC ranging from 0.883 to 0.907 and Cronbach’s $\alpha$ of 0.6772.

The validity of EQ-5D to measure health-related quality of life in knee OA patients in this study was assessed using two methods: external validity by comparing EQ-5D and SF-36 of the Indonesian version, and the construct validity of EQ-5D.

In Great Britain, EQ-5D and SF-36 had been proven valid for measuring the health-related quality of life in the elderly. SF-36 was also used to measure the quality of life in Indonesia.14,21–25

We analyzed the external validity of EQ-5D compared to SF-36 by using the Pearson’s correlation coefficient test and found a significant correlation ($p<0.01$) that included the correlation between the EQ-5D dimension, EQ-5D index with SF-36 dimension and total score of SF-36. The correlation test for EQ-5D VAS with the physical function dimension and the SF-36 role-physical, or SF-36 total score also had significant correlation ($p=0.01$).

Such type of validation method, comparing one questionnaire with another, is commonly used to assess the validity of the quality of life questionnaire, including the questionnaire for knee OA patients. For example, Fransen et al. compared EQ-5D, WOMAC, and SF-36.

A similar study had been conducted by Brazier et al. in Great Britain in 1993, who studied the validity of EuroQol of the general population by comparing it with SF-36. EuroQol was a questionnaire similar to EQ-5D but with one additional question: family activity. They obtained a similar outcome, in which EuroQol had significant correlation with SF-36 with the exception of the correlation of SF-36 mental health dimension with EuroQol mobility and self-care dimension.

From the above data, comparing EQ-5D with SF-36 could be used as a mean to assess the external validity of EQ-5D; thereby we could say that the EQ-5D form has external validity to measure the quality of life of knee OA patients.

The construct validity in this study was conducted by finding the correlation of values of each dimension with the EQ-5D index score. Ancoz stated that this is a permissible method to determine construct validity. Ohinmaa et al. also used the same method to measure the health-related quality of life of the elderly in Finland.

The EQ-5D construct was tested using Pearson’s correlation test, which showed that EQ-5D had a good construct. All EQ-5D dimensions were significantly correlated with EQ-5D index ($p<0.01$). A study in Finland conducted by Ohinmaa et al. obtained the same result, in which all EQ-5D dimensions were correlated with EQ-5D index.

By passing the two methods of validity test, this study proved that the EQ-5D form is a valid measurement tool to measure the health-related quality of life of knee OA patients.

The EQ-5D form could be used to assess health-related quality of life. In this study we could see an example of assessment of health-related quality of life of knee OA patients in table 4, table 5, and figure 2 in further detail.

The mean value of health-related quality of life of knee OA patients in this study using EQ-5D index was 0.734 and the mean value of EQ-5D VAS was 71.98. Below are studies from other countries for comparison. Fransen et al. in Australia in 1999 conducted a reliability and validity study of knee OA patients above 50 years old and found that the mean value of EQ-5D index was 0.58 and EQ-5D VAS was 71.3. Ohinmaa et al. in Finland in 2001 conducted a survey of health-related quality of life of a general population of above 75 years old and found that the mean EQ-5D index was 0.67 and EQ-5D VAS was 51. Brazier et al. in Great Britain in 1996 found that the mean EQ-5D index was 0.61 and the EQ-5D VAS was 68 in the female population of above 75 years old. Kind et al. in 1998 studied the health-related quality of life using EQ-5D in the general population and found that the mean EQ-5D VAS of those above 80 years old was 72. Badia et al. found that the value of EQ-5D VAS was 60.6 in those aged above 65.

The value of EQ-5D index in this study was higher than the ones of other countries. This is because the respondents in this study were patients of knee OA who must also had suffered from chronic diseases and have adapted to the Indonesian sociocultural environment while the respondents in the studies conducted in other countries were knee OA sufferers. This community with or without comorbidity and had a sociocultural environment that was different from that in Indonesia.30–33

The value of EQ-5D VAS in this study was similar to that in a study conducted by Fransen et al. in Australia. We must note that in the assessment of the quality of life, it is difficult to determine whether the level of one’s quality of life is better or worse than that of another by only comparing the outcome of one study with another.

Quality of life is dynamic and influenced by many factors.34–43 When we use the EQ-5D index or EQ-5D VAS to assess the quality of life of an individual/society, it is better to evaluate the change of values rather than evaluate the value at
Although the score of EQ-5D index in this study was higher and the EQ-5D VAS was almost the same as those of other countries, the health-related quality of life in Indonesia is not always better than those in other countries. Further studies are needed to obtain the data of quality of life of knee OA patients in Indonesia. Kline\(^1\) determined that the value of \( r = 0.3 \) was the level of correlation coefficient that could be accepted to assess the validity of a questionnaire if there are not any measurement tools as a gold standard to measure a variable. In Indonesia there has not been any gold standard to measure the health-related quality of life of knee OA patients.

The result in this study showed that the value of \( r \) (absolute) of all the EQ-5D dimensions was above 0.3. This indicated that all the EQ-5D dimensions could be used for clinical applications to determine the quality of life of knee OA patients.

CONCLUSIONS

The EQ-5D index had significant correlation with the SF-36 pain dimension and SF-36 total score while EQ-5D VAS was correlated with the SF-36 dimensions of physical functioning, role-physical, and SF-36 total score.

In clinical practice, if there is a difference in the scores of EQ-5D index and EQ-5D VAS (for example, if the EQ-5D index is maximum (score of 1) and EQ-5D VAS is only 50), the EQ-5D index is more reliable as the value of health-related quality of life since the value of health-related quality of life using VAS is the subjective expression of an individual and is influenced by cognitive factors.\(^{44}\)

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Correlation of interleukin-17 with disease activity and hand joint damage in patients with rheumatoid arthritis

JA Ongkowijaya,1 B Setiyohadi,1 IARW Manuaba,2 YI Kasimir1

ABSTRACT

Background: Rheumatoid arthritis (RA) is a disease involving various types of cytokines. One of them is interleukin-17 (IL-17), which is known to have a pleiotropic effect on various cells and is thought to be a cytokine effector contributing to the pathogenic condition in RA.

Methods: The study was conducted on 46 RA patients at rheumatology clinic at the Cipto Mangunkusumo General Hospital who were diagnosed based on the 1987 American College of Rheumatology criteria. Sample selection was done using consecutive sampling. Tests on patients were conducted to collect data needed to obtain the scores for 28-joint Disease Activity Score (DAS28), global health visual analogue scale, swollen joint count, tender joint count, sedimentation rate, Sharp score (radiograph of both hands), and the IL-17 level.

Results: The majority of patients (87%) were women. The largest percentage was in the 51- to 60-year-old group (39.1%). Most patients (43.1%) had moderate disease activity. There were 27 patients (58.69%) with positive rheumatoid factor. The mean IL-17 level was 17.28 pg/mL with a standard deviation of 11.43 pg/mL. There was no correlation of IL-17 level with disease activity (p = 0.446, r = 0.021) and Sharp score (p = 0.304, r = 0.077) in subjects of this study.

Conclusion: There was no significant correlation of IL-17 with disease activity and joint damage.

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by polyarthritis and chronic synovitis resulting in joint damage. Although the pathogenesis of RA is not yet fully understood, it has been proven that the mechanism involves T cells, B cells, macrophage, neutrophil, and synovial fibroblast.1–4 The various types of cytokines produced by those cells play an important role in the development of inflammation, articular destruction, and other comorbid related to RA. Since the disease activity of RA patients is closely related to changes in levels of those cytokines, the management of RA today involves manipulation of the cytokine tissue.5–7

Tumor necrosis factor α (TNFα) is the main cytokine in the pathogenesis of RA. Although inhibition of TNFα had showed good results in RA treatment, there are still cases that did not show good response; thus there must be other cytokines involved that could be used as alternative targets for intervention.7 One of them is interleukin (IL)-17, the cytokine produced by T cells. Interleukin-17 has a pleiotropic effect on various cells including macrophage and fibroblast and could be a strong candidate for being the cytokine effector that contributes to pathogenic RA. In this study, we examine the correlation of serum IL-17 level with disease activity and Sharp score in RA patients.

METHODS

This is an analytical study using cross-sectional method. The study was performed at the Division of Rheumatology of the Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta from January until February 2010. This study has passed the ethical clearance set by the ethical committee.

The subjects of this study were new and existing RA patients at rheumatology clinic at the Cipto Mangunkusumo General Hospital. The subjects were selected using consecutive sampling. The size of the sample was calculated using the correlation coefficient equation for single sample in which α = 5% and β = 10%, Zα = 1.96 and Zβ = 1.28. The correlation coefficient (r) of serum IL-17 level with disease activity and joint damage in hand radiography of RA patients were estimated at 0.5; so the result for the sample size was 37.7 (rounded up to 40).

The inclusion criteria were RA patients who fulfilled the 1987 American College of Rheumatology criteria, older than 16 years during the onset of disease, and willing to participate in the study by signing informed consent. The exclusion criteria were presence of clinical signs of acute infection or other inflammatory process. The patients underwent routine examinations (history taking, physical examination, laboratory tests according to the needs for data collection) and finally radiography of both hands. The data collected were processed using Statistical Package for the Social Sciences (SPSS) program.

Interleukin-17 is a cytokine present in the circulation of RA patients. IL-17 level was quantified using enzyme-linked immunosorbent assay and
measured in pg/mL. The reagent used was Quantikine Human IL-17 Immunoassay (R and D System Inc., Minneapolis, USA). The measurement scale is numeric.

Disease activity was measured using 28-joint Disease Activity Score (DAS28) with four variables: swollen joint count (SJC, total 28), tender joint count (TJC, total 28), sedimentation rate (SR), and global health assessment using visual analogue scale (VAS) with a scale ranging from 0 to 100. The measurement scale is numeric.

Joint damage in hand radiograph was measured using Sharp score and obtained from the total score of joint space narrowing in 16 areas and bone erosion in 17 areas of the radiographic image of the right and left hands. Hand radiographs were taken in the anterior-posterior position using the device from Toshiba KXO-15E, DRYFIX 7000, Capsula FCR XLII. The measurement scale is numeric.

RESULTS
Characteristics of subjects
Of the 46 subjects involved in this study, 40 patients were women (87%) and 6 were men (13%). Their ethnic background and origins varied: Javanese 15 patients (32.6%), Sundanese 12 (26.1%), Batak 7 patients (15.3%), Betawi 3 patients (6.6%), Minang 3 patients (6.6%), Lampung origin 2 (4.5%), and one patient of each of Dayak, Malay, and Aceh origin (2.2%).

Mean age of the subjects was 48.6 years old, mostly were in the 51- to 60-year-old age group. The distribution of the age group were as follows: 1 patient (2.2%) was in the 21- to 30-year-old group, 8 patients (17.4%) in 31- to 40-year-old group, 15 patients (32.6%) in 41- to 50-year-old group, 18 patients (39.1%) in 51- to 60-year-old group, and 4 patients (8.7%) in 61- to 70-year-old group.

The outcome of the disease activity score based on DAS28 were as follows: 13 patients (28.3%) had high activity (DAS28 >5.1), 19 patients (41.3%) had moderate activity (3.2<DAS28≤5.1), 8 patients (17.4%) had low activity (2.6<DAS28<3.2), and 6 patients (13%) had remission (DAS28 ≤2.6).

Twenty seven (58.69%) patients had positive rheumatoid factor while 19 patients (41.31%) had negative rheumatoid factor.

Other characteristic data obtained such as the tender and swollen joint counts, global health VAS score, DAS28 score, IL-17 level, and Sharp score are presented in table 1 while the distribution of serum IL-17 levels of the RA patients according to the disease activity are presented in table 2.

Correlation between IL-17 level and disease activity
Serum IL-17 level tests were conducted on the 46 patients. The mean level obtained was 17.28 pg/mL with a standard deviation of 11.43 pg/mL. Normality test of the transformed IL-17 data and DAS28 showed a normal distribution; hence Pearson’s correlation test was used. Although IL-17 level was assumed to fluctuate in the serum according to disease activity, the outcome of the Pearson’s test in this study showed that there was no significant correlation between IL-17 level and disease activity measured with DAS28 (p = 0.446, r = 0.021). The scatter diagram of the correlation between IL-17 level and DAS28 is presented in figure 1.

Correlation between IL-17 level and hand joint damage
Hand joint damage in this study was measured using Sharp score that consists of joint space narrowing and bone erosion score based on the radiographic examination.

Correlation between IL-17 level and joint space narrowing score
Normality test revealed that the variable data of joint space narrowing had an abnormal distribution; so nonparametric statistics was used for the bivariate analysis. The outcome of the Spearman’s test between IL-17 level and joint space narrowing in hand radiograph showed no significant correlation (p = 0.406, r = 0.036). Figure 2 shows the scatter diagram of the correlation between IL-17 level and joint space narrowing score.

Table 1 Characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>48.61 (9.23)</td>
<td>50 (29–67)</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>5.41 (6.28)</td>
<td>3 (0–22)</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>2.54 (3.67)</td>
<td>0 (0–14)</td>
</tr>
<tr>
<td>Global health VAS</td>
<td>17.50 (17.76)</td>
<td>10 (0–70)</td>
</tr>
<tr>
<td>Sedimentation rate, mm/hr</td>
<td>58.50 (32.10)</td>
<td>52.5 (3–116)</td>
</tr>
<tr>
<td>DAS28 score</td>
<td>4.24 (1.37)</td>
<td>4.30 (1.74–7.46)</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td>5.41 (6.22)</td>
<td>3 (0–21)</td>
</tr>
<tr>
<td>Bone erosion score</td>
<td>3.48 (4.71)</td>
<td>2 (0–18)</td>
</tr>
<tr>
<td>Sharp score</td>
<td>8.89 (9.87)</td>
<td>5 (0–34)</td>
</tr>
<tr>
<td>Interleukin-17 level, pg/mL</td>
<td>17.28 (11.43)</td>
<td>13.44 (8.11–73.23)</td>
</tr>
</tbody>
</table>

VAS, visual analog scale; DAS28, 28-joint Disease Activity Score.

Table 2 Distribution of serum interleukin-17 (IL-17) level of RA patients according to the disease activity

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>6</td>
<td>14.03 (4.33)</td>
<td>9.83–20.68</td>
</tr>
<tr>
<td>Active</td>
<td>40</td>
<td>17.77 (12.10)</td>
<td>8.11–73.23</td>
</tr>
</tbody>
</table>

Figure 1 Correlation between interleukin-17 (IL-17) level and 28-joint Disease Activity Score (DAS28).

Figure 2 Correlation between IL-17 level and joint space narrowing score.
Figure 2: Correlation between interleukin-17 (IL-17) level and joint space narrowing score.

Correlation between IL-17 level and bone erosion score
The normality test of the variable data of bone erosion showed an abnormal distribution; so nonparametric statistics was used for the bivariate analysis. The correlation between IL-17 level and bone erosion showed a trend in which the higher the IL-17 level, the greater the erosion becomes. However, statistical test using Spearman’s test failed to show a significant correlation (p = 0.181, r = 0.138). The scatter diagram of the correlation between IL-17 level and bone erosion score is shown in figure 3.

Figure 3: Correlation between interleukin-17 (IL-17) level and bone erosion score.

Correlation between IL-17 level and Sharp score
The Sharp score is the total value of the joint space narrowing and bone erosion in hand radiograph. The normality test of variable data of the Sharp score showed an abnormal distribution; so nonparametric statistics was used for the bivariate analysis. The outcome of the Spearman’s test between IL-17 level and Sharp score showed no significant correlation (p = 0.304, r = 0.077). The scatter diagram showing the correlation between IL-17 level and the Sharp score is presented in figure 4.

Figure 4: Correlation between interleukin-17 (IL-17) level and Sharp score.

DISCUSSION
In recent years there are increasing numbers of RA cases found, which may likely be related to the increased awareness of this disease. In the general population, the prevalence of RA is higher in women and increases with age. Approximately 0.12% of patients was in the age group of 16 to 44 years old and rises to 2.99% in the above 75-year-old age group. In this study we found more female patients (87%) than male patients with a ratio of 6.7 to 1. The subjects were from different ethnic groups of Indonesia but were not representative of the various ethnic groups spread across Indonesia. The ethnic factor is reported to influence the prognosis of RA. The subjects in this study were mostly in the 51- to 60-year-old age group; however, the tendency of RA prevalence in Indonesia is in the younger age group. The reason for this different finding is still not clear.

The mean serum IL-17 level of the subjects was 17.28 pg/mL with a range of 8.11–73.23 pg/mL. It is higher than the level found in healthy individuals in other studies: 0.28–5.47 pg/mL as reported by Ciprandi et al., 0.0–13.4 pg/mL with a mean of 7.4 pg/mL by Arican et al., and a mean of 0.01±0.0 pg/mL by Hussein et al. The IL-17 levels found in this study were also higher than those in psoriatic arthritis patients. However, due to the lack of control group we cannot yet draw a conclusion whether IL-17 level in the subjects of our study was higher than healthy individuals in our population. Regarding this issue, we are planning to publish an extended report of this study with inclusion of a control group.

Table 3: Interleukin-17 levels (pg/mL) in healthy people, arthritis, and allergy

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Arthritis</th>
<th>Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprandi et al</td>
<td>0.28–5.47</td>
<td>-</td>
<td>1.81–141.29</td>
</tr>
<tr>
<td>Arican et al</td>
<td>0.0–13.4</td>
<td>8.3±3.8*</td>
<td>-</td>
</tr>
<tr>
<td>Hussein et al</td>
<td>0.01±0.0</td>
<td>0.2±0.1**</td>
<td>-</td>
</tr>
<tr>
<td>This study</td>
<td>-</td>
<td>8.11–73.23</td>
<td>-</td>
</tr>
</tbody>
</table>

*psoriatic arthritis; **rheumatoid arthritis.
Based on the disease activity, only 6 patients (13%) had remission while most patients (41.3%) had moderate activity. The cause of low remission rate among patients in this study—either suboptimal treatment or others—is still open for further studies.

Routine clinical follow-ups of RA patients should be performed by their personal doctors. Evaluation of disease activity score is important in the follow-ups, since the result will have an effect on the disease management. As one of the inflammatory cytokines that played role in the pathogenesis of RA, fluctuations of IL-17 concentration will influence disease activity. Shaharara et al\(^6\) reported an increased number of Th17 cells found in the synovial fluid and peripheral blood of RA patients. Hussein et al\(^{15}\) reported higher levels of serum IL-17 in RA patients than those in healthy control subjects. In addition, Anderson et al\(^2\) reported high expression of IL-17 in the synovial tissue and circulation. Romagnani\(^{17}\) also explained the presence of high IL-17 level in the serum that plays a role in the process of recruitment, activation, and migration of neutrophils and stimulates production of IL-22, which greatly increases in chronic inflammation. The involvement of the above cytokine will cause migration of inflammatory cells and an increase in immune complex formation. These conditions will clearly result in an increase in disease activity.

We found no significant correlation between serum IL-17 level and disease activity (\(p = 0.446, r = 0.021\)) in this study. There are several possible explanation for this finding. First, IL-17 may not be the dominant cytokine in the subjects. Second, it has to act through certain mediator and thus has only indirect effect on the disease activity. Further studies using other methods are needed to determine the actual role of IL-17 and its relation to disease activity. The outcome in this study was similar to those of Yamada et al\(^{18}\) and Zrioual et al,\(^9\) who also found no significant correlation between IL-17 and DAS28.

It is clear from the distribution of IL-17 level according to disease activity that patients in remission or active state have higher mean levels than healthy people with a tendency that IL-17 levels are higher in active RA. Despite this finding, we found that the two groups showed no significant difference (\(p = 0.29\)).

Hand joint damage in this study was evaluated using Sharp score, a radiographic examination to evaluate two conditions: joint space narrowing and bone erosion score. Narrowing of joint space (which occurs primarily as a result of the deterioration of the joint cartilage) and bone erosion are irreversible conditions, the process of which occurs during a certain period of time.

Cytokine synthesis is a cellular activity mediated by the messenger ribonucleic acid (mRNA), an unstable molecule that causes the cytokine synthesis to be a transient process. The involvement of cytokine in RA pathogenesis, mainly in synovitis, is characterized by the migration of inflammatory and immune cells to the synovial tissue. Besides local effect, cytokine also causes systemic effect, especially in acute attacks, with severe inflammation and constitutional symptoms of fever, weakness, fatigue, and muscle pain. Despite this, chronic inflammatory process seems to be dominant in the joint space and tissue.\(^{20}\)

Interleukin-17 will bind to the IL-17 receptor and is expressed in the epithelial cell, endothelial cell and fibroblast, then it will trigger transcription activation of nuclear factor-\(\kappa\)B (NF-\(\kappa\)B) and protein-38, which is a mitogen-activated protein kinase, and finally will stimulate secretion of IL-1, TNF\(\alpha\), IL-6, IL-8 or prostaglandin E2; therefore, IL-17 has an important role in immune regulation and inflammatory response, tissue homeostasis, and progression of autoimmune disease. In addition, IL-17 also has a synergic effect with TNF\(\alpha\) and IL-1 in inducing joint inflammation and destruction of bone and joint cartilage.\(^{21,22}\)

From the analysis of this study, we could not obtain enough evidence to show statistically significant correlations of serum IL-17 level with joint space narrowing, bone erosion, and Sharp score. Correlation between IL-17 and hand joint damage could possibly be proven if the tests were conducted in serial. Moreover, the subjects were not in the acute phase. Local inflammation in the form of synovitis was dominant in the subjects even when they were not in remission, which could possibly be caused by the indirect role of IL-17 in causing bone and cartilage destruction. In addition, Moran et al\(^{23}\) reported that the joints of RA patients during an inflammatory state also produces IL-17 locally, resulting in joint cartilage damage, especially with presence of other cytokines such as TNF\(\alpha\) and oncostatin M.

CONCLUSIONS

The mean serum IL-17 level in RA patients in this study was 17.28 pg/mL. A more definitive conclusion regarding IL-17 level in our population may be achieved by the inclusion of a control group. The serum IL-17 levels in active RA patients were higher than those of patients in remission. The serum IL-17 level of RA patients in this study was not significantly correlated with disease activity (DAS28) and hand joint damage (Sharp score). The actual role of IL-17 in the pathogenesis of RA is still to be proven in further studies.

REFERENCES


Prevalence of anti–C-reactive protein autoantibody and its correlation with disease activity in systemic lupus erythematosus patients at Cipto Mangunkusumo General Hospital

Lusiani,1 B Setiyohadi,2 N Sukmana,3 M Abdullah4

ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease with various underlying mechanisms characterized by autoantibody overproduction. It has been known that mortality and morbidity of SLE was higher in Asian patients compared with white patients. Several studies had showed that C-reactive protein (CRP) has the ability to suspend the progression of SLE through regulatory and clearance pathway, and low level of CRP and high level of anti-CRP antibody has been detected in SLE patients. A question raise whether mortality and morbidity in Asian SLE patients are associated with anti-CRP antibody.

Objective: To study the prevalence of anti-CRP antibody and its relationship with disease activity in SLE patients at Cipto Mangunkusumo General Hospital, Jakarta.

Methods: This is a cross-sectional study conducted at Cipto Mangunkusumo General Hospital from December 2009 until May 2010. Subjects were SLE patients who were diagnosed based on the 1982 American College of Rheumatology criteria. Disease activity was measured using the Mexican SLE Disease Activity Index scoring system. Anti-CRP antibody assay was performed using the Western blot analysis. Correlation between the presence of anti-CRP antibody and disease activity was evaluated using the T-test and multivariate logistic regression analysis.

Result: Forty SLE patients with a mean age of 31.65 (SD 8.84) were enrolled in the study, 33 of which (82.5%) had positive autoantibody to CRP pentamer. The anti-CRP antibody was significantly correlated (p = 0.024) with disease activity.

Conclusions: There was a relatively large proportion of patients with positive anti-CRP antibody among SLE patients in Cipto Mangunkusumo General Hospital. There was also a significant correlation between anti-CRP antibody and the disease activity.

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by autoantibody overproduction, with a very wide clinical symptoms and various etiopathology that are yet to be discovered.1,2 Many interesting researches have been done to investigate the mechanism that lies underneath this unique and dynamic disease. We now know several autoantibodies involved in this disease, including autoantibody against nuclear antigens, circulating immune complex, activated complement, and extracellular antigens (including plasma protein such as C-reactive protein (CRP) and sphingolipid activator protein).

The prevalence of SLE is 3 times higher in Asian compared with white population.3,4 A study that reviewed medical journals published between 1950–2006 found a wide variations of incidence and prevalence of SLE in many countries. This variation described the differences among different populations, geography, race, and time. It also provide important clues concerning the etiology of this disease,5 and suggest the possibility of a specific SLE etiopathology in Asian race.

There are many factors that contribute to the pathogenesis of SLE, including genetic, sex, environmental exposure, certain diseases, disorder of the immune system, and autoantibody formation.4 Recent studies revealed that besides the common autoantibodies in SLE patients, antibody to C-reactive protein also played some roles in the pathogenesis of SLE. C-reactive protein is believed to possess the ability to limit SLE disease progression through clearance and regulatory pathways.

There have been several researches, with varying results, regarding the presence of anti-CRP antibody and its relationship with disease activity. Bell et al6 in 1998 reported no relationship between anti-CRP antibody and disease activity. However, Sjowall et al7 in 2004 reported contrasting results. Regarding this fact, a question raises whether any relationship exist between higher mortality and morbidity in Asian SLE patients and formation of anti-CRP antibody. Fischbacher et al8 in 2003 had found that autoantibody formation was higher in Asian patients in comparison with white population (13.5 g/dL vs. 7.4 g/dL, respectively).

Based on those findings, we would like to investigate the prevelance of antibody to CRP among SLE patients in Cipto Mangunkusumo General Hospital and its association with disease activity.
METHODS
Study design
This is a cross-sectional study conducted at rheumatology, hematology and allergy-immunology clinic at Cipto Mangunkusumo General Hospital, Jakarta from December 2009 until February 2010. The sample size was calculated using formula for proportion estimation of a population and coefficient correlation for single sample. The dependent variable in this study was the positivity of anti-CRP antibody, while the independent variable was disease activity according to Mexican Systemic Lupus Erythematosus Disease Activity Index (Mex-SLEDAI) scoring system. Guzman et al in a study that compared three clinical indices (Lupus Activity Criteria Count, SLE Disease Activity Index (SLEDAI), and Mex-SLEDAI) in measuring disease activity in SLE patients found that all those indices showed significant association with experts’ judgment, managing physician’s opinion, changes in treatment and clinical course, with good convergent validity (rs = 0.76 to 0.79, p<0.0001), and responsiveness. The study also concluded that Mex-SLEDAI was the least expensive instrument.

Subjects
Inclusion criterion were native Indonesian patients who fulfilled the 1982 revised American College of Rheumatology criteria for SLE. The study protocol had been approved by the appropriate local ethical board. All patients were then asked to give informed consent.

Measurement
Blood and urine sample collection was performed to acquire necessary data to measure disease activity according to Mex-SLEDAI (complete blood count, differential count, reticulocyte count, serum creatinine, creatine kinase, urinalysis, and 24-hour quantitative protein) as well as level of CRP and anti-CRP antibody. Anti-CRP antibody was bound with alkaline-phosphatase-conjugated anti-human IgG (Dako, Glostrup, Denmark). Human CRP (Sigma Chemical Co., St. Louis, USA) was used for negative marker. We also examined factors contributing to the increase in IgG autoantibody: statin and/or steroid use, smoking, alcohol consumption, body mass index, duration of illness, ethnicity, and number of involved organ/organ system.

Anti-CRP autoantibody assay
Anti-CRP autoantibody was quantified using the mini Westerblot assay. The sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) procedure was carried out by making 5 mL of 8% separating gel, which was left overnight at room temperature, followed by preparation of 2 mL of 5% stacking gel. After 45 minutes, CRP + reducing sample buffer (RSB) (each contain 10 μg of CRP) and marker were poured in each appropriate wells. Running the SDS-PAGE procedure until the protein move at the ± 2 mm bottom glass plate. And then run the transfer procedure using polyvinylidene fluoride (PVDF) and filter paper with voltage set for about 1.5 hours in 150 mV. After the transfer process was done, the PVDF paper was blocked by 5% of phosphate-buffered saline with skim milk and was stored overnight at temperature of 4°C. In the following day, the PVDF paper was washed three times with phosphate-buffered saline Tween 20 (PBST) and was cut into 10 lanes/well. Each lane was mixed with appropriate sample serum at a concentration of 1:500 and was stirred for about 1 hour at room temperature. The PVDF was then washed with PBST for three times, each take as long as 5 minutes. Each PVDF was added with secondary autoantibody at a concentration of 1:2000 and left for 1 hour at room temperature, then washed three times with PBST. PVDF will be set in the hypercassette and added with electrochemiluminescence solution and then exposed in the dark room to get the result.

Statistical analysis
In this study we analyzed the correlation of demographic and clinical characteristics with the positivity of anti-CRP antibody. We used bivariate analysis for correlation test using unpaired T-test (or Fischer’s exact test for abnormally distributed data), then continued with multivariate logistic regression analysis.

RESULTS
A total of 40 SLE patients were recruited, with the following characteristics: all were women, ranging from 20 to 57 years old; 60% had medium educational level, 57.5% were married, 47.5% worked as homemakers, 60% belonged to the low income level group, and the majority (42.5%) were Javanese. The demographic and clinical characteristics of the patients are elaborated in table 1 and 2.

Table 1 Demographic characteristics of patients (N = 40)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Female</td>
<td>40 (100.0)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>13–45 years old</td>
<td>35 (87.5)</td>
</tr>
<tr>
<td>&gt; 45 years old</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
</tr>
<tr>
<td>Low (none–primary school)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Medium (junior high school–senior high school)</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>High (diploma, bachelor, master degree, or higher)</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Married</td>
<td>23 (57.5)</td>
</tr>
<tr>
<td>Job</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Civil servant</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Entrepreneur</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Student</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Employee</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>Income level</td>
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<tr>
<td>Low (&lt;1 million rupiah/month)</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>Middle (1–5 million rupiah/month)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Middle–high (&gt;5 million rupiah/month)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Ethnicity</td>
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</tr>
<tr>
<td>Javanese</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Sundanese</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Betawi</td>
<td>10 (25.0)</td>
</tr>
<tr>
<td>Batak</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Minang</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Lampung</td>
<td>1 (2.5)</td>
</tr>
</tbody>
</table>

*Unless otherwise specified.
Table 2 Clinical characteristics of patients (N = 40)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)*</th>
<th>Anti-CRP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti–C-reactive protein</td>
<td></td>
<td>Positive</td>
<td>33 (8.25)</td>
</tr>
<tr>
<td>Negative</td>
<td>7 (17.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mex-SLEDAI score</td>
<td></td>
<td>&lt;5</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>≥5</td>
<td>29 (72.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP level, mg</td>
<td></td>
<td>&lt;5</td>
<td>31 (77.5)</td>
</tr>
<tr>
<td>≥5</td>
<td>9 (22.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid (prednisone-equivalent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dose, mg/day</td>
<td></td>
<td>&lt;11</td>
<td>28 (70)</td>
</tr>
<tr>
<td>11–40</td>
<td>11 (27.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41–100</td>
<td>1 (2.5)</td>
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<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td></td>
<td></td>
<td>22.32 (4.39)</td>
</tr>
<tr>
<td>Alcohol consumption**</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td>1</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Statin use</td>
<td></td>
<td>4</td>
<td>(10.0)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td></td>
<td>24</td>
<td>(60)</td>
</tr>
<tr>
<td>Number of involved organ/organ system, mean (SD)</td>
<td>3.4 (1.39)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unless otherwise specified.
**Defined as alcohol consumption of >2 servings/day (male) or >1 serving/day (female).
Mex-SLEDAI, Mexican Systemic Lupus Erythematosus Disease Activity Index.

Anti-CRP antibody was found in 33 out of 40 patients (82.5%). Mex-SLEDAI score ranged from 0 to 22, with median value of 6. The mean number of involved organ/organ system was 3.40 with standard deviation of 1.39. Arthritis is the most common (62.5%) organ involvement, followed by mucocutaneous disorder (42.5%), fever (35%), hemolysis (25%), lymphopenia (25%), renal disorder (22.5%), serositis (15%), and vasculitis (2.5%). This study has a sensitivity and specificity of 91% and 100%, respectively.

Statistical analysis showed that positivity of anti-CRP antibody had significant correlation with the disease activity, but it had no significant correlation with most of the other variables (the demographic and clinical characteristics), except for two variables: renal disorder and number of involved organ/organ system (table 3). On subsequent multivariate analysis of these 3 variables we found that the Mex-SLEDAI score had significant correlation with anti-CRP (OR = 0.739, 95% CI 0.557–0.981) (table 4).

Table 3 Bivariate analysis of several clinical characteristics with anti–C-reactive protein (anti-CRP) antibody

<table>
<thead>
<tr>
<th>Variables</th>
<th>Positive</th>
<th>Negative</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mex-SLEDAI score, mean (SD)</td>
<td>8.33 (4.88)</td>
<td>3.57 (4.79)</td>
<td>0.024</td>
</tr>
<tr>
<td>CRP level, n (%)</td>
<td>26 (83.9)</td>
<td>5 (16.1)</td>
<td>0.645*</td>
</tr>
<tr>
<td>≥5 mg</td>
<td>7 (77.8)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Renal disorder, n (%)</td>
<td>22 (91.7)</td>
<td>2 (8.3)</td>
<td>0.094*</td>
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*Data have abnormal distribution; statistical analysis was performed using Fischer’s exact test.
Mex-SLEDAI, Mexican Systemic Lupus Erythematosus Disease Activity Index.

DISCUSSION

It is already known that SLE has higher incidence and prevalence among Asian patients, with higher morbidity and mortality. Related to the role of anti-CRP antibody in SLE, in this study we aimed to investigate the prevalence of anti-CRP antibody and its correlation with disease activity in Indonesian SLE patients at Cipto Mangunkusumo General Hospital, Jakarta. Because this study only included native Indonesian patient, we hope to be able to represent the diversity of different ethnicity in Indonesia.

Subjects in this study had a mean age of 31.65, with standard deviation of 8.84. This result differs from the result of a study by Juariah12 conducted at rheumatology outpatient...
clinics at Cipto Mangunkusumo General Hospital in 2008, which reported a mean age of 27.48. This discrepancy may be due to the relatively small sample size of this study. However, the mean age of patients in this study is relatively similar to those by Ndiaye et al in Dakar (mean age 34 years old) and Doria et al in Italy (mean age 36 years old). These findings emphasize the importance and influence of factors such as geography, methods and aim of the study, and genetics of the subjects on the result of a study.

We attempted to study the correlation of the demographic and clinical characteristics of our patients with the positivity of anti-CRP antibody; however, the statistical analysis revealed no significant correlation. This may be due to the fact that this study was conducted in one hospital with limited samples. A larger sample size may be needed for those variables to show a more significant correlation. Further studies should also take into consideration the fact that Indonesia consists of various ethnicity with very wide genetic difference.

In this study we used the Western blot analysis to measure anti-CRP antibody. The decision to use this qualitative method instead of the ideal enzyme-linked immunosorbent assay (ELISA) was made after previous attempts to use the method had failed due to optimization failure. The kappa value of the Western blot analysis was 0.7.

From the Western blot analysis we obtained two bands of proteins (figure 1). One contained molecules with weight ranging from 96 to 123 kDa. The anti-CRP antibody, which has a molecular weight of 105 kDa, was contained in this band. The other protein band contained molecules with weight ranging from 40 to 60 kDa. Autoantibodies to protein kinase-C, guanine nucleotide-binding protein Gi3, insulin-like growth factor–binding protein, actin-protein, ovalbumin, bovine serum albumin, and Hsp60 are molecules that may be contained in this band. The emergence of the latter protein band may result from the impurity of the reagents or the low specificity of the IgG reagents used for the detection of anti-CRP antibody.

There was a relatively larger proportion (82.5%) of positive anti-CRP antibody compared with a previous study by Sjowal et al who obtained a proportion of 40% (out of 10 subjects). The disparity may be explained by the different technique of anti-CRP measurement. Sjowal et al in his study used ELISA technique with normal control, while in this study we only utilized the qualitative Western blot analysis. Besides, the difference in sample size may also play a role.

The proportion of positive anti-CRP in this study is relatively similar to the study by Bell et al, which showed 78% positive anti-CRP. The study also detailed that they found autoantibody to m-CRP. CRP has two different conformational form: native CRP and the denaturated form called modified CRP (m-CRP). Hee Gu Lee et al conducted a research in the purification of CRP and found that pentamer CRP (naive CRP) had molecular weight of 118 kDa, and the sub unit (m-CRP) had molecular weight of 23.6 kDa. We reviewed several studies and found that molecular weight of pentamer CRP varies between 105 and 123 kDa. In this study we found IgG autoantibody formation to pentamer (native) CRP.

The mechanism of anti-CRP antibody formation in SLE is yet to be fully understood. Abnormality of innate and adaptive immune system may explain this phenomenon. Immune system imbalance in SLE is marked by an increase in B lymphocyte activity, which results in formation of a large number of autoantibodies, and decreased in vitro and in vivo cellular immune response. Dysfunction of T-helper lymphocytes and antigen-presenting cells could also play a role. Interleukin (IL)-10 is the most potent inductor of B lymphocyte differentiation and regulator of T-helper lymphocyte; thus overproduction of IL-10 or immune cells hypersensitivity to this cytokine may result in immune system imbalance. Recent studies have also found increased production of IL-10 by peripheral blood mononuclear cells (PBMC), which spontaneously release a large number of IL-10 in untreated patients. It was also stated that IL-6 plays an important role in the induction of autoimmunity in SLE, and at least half of the autoantibody production depends on IL-6.

Another theory stated that SLE patient have low level of regulatory T cells that express CD4, IL-2 receptor chain a (CD25), and CD45RO. Barreto et al found that there were decreased number of CD4+CD25+CD45RO+ T cells in SLE patient due to defect in conversion of FOXP3+CD25− to FOXP3+CD25+ cells. Frequency of CD4+CD25+CD45RO cells had a negative correlation with disease activity and level of anti–double-stranded DNA in patient and control groups.

In this study we found a significant correlation between anti-CRP antibody and disease activity, with an odds ratio of 0.739 (95% CI 0.557–0.981). It seems from this result that high disease activity “protects” the incidence of anti-CRP antibody formation. We propose several explanations for this contradictory result. Firstly, this study did not separate subjects according to disease activity. Such result may occur if the number of patients in remission were higher or almost equal with patients in active state of disease. Secondly, more than half of the patients (28 out of 40) were receiving corticosteroid therapy, with a dose equivalent to <11 mg/day of prednisone, which would suppress autoantibody formation.

Although statistical analysis showed significant correlation between anti-CRP antibody and disease activity, it is important to consider that the measurement of anti-CRP antibody was only done at one point and this is the limitation of this study. A larger, multi-centered, and multi-ethnic study using longitudinal design would provide a more reliable result concerning the association between anti-CRP antibody and disease activity.}

**CONCLUSIONS**

We found a high prevalence of anti-CRP antibody in SLE patient in Cipto Mangunkusumo General Hospital, Jakarta. There was also a significant correlation between anti-CRP antibody and disease activity. Further studies, ideally with larger sample size that may better encompass the diverse ethnic groups and genetic difference in Indonesia is needed to obtain better understanding of the various mechanisms involved in the pathogenesis of SLE.
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Invasive aspergillosis in a systemic lupus erythematosus patient

B Setiyohadi, MS Azizi, IW Yuliani, N Sukmana, Suhendro, M Simadibrata, CM Rumende, AS Sulaiman, R Wahyuningsih, Lisnawati, MA Yudharto, N Anggraini, R Sandra, F Oktaviana

Systemic lupus erythematosus (SLE) is an autoimmune disease with a broad clinical manifestation characterized by production of antibodies against cellular nuclear components. The prevalence of SLE among many countries is variable, ranging from 2.9 to 400 per 100,000. In Cipto Mangunkusumo General Hospital, the incidence of SLE between 1990 and 1998 is 37.3 per 10,000 hospitalization.

Patients with autoimmune disease have at least twofold risk of acquiring infections compared with healthy individuals. This may be due to the immunosuppressant therapy but could also caused by the primary immune dysregulation that was the basis for the pathogenesis of their disease, or other autoimmune disease manifestations such as lymphopenia. Infection is the main factor increasing the mortality and morbidity of SLE patients. A study in New York conducted between 1966 and 1976 involving 223 SLE patients reported 150 cases of infection, of which 23 were opportunistic infection: 12 were candidiasis while 11 others were deep fungal infection. The use of corticosteroids in SLE is the main factor that predispose patients to infection, particularly fungal infection.

Aspergillosis is the term used to denote all disease caused by any one of the pathogenic and allergenic species of Aspergillus. The annual incidence of aspergillosis in the United States is reported to be 1–2 per 100,000. Aspergillus fumigatus is the cause of most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes. The mortality rate of invasive aspergillosis is 50% when properly diagnosed and treated; otherwise it could be as high as 100%.

CASE REPORT
A 21-year-old woman presented with one-week history of throbbing headache. The pain, which radiated to the upper molar, was intermittent at first but had been gradually increasing in intensity and eventually became constant. The pain was not relieved by analgesics such as paracetamol or mefenamic acid.

The patient was diagnosed with SLE 4 years earlier and had since had regular follow-ups at the rheumatology clinic at our institution. She was treated with methylprednisolone 16 mg t.i.d. and mycophenolate mofetil (MMF) 500 mg b.i.d.

Four months prior to the admission, she began to notice enlargement of her left eye, which became gradually increasing in size, accompanied with mild and intermittent pain. She also experienced diplopia and a decrease in visual acuity of her left eye, but there was no complain of floaters. The ophthalmologist who examined her at that time suspected a neurological problem of the extraocular muscles of her left eye, and she was subsequently hospitalized for further investigations.

Head magnetic resonance imaging (MRI) conducted at that time revealed left maxillary, left frontal, and left ethmoid sinusitis. Three weeks after the MRI, the patient underwent head computed tomography (CT) scan, which showed left retrobulbar mass infiltrating the medial rectus and inferior rectus muscle of the left eye and roof of the left maxillary and left ethmoid sinus with destruction of the inferior orbital rim (figure 1A).

Figure 1 Head computed tomography of the patient at the time of admission (A) and after the administration of voriconazole (B).

For numbered affiliations see end of article
Three months prior to the admission, the patient began experiencing throbbing headache, which radiated to the upper molar and accompanied with nausea and vomiting. Since then she also had 15 kg decrease in body weight.

With suspicion of a tumor, the patient had a nasopharyngeal biopsy, which at that time only showed chronic sinusitis. A retrobulbar biopsy guided by nasoendoscopy conducted one week before the admission showed large necrotic areas containing *Aspergillus* hyphae (figure 2). There were also found fragments of granulation tissue and blood clots resembling the histopathological feature of aspergillosis.

Physical examination at the time of admission showed a blood pressure of 100/70 mmHg, pulse rate of 84 beats/min with good pulse volume, and respiratory rate of 16 breaths/min. Her body weight and height was 48 kg and 158 cm, respectively, with BMI of 19.27 kg/m². On eye examination we found proptosis, erythema, and edema of the left eye. There was no supra- or infraorbital tenderness.

Laboratory examination revealed anemia with hemoglobin of 10.3 g/dL, mean corpuscular volume of 76 fL, mean corpuscular hemoglobin of 25 pg, and mean corpuscular hemoglobin concentration of 33 g/dL; hematocrit was 32%, leukocyte count was $9.9 \times 10^3/mm^3$ (differential count: basophils 0%, eosinophils 0%, stabs 2%, segmenters 85%, lymphocytes 13%, and monocytes 0%), platelet count was $422 \times 10^3/mm^3$. Serum ureum level was 37 mg/dL (normal value <50 mg/dL), serum creatinine was 0.5 mg/dL (normal value 0.6–1.2 mg/dL), aspartate aminotransferase (AST) was 19 IU/L (normal value <27 IU/L), alanine aminotransferase (ALT) was 12 IU/L (normal value <36 IU/L), albumin was 3.8 g/dL, random blood glucose was 99 mg/dL, sodium was 139 mEq/L, potassium was 3.8 mEq/L, and chloride was 103 mEq/L. Complement component (C)3 and C4 was 95.40 mg/dL (normal value 90–180 mg/dL) and 39 mg/dL (normal value 90–180 mg/dL) respectively. Anti–double-stranded DNA (anti-dsDNA) was 1061 IU/mL (normal value 0–100 IU/mL). Her chest radiograph and electrocardiograph were unremarkable.

The patient’s diagnoses at the time of admission were chronic headache; retrobulbar aspergillosis; SLE with renal, hematological, and musculoskeletal involvement; and microcytic hypochromic anemia.

The patient was treated with tramadol 1 amp diluted in 500 mL of normal saline infused intravenously over 8 hours, paracetamol 750 mg, ibuprofen 200 mg, amitriptyline 5 mg, diazepam 1 mg, diclofenac sodium 50 mg t.i.d, MMF 500 mg b.i.d, methylprednisolone 4 mg t.i.d, calcium hydrogen phosphate 500 mg and cholecalciferol 133 IU t.i.d., folic acid 1 tab t.i.d., lansoprazole 30 mg q.d., and sucralfate syrup 5 mL t.i.d.

For the aspergillosis, she was treated with amphotericin B with a dose of 5 mg/day, which was gradually increased (5 mg/day) until a dose of 0.5–1 mg/kg body weight/day. After 14 days, the treatment was continued with oral itraconazole 400 mg q.d.

After one month of hospitalization, the headache and orbital edema had improved. The patient was thus discharged with outpatient follow-up and instruction to continue therapy with itraconazole 400 mg q.d, MMF 500 mg b.i.d., and methylprednisolone 8 mg t.i.d. At the time of discharge, she was in good condition with stable hemodynamics.

Magnetic resonance imaging at the end of the hospitalization showed malignant mass in the left retrobulbar area, which infiltrated the medial and lateral rectus muscle, left distal optic nerve, and left maxillary sinus. There were also left maxillary, ethmoid, and sphenoid sinusitis. Intracerebral area showed no abnormalities.

Two weeks after being discharged, the patient was rehospitalized because her headache, now worse than before, and left eye swelling had recurred. Laboratory examination results at that time were as follows: hemoglobin 8.7 g/dL, leukocyte count $22.43 \times 10^3/mm^3$, platelet count $271 \times 10^3/mm^3$, erythrocyte sedimentation rate 6 mm/hr, anti-dsDNA 370.5 IU/mL, C3 80.04 mg/dL, C4 39.36 mg/dL, antinuclear antibodies was positive at 1:3200 dilution with speckled and centromere pattern; aspartate aminotransferase was normal (29 U/L), but there was an increase in ALT level (167 U/L);
serum urea 36 mg/dL, serum creatinine 0.3 mg/dL, IgM anticardiolipin antibodies (ACA) 5.3, IgG ACA 6.8, IgM β2-glycoprotein I (β2GPI) 3.9, IgG β2GPI 1.9. Hemostasis: prothrombin time 13.1 sec (1 × control; normal value 9.8–12.6 sec), activated partial thromboplastin time 36.2 sec (1 × control; normal value 31.0–47.0 sec), and international normalized ratio 1.18.

Electroencephalography showed slow activity in the bilateral (predominantly left) frontal area. Diagnosis of the Department of Neurology was paraparesis ec. corticosteroid-induced myopathy. Referral to the Department of Ophthalmology returned with these results: proptosis of the left eye; visual acuity was >3/60 (right eye) and 0.5/60 (left eye); the anterior segment of both eyes and fundus of the right eye was normal but there was optic nerve head atrophy of the left eye; intraocular pressure of the right and left eye was 15.5 and 13, respectively. Head CT scan showed left retrobulbar mass filling the sphenoid, ethmoid, and left maxillary sinus, with infiltration of rectus muscles of the eye, apical segment of the left optic nerve, and intracranially into the left parasellar area.

Due to the deteriorated condition of her left eye, the patient was planned to undergo left orbital exenteration. However, her family did not consent to the plan; so we decided to administer an alternative treatment course of intracranal irrigation of amphotericin B 2.5 mg (25 mL) for 10 days. Before the initiation of treatment, we performed biopsy to obtain specimen for culture and susceptibility test.

On day 9 of the amphotericin B treatment, the patient developed fever. On physical examination we found a temperature of 38.1°C with normal pulse rate (96 beats/min). Laboratory examination revealed leukocytosis (18.28 × 10^3/mm^3); C-reactive protein was 51.4 mg/L and procalcitonin was >5 μg/L. She was diagnosed with sepsis ec. left orbital cellulitis. Amphotericin B was substituted with itraconazole 400 mg q.d. and meropenem 1 g t.i.d. for 10 days. Blood and pus cultures showed Aspergillus fumigatus, which in susceptibility test showed sensitivity to voriconazole and amphotericin B (with dose adjustment), and resistant to itraconazole. It was thus decided to administer intravenous voriconazole 300 mg b.i.d. on the first day continued with a dose of 200 mg b.i.d. for 10 days. At day 10 her treatment was continued with oral voriconazole 200 mg b.i.d. for 4–6 weeks.

Computed tomography after the administration of voriconazole showed pathologically enhanced heterogeneous lesion with air component in the left retrobulbar (intra- and extraconal) area infiltrating the rectus and oblique muscles of the eye and left optic nerve, with destruction of the ethmoid, sphenoid, inferior orbital wall and sphenoid wing, extending intracranially into the left parasellar area, and filling the left ethmoid, left maxillary, and sphenoid sinus (figure 1B). There was significant reduction of the mass in comparison with the previous CT. There was also left buccal cellulitis suggestive of fungal infection. The Department of Radiology confirmed the presence of intracranial infiltration; however, the intracerebral area in cavernous sinus was still intact.

**Figure 3** Results of blood and pus cultures: (A) colonies of *Aspergillus fumigatus*; (B) susceptibility test showed resistance to itraconazole (1) and sensitivity to amphotericin B (2) and voriconazole (3).

**Figure 4** Condition of patient’s left eye at the time of rehospitalization (left) and 4 weeks later (right).

After 4 weeks of hospitalization, the symptoms of headache and orbital edema had improved, although the vision loss of her left eye was permanent. Laboratory results were normal; ALT had decreased to 52 U/L, and was 7 U/L in a follow-up examination one month later. The patient’s lupus activity was also under control.

**DISCUSSION**

Systemic lupus erythematosus is a multisystem disorder caused by production of immune complex-forming autoantibodies and complement resulting in tissue damage. Infection is the main cause of morbidity and mortality in SLE patients, whose dysfunction of immune system is considered to play a role. Besides, administration of steroids and other immunosuppressive agents also contribute to the increased susceptibility to infection. Our patient, who was diagnosed with aspergillosis of the retro-orbital area and paranasal sinuses, had suffered from SLE and received long-term steroid and immunosuppressive medication, rendering her vulnerable to opportunistic infections.

Aspergillus sp. is very common in the environment. This group of fungi has hyaline (nonpigmented), septate, and branching hyphae that give rise to numerous conidia (spores). *Aspergillus fumigatus* is the most common cause of invasive aspergillosis. The main risk factors are severe neutropenia and the use of corticosteroids, although this disease can also occur in individuals without those conditions. The risk of invasive aspergillosis and mortality associated with this disease are also increased with longer duration and higher dose of corticosteroids. The incubation period varies between 2–90 days.
The initial presentation of our patient was a condition called orbital apex syndrome, a group of rarely encountered symptoms consisting of ophthalmoplegia, ptosis, and vision loss. Several conditions that can cause orbital apex syndrome are malignancy, inflammation, or, as in our case, infection. Because of its poor prognosis, diagnosis must be made early, especially when there is evidence of immunodeficiency risk factors.\(^5\)–\(^11\) Unfortunately, due to the posteriorly located mass at the orbital apex, the diagnosis of our patient was made 4 months after the development of initial symptoms.

Sinus involvement occurs in 5–10% cases of invasive aspergillosis. Other than fever, common symptoms are uncomfortable sensation in the nose or face, nasal congestion, and rhinorrhea, which sometimes are accompanied with blood. Asymmetric and swollen face, epistaxis, proptosis, cranial nerve abnormalities, and bone erosion are suggestive of fungal infection. Computed tomography or MRI are important diagnostic procedures but they lack the ability to distinguish between sinusitis caused by invasive aspergillosis and other forms of sinusitis, such as allergic, bacterial, or other fungal sinusitis.\(^5\)\(^,\)\(^9\)

Definitive diagnosis is made when one of the following is found: (1) positive culture of samples obtained from the affected lesion (e.g. brain abscess); or (2) positive histological examination and culture from samples obtained from the affected organ (e.g. sinus or skin). In our case, the patient had positive culture and showed histological feature of invasive aspergillosis.

Diagnosis of invasive aspergillosis can also be made by detection of galactomannan antigen or \(\beta\)-D-glucan; both are components of fungal cell wall. Galactomannan antigen is more specific in diagnosing invasive aspergillosis, while \(\beta\)-D-glucan may be detected in other invasive fungal infections. A meta-analysis showed that serum galactomannan antigen test has sensitivity and specificity of 71% and 89%, respectively. Histopathological examination may reveal area of infarction, invasion of hyphae into the blood vessels, or acute necrosis with limited inflammation. *Aspergillus* hyphae could be characterized as hyaline, narrow, septate, and dichotomously branching hyphae.\(^9\)

Culture is important in confirming the diagnosis of aspergillosis, since there are only very few other species of fungi that have similar histological features. Fungal growth medium is more sensitive than bacterial medium. From all cases of invasive aspergillosis, only 10–30% show positive culture, and about 40% are only diagnosed at autopsy.\(^5\)\(^,\)\(^9\)

Several antifungals have been known to be effective in treating invasive aspergillosis, such as voriconazole, itraconazole, posaconazole, caspofungin, micafungin, and amphotericin B. Voriconazole is the first line agent, while caspofungin, posaconazole, and amphotericin B lipid complex are second line agents. Intravenous administration is usually preferred in invasive aspergillosis. Duration of treatment varies from 3 months to several years, depending on host immunity and treatment response. Recurrence of infection may happen if there is suboptimal response to treatment or defective immune system.

Due to several limitations, our patient did not receive voriconazole as her treatment. It was then decided to give her amphotericin B as an alternative, administered both intravenously and locally (as intraconal irrigation). Amphotericin B exhibit fungicidal activity. Its potency depends on serum concentration and pathogen susceptibility. Amphotericin B may be administered intravenously, topically, or, in cases of ophthalmic infection, intravitreally and intracameraly.\(^12\)\(^–\)\(^14\) Reported adverse effects of amphotericin B include cardiac arrhythmia, acute kidney injury, and anemia.\(^15\)\(^,\)\(^16\)

After 14 days, the treatment of our patient was continued with oral itraconazole. Itraconazole is the oral agent of choice for treating chronic and allergic form of aspergillosis. It is one of theazole derivatives, which exert their fungicidal activity by inhibiting cell growth, resulting in cell death. Except fluconazole, all of the azole derivatives may lower the immune system; thus they may reduce inflammation, although this effect will also decrease their activity. For fungal infection in orbital area, the azoles can only act as fungistatic.\(^12\) Resistance to one or more of the azoles may occur in long-term treatment. A prospective study that collected isolate culture from several hospitals in the Netherlands had showed that the annual prevalence of resistance to itraconazole ranged between 1.7 and 6%. The study also found that the itraconazole-resistant isolates showed elevated minimum inhibitory concentration of voriconazole and posaconazole. Besides resistance, it is also important to consider potential interaction with other drugs before administering voriconazole and itraconazole.\(^15\)–\(^19\)

Culture results showed that the *Aspergillus* infecting the patient’s left eye was resistant to itraconazole, and no satisfying result was obtained from the treatment with itraconazole or amphotericin B; hence readministration of voriconazole was decided. A study had showed that as initial treatment of invasive aspergillosis, voriconazole was more superior in treatment response, survival rates, and safety than amphotericin B. The adverse effect commonly found is temporary visual disturbance.\(^15\)

Surgical intervention for invasive aspergillosis can sometimes be curative, as in some forms involving bone, heart valve, parasenal sinuses, proximal lung, large veins, and in cases of brain abscess, keratitis, and endophthalmitis.\(^5\) Our patient did not undergo surgical treatment since her family did not consent to the orbital exenteration.

In situations where there is a medium to high risk of fungal infection, antifungal prophylaxis administration for superficial or systemic candidiasis has been widely accepted. Fluconazole and oral itraconazole have no activity against *Aspergillus* sp., and itraconazole solution show only medium efficacy; posaconazole solution may be more effective. Some data supports the use of low-dose intravenous micafungin. In general, there has not been yet truly effective prophylactic regimens.\(^5\)

In invasive aspergillosis, cure is possible if there is improvement of the immune system, while the allergic and chronic form is generally incurable. Mortality rate of invasive aspergillosis is 50% when properly diagnosed and treated;
otherwise it could be as high as 100%. A case report described a fatal case of aspergillus sinusitis, in which the infection had spread intracerebrally.⁵⁻²⁰ One of the factors that improve our patient’s chance of survival was that there was no intracerebral extension of the infection.

In summary, corticosteroids and immunosuppressants treatment in SLE predispose patients to fungal infection, including invasive aspergillosis, which is caused by a group of fungi called *Aspergillus*. This disease is known to have poor prognosis, high recurrence rates, and there has not been yet prophylaxis with proven efficacy. Diagnosis of aspergillosis often presents challenges to the clinicians. There are various regimens in treating fungal infection, depending on the etiology and severity of infection. Voriconazole has become the treatment of choice in severe *Aspergillus* infection, followed by amphotericin B. Resistance to antifungal drugs has been reported, resulting in high recurrence rates. In invasive aspergillosis, surgical intervention can be considered and sometimes is curative.

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Tuberculous osteomyelitis in an immunocompetent patient with miliary tuberculosis

Gunawan,¹ A Harahap,² B Setiyohadi,³ CM Rumende⁴

Osteomyelitis is an infection of the bone, which may be caused by direct pathogen inoculation following trauma of surgery, contiguous spread from adjacent soft tissue or joint, or hematogenous spread from a focus of infection. Hematogenous osteomyelitis accounts for 20% of all cases of osteomyelitis.¹ This type of osteomyelitis most often affect the long bones and vertebrae, although it could also affect other sites such as pelvic bones or clavicle.¹ Mycobacterium tuberculosis is one of the causes of hematogenous osteomyelitis, comprising of 10 to 35 percent of extrapulmonary tuberculosis, or 2% of all tuberculosis cases.²³ Joint involvement, when occur, is usually monoarticular, and mainly affect the weight-bearing joints such as hip or knee. Polyarticular cases occur in 10–15% of extrapulmonary tuberculosis cases in developing countries.⁴ Tuberculous osteomyelitis cases are reported to be decreasing in number, probably because of earlier diagnosis and prompt management. In this article we report a case of tuberculous osteomyelitis in a patient with miliary tuberculosis.

CASE REPORT

A 32-year-old male was admitted with complaint of 1-month history of worsening pain in the left ankle. The pain was intermittent and worsened by movement of the ankle. The pain was first experienced 4 months earlier after a trauma to the ankle when the patient was doing an exercise. At that time the ankle was swollen and the patient was unable to walk for 1 week. He then went to a traditional massage therapist. After the massage therapy he regained his ability to walk, although the ankle was still swollen and painful. The patient reported no redness or warmth on the ankle.

One month prior to the admission, the pain and swelling worsened. On the skin of the ankle there was now a wound with blood and purulent discharge. The patient went to a community health center (Puskesmas) and was given cefadroxil, amoxicillin, paracetamol, and piroxicam as medication, but he reported no improvement of his symptoms. Two weeks prior to the admission, the patient began having intermittent fever, followed with productive cough with yellow sputum which began one week later. The patient reported no night sweats, decrease in body weight, shortness of breath, or exercise intolerance.

Physical examination at the time of admission revealed blood pressure of 110/80 mmHg, pulse rate of 88 beats/min, respiratory rate of 24 breaths/min, and normal body temperature. The patient appeared asthenic with body mass index of 17.6 kg/m². On chest auscultation we found vesicular breath sound, which was decreased in intensity at the right fifth intercostal space, and coarse crackles over all lung field. There was no lymph node enlargement.

On examination of the ankle we found that the skin around the left ankle was scaly and hyperpigmented. There were no signs of inflammation, but there was a 2.5-cm ulceration, which extended to the underlying connective tissue and muscle, on the medial malleolus. There was pain on palpation and movement of the ankle along with crepitation.

On laboratory examination we found that the patient had normochromic normocytic anemia with hemoglobin of 9 g/dL, normal leucocyte count, increased erythrocyte sedimentation rate, and positive C-reactive protein (table 1). On sputum examination twelve days after the admission we found positive acid-fast bacilli (+4 on three separate sputum collection). Pleural fluid analysis showed exudates with positive adenosine deaminase test. We also performed anti-human immunodeficiency virus test with enzyme-linked immunosorbent assay method, which showed negative result. Culture of the pus showed presence of Pseudomonas aeruginosa.

Chest radiograph showed miliary tuberculosis and right pleural effusion (figure 1). Radiographic examination of the left ankle showed signs of osteomyelitis with periosteal destruction of the tarsal bones (figure 2).

The patient was thus diagnosed with pulmonary tuberculosis and osteomyelitis of the left ankle bone, which was suspected as being the result of hematogenic spread of infection from the lung. He received an antituberculosis regimen consisting of rifampicin, isoniazid, ethambutol, and streptomycin (given as substitute for pyrazinamide due to the increased hepatic transaminases). In addition, the patient also received cefotaxime 1 g i.i.d for 14 days, but with no improvement of the left ankle infection. After the cefotaxime treatment, the patient underwent debridement of the left ankle and have a
biopsy specimen taken from the calcaneus. Histopathological examination showed caseation necrosis with surrounding lymphocytes and other chronic inflammatory cells (figure 3). The patient was then discharged and planned for regular evaluation in the outpatient clinic.

**Table 1** Laboratory results

<table>
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<tr>
<td>Hematocrit, %</td>
<td>29</td>
</tr>
<tr>
<td>Leukocyte count, $\times 10^9$/mm$^3$</td>
<td>5.3</td>
</tr>
<tr>
<td>Trombocyte count, $\times 10^9$/mm$^3$</td>
<td>615</td>
</tr>
<tr>
<td>Mean corpuscular volume, fL</td>
<td>77.9</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin, pg</td>
<td>24.5</td>
</tr>
<tr>
<td>MCHC, g/dL</td>
<td>31.4</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>110</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>111</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>79</td>
</tr>
<tr>
<td>Random blood glucose, mg/dL</td>
<td>102</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.453</td>
</tr>
<tr>
<td>pCO$_2$, mmHg</td>
<td>29.5</td>
</tr>
<tr>
<td>pO$_2$, mmHg</td>
<td>75.8</td>
</tr>
<tr>
<td>HCO$_3^-$, mmol/L</td>
<td>20.2</td>
</tr>
<tr>
<td>O$_2$ saturation, %</td>
<td>96</td>
</tr>
<tr>
<td>Electrolyte, mmol/L</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>132</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.15</td>
</tr>
<tr>
<td>Chloride</td>
<td>92</td>
</tr>
<tr>
<td>C-reactive protein (qualitative)</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-HIV (rapid)</td>
<td>Negative</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.3</td>
</tr>
<tr>
<td>Prothrombin time (control), sec</td>
<td>15.6 (13.2)</td>
</tr>
<tr>
<td>aPTT (control), sec</td>
<td>44 (37)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>424</td>
</tr>
<tr>
<td>D-dimer</td>
<td>300</td>
</tr>
</tbody>
</table>

MCHC, mean corpuscular hemoglobin concentration; ESR, erythrocyte sedimentation rate; aPTT, activated partial thromboplastin time.

**Figure 1** Chest radiograph (postero-anterior view) showing miliary tuberculosis and right pleural effusion.

**Figure 2** Radiograph of the left ankle (antero-posterior (left) dan lateral view (right)) showing periosteal destruction of the calcaneus, talus, and parts of the proximal tibia with narrowing of the ankle joint space.
immunode from a focus in the lung. We found no risk factors for occur as a result of lymphogenous or hematogenous spread

Figure 3 Histopathological examination of a specimen taken from the calcaneus showing caseation necrosis surrounded by lymphocytes and chronic inflammatory cells. Original magnification 400 ×.

DISCUSSION
Tuberculosis cases in the developing countries often present with various organ involvement, with lymph node and pleural effusion as the most common extrapulmonary manifestations. Tuberculosis affecting bone and joint were found in 15–20% of all extrapulmonary tuberculosis. Among cases of musculoskeletal tuberculosis, spine is the most commonly affected site (nearly 50% of all cases), followed with femur, tibia, fibula, and the joints. Tuberculous osteomyelitis of the spine most often affect the thoracic and lumbar spine, which causes severe morbidity. Tuberculous arthritis usually occur in weight-bearing joints such as hip or knee, and is usually localized to one joint; however, some multiartricular cases were found in 10–15% cases in developing countries.

Extrapulmonary tuberculosis is more often found in patients with immunocompromised patients, or patients with malnourishment, advanced age or patients with kidney failure. In immunocompromised patients, such as in patient with human immunodeficiency virus infection or acquired immunodeficiency syndrome, tuberculous osteomyelitis occur as a result of lymphogenous or hematogenous spread from a focus in the lung. We found no risk factors for immunodeficiency in our patient, and he was negative on the anti-HIV test; however, the fact that the patient had miliary tuberculosis rose a high suspicion that the osteomyelitis of the ankle occurred as a result of hematogenous spread of tuberculosis from the lung.

Tuberculous osteomyelitis has a low prevalence (1–3%); therefore, accurate and timely diagnosis often requires a high index of suspicion. Challenges in accurate diagnosis of this disease include inadequate knowledge and experience of the various manifestations of tuberculous osteomyelitis, and lack of consideration of this disease in the differential diagnoses.

Clinical manifestations are often nonspecific and patients may present with pain, swelling, decrease in range of motion or limitation of movement. Symptoms of tuberculosis infection may also present, such as decreased body weight, night sweats, malaise, and decreased appetite. Skeletal tuberculosis may go unnoticed for a long time until the adjacent structures such as skin, tissue, or joint are involved.

Result of acid-fast smear examination often come negative, which causes delay in diagnosis. Besides, culture of the causative pathogen take a long time to grow. Polymerase chain reaction technique or nucleic acid amplification test may help in making early diagnosis, but negative result do not exclude the possibility of tuberculosis.

Radiologic findings may include metaphyseal or epiphyseal destruction without sclerosis, periosteal reaction, and joint involvement. Unlike pyogenic osteomyelitis, there is no disruption in articular margin and joint space. Solitary litic lesion that may mimic neoplasia may be visible occasionally.

Positive tuberculin test is an important clue in patients with tuberculosis, but negative result could be seen in 10% of patients. Although erythrocyte sedimentation rate may be elevated, it could be normal in some patients. The gold standard for diagnosis is isolation of Mycobacterium tuberculosis from culture of bone biopsy specimen. Histopathological examination of the specimen taken from the bone lesion that show caseation or specific chronic inflammation is also very important in making the diagnosis.

Patients with tuberculous osteomyelitis are treated with antituberculosis therapy. First line agents consist of isoniazid (with vitamin B6 supplementation), rifampicin, ethambutol, and pyrazinamide. However, definitive therapy must be based on the result of susceptibility test of Mycobacterium tuberculosis. Second line agents include aminoglycoside and quinolones.

Duration of treatment may be varied from 6 to 12 months. Some patients may need additional 12 months or even more depending on clinical response. The Centers for Disease Control and Prevention recommends a regimen of 6–9 months (2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed with 4–7 months of isoniazid and rifampicin) for extrapulmonary tuberculosis. Surgery was not usually needed in the early stage of disease. Radical debridement is only intended for advanced stage or in cases when medication failed to provide improvement. Patients with significant involvement of joint may need arthrodesis or total arthroplasty.

In summary, we have described a case of tuberculous osteomyelitis in a miliary tuberculosis patient. Hematogenous spread from a focus in the lung was suspected as the pathogenesis in this case. Because of the low prevalence, high index of suspicion in clinical and physical examination is needed in order to accurately diagnose tuberculous osteomyelitis. Several diagnostic tests are necessary in making the diagnosis, and the choice of one diagnostic test must be based on cost-effectiveness consideration in each case. Antibiotic regimen in tuberculous osteomyelitis is similar to pulmonary tuberculosis but with longer duration of treatment.
REFERENCES


ERRATUM

In the previous edition, the volume and number of the edition, ‘volume 3 number 1’ should be ‘volume 2 number 2.’ We regret the error.
Elevated levels of IL-6 in RA:
Chronic Inflammation. Articular damage. Systemic risk.

A different perspective. A new focus.