Acquired Heart Diseases in Children

Yuttipong Wongswadiwat, M.D.
Assistant professor, Division of Pediatric Cardiology
Department of Pediatrics, Faculty of Medicine, KhonKaen University
Lecture outline

- Acute rheumatic fever
- Kawasaki disease
- Infective endocarditis
- Acute myocarditis
Acute rheumatic fever (Courtesy of Professor Manat Panamonta)
Acute rheumatic fever

- **Inflammatory syndrome** including: carditis, polyarthritis, chorea, subcutaneous nodules, erythema marginatum
- **Non-suppurative sequel** to Group A β hemolytic streptococcal infection of throat.
- **Latent period** of 1 to 5 weeks (3 weeks) following streptococcal pharyngitis.
- 0.3-3% of streptococcal pharyngitis develop **rheumatic fever**.
- Streptococcal pharyngitis has a peak incidence in children **5-15 years of age** (peak at 8 years)
Acute rheumatic fever

ประวัติโรคใช้รูมาติก

Joint Disease
Rheumatic fever syndrome
Jones criteria
Post-streptococcal disease
Resurgence in USA
Prevalence in developing countries

400 ปี

Acute rheumatic fever

From 1605-1885

Carditis
Polyarthritis
Chorea

In 1886

Carditis
Polyarthritis
Chorea

Rheumatic fever syndrome
Acute rheumatic fever worldwide (1970-1990)

Acute rheumatic fever worldwide (1991-2011)

Incidence of Rheumatic fever

Pre-Industrial Society

- Increased crowding and urbanization
- Industrial revolution

Post-Industrial Society

- Improved delivery of medical care and access to antibiotics
- Increased standard of living
- Economic development
- Unknown factors
- Decreasing strain virulence

Industrialized countries or Developed countries

Introduction of penicillin

Developing countries
• **Worldwide incidence:** Approximately 300,000-500,000 cases per year. (Wallace MR. Medscape, 2021)

• **Number of ARF cases in Khon Kaen University hospital**
  1980-2000: 20-50 cases/yr decreasing to less than 10 cases/yr

• **RHD Prevalence in NE Thailand**
  1986: 1.12 cases per 1,000 school children
  2006: 0.23 case per 1,000 school children
  (Chaikitpinyo A et al. 2014)
Agent, Host, and Environment

- **Agent:** Group A beta hemolytic streptococcus
  
  **Rheumatogenic strains:**
  M serotypes 1, 3, 5, 6, 14, 18, 19, 24, 27, 29, 74 (KhonKaen)
Pathogenesis of acute rheumatic fever

Host or Patient

- Age
- Previous attack
- Family history of rheumatic fever
- HLA-DR 4,2,1,3,7 or B-cell alloantigen D8/17

Environment

- Overcrowding
- Poverty
- Undernutrition
Pathogenesis of acute rheumatic fever

Immunologic mechanism: Cross-reactive antibody and/or Cell-mediated immune response

Inflammatory process: Heart, Joint, Brain, Subcutaneous tissue and Skin
Diagnosis of acute rheumatic fever

### Revised Jones Criteria 2015

<table>
<thead>
<tr>
<th>MAJOR MANIFESTATIONS</th>
<th>MINOR MANIFESTATIONS</th>
<th>SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION*****</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Clinical features:</td>
<td>- Elevated or increasing streptococcal antibody titer</td>
</tr>
<tr>
<td></td>
<td>1. Fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Polyarthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorea</td>
<td>Laboratory features:</td>
<td>History of</td>
</tr>
<tr>
<td></td>
<td>1. Elevated acute</td>
<td>- Positive throat culture or rapid streptococcal antigen test or</td>
</tr>
<tr>
<td></td>
<td>phase reactants: ESR,</td>
<td>streptococcal sore throat</td>
</tr>
<tr>
<td></td>
<td>C-reactive protein</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>2. Prolonged PR</td>
<td></td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>interval</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7. Revised Jones Criteria

**A. For all patient populations with evidence of preceding GAS infection**

| Diagnosis: Initial ARF | 2 Major manifestations or 1 major plus 2 minor manifestations |
| Diagnosis: Recurrent ARF | 2 Major or 1 major and 2 minor or 3 minor |

**B. Major criteria**

- **Low-risk populations***
  - Carditis†
  - Clinical and/or subclinical
  - Arthritis
  - Polyarthritis only
  - Chorea
  - Erythema marginatum
  - Subcutaneous nodules

**C. Minor criteria**

- **Low-risk populations***
  - Polyarthritis
  - Fever ≥38.5°C
  - ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL§
  - Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

---

**Moderate- and high-risk populations**

- Carditis
- Clinical and/or subclinical
- Arthritis
- Monoarthritis or polyarthritis
- Polyarthritis†
- Chorea
- Erythema marginatum
- Subcutaneous nodules

**Prevalence less than 1:1000**

- Moderate- and high-risk populations
- Monoarthritis
- Fever ≥38°C
- ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL§
- Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)
Clinical manifestations of the first episode of ARF

- Carditis (50%-79%)
- Arthritis (35%-66%)
- Chorea (10%-30%)
- Subcutaneous nodules (2%-10%)
- Erythema marginatum (0%-6%)
Clinical features of rheumatic carditis

Endocarditis/valvulitis -> Myocarditis -> Pericarditis
Echocardiography in ARF

- **Echocardiography** can provide early evidence of valvular involvement, can confirm suspected valvular regurgitation, and can exclude non-rheumatic causes of valvular involvement.

- Prevalence of subclinical carditis was 16.8% (95% CI: 11.9%-21.6%) (Gewitz MH, et al. Circulation 2015;131:1806-18)
Polyarthritis in ARF

- swelling
- heat
- redness
- severe pain
- tenderness to touch
- limitation of motion
- larger joints involved particularly knees, ankles, elbows, and wrists.
- migratory arthritis
- pain disproportionately greater than effusion
- prompt resolution of joint symptoms with salicylates and other anti-inflammatory drugs
Sydenham’s chorea

- Emotional lability
- Uncoordinated movements
- Muscular weakness
- Poor hand writing, Fidgety
- Fretful, Irritable, Inattentive to school work
Sydenham’s chorea

- Protuding tongue sign
- Choreic hand
- Milkmaid grip
- Pronator sign
Subcutaneous nodules

- round, firm, freely movable, **painless**, varying in size from 0.5-2.0 cm
- occur over bony prominences or extensor tendons.
- common locations are the **elbows, wrists, knees, ankles, scalp, spine or achilles tendons**
- frequently associated with carditis, severe carditis, chronic carditis and recurrent rheumatic carditis
Erythema marginatum

- bright pink macule or papule
- spread in a circular or seripiginous pattern
- appearing on the trunk or proximal extremities
- nonpruritic and nonpainful
Uncertainty in Diagnosis

- Offering 12 months of secondary prophylaxis
- Re-evaluate with color Doppler Echocardiography.
Treatment of acute rheumatic fever

- Eradicate streptococcus
- Anti-inflammatory agents
- Supportive care
- Prophylaxis
Treatment of acute rheumatic fever

- **Antibiotic Therapy:**
  10 days of orally administered penicillin or erythromycin or a single intramuscular injection of benzathine penicillin to eradicate GABHS from the upper respiratory tract

- **Typical migratory polyarthritis & with carditis without cardiomegaly or congestive heart failure:**
  Oral salicylates, 100 mg/kg/day in 4 divided doses PO for 3-5 days, followed by 75 mg/kg/day in 4 divided doses PO for 4-8 wk
Treatment of acute rheumatic fever

- Patients with carditis & cardiomegaly or congestive heart failure: treatment with corticosteroids:
  Prednisone 2 mg/kg/day in 4 divided doses for 2-6 wks followed by a tapering of the dose that reduces the dose by 5 mg/24 hr every 2-3 days.

- At the beginning of the tapering of the prednisone dose, aspirin should be started at 75 mg/kg/day in 4 divided doses to complete 12 wks of therapy.
Sydenham Chorea

Occurs after the resolution of the acute phase of the disease
• Anti-inflammatory agents are usually not indicated
• **haloperidol** (0.01-0.03 mg/kg/24 hr divided bid PO) or **chlorpromazine** (0.5 mg/kg every 4-6 hr PO)
• Long-term antibiotic prophylaxis
## SECONDARY PREVENTION

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever <strong>without carditis</strong></td>
<td>At least for 5 yr or until age 21 years, whichever is longer</td>
</tr>
<tr>
<td>Rheumatic fever <strong>with carditis but without residual heart disease</strong></td>
<td>For 10 yr after the last attack, or until age 21 years of age whichever is longer</td>
</tr>
<tr>
<td>Rheumatic fever <strong>with carditis &amp; residual heart disease</strong> (persistent valvular disease)</td>
<td>For 10 yr after the last attack &amp; at least until age 40 yr or lifelong</td>
</tr>
<tr>
<td>After valve surgery</td>
<td>lifelong</td>
</tr>
</tbody>
</table>
# Secondary Prevention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G benzathine</td>
<td>600,000 U for children, ≤27 kg&lt;br&gt;1.2 million U for children &gt;27 kg, every 3-4 wk</td>
<td>Intramuscular</td>
</tr>
<tr>
<td></td>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td>Penicillin V</td>
<td>250 mg, twice a day</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td>Sulfadiazine or sulfisoxazole</td>
<td>0.5 g, once a day for patients ≤27 kg&lt;br&gt;1.0 g, once a day for patients &gt;27 kg</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>For people who are allergic to penicillin and sulfonamide drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolide or azalide</td>
<td>Erythromycin 250 mg twice daily</td>
<td>Oral</td>
</tr>
</tbody>
</table>
Kawasaki disease
Kawasaki disease

- First described in Japan in 1967 by Tomisaku Kawasaki
- One of the most common vasculitis of childhood
- Typically a self-limited condition
- Cause a variety of cardiovascular complications
- Remains unknown etiology
- Multiple theories exist:
  - Immunologic response, infectious etiology
  - Genetic factors
Kawasaki disease

- Systemic, inflammatory illness affects medium-sized arteries (coronary arteries)
- Inflammatory cell infiltration into vascular tissues include neutrophils, T cells (CD8 T cells) eosinophils, plasma cells (IgA producing)
- The destruction of elastin and collagen fibers and loss of structural integrity of the arterial wall lead to dilatation and aneurysm formation
Kawasaki disease & coronary aneurysm
Clinical features and diagnosis

Epidemiological case definition (Classic clinical criteria)

* Fever persisting at least 5 days
* Presence of at least 4 principal features:
  1. **Changes in extremities**
     - Acute: Erythema of palms, soles; edema of hands, feet
     - Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
  2. **Polymorphous exanthem**
  3. **Bilateral bulbar conjunctival injection** without exudate
  4. **Changes in lips and oral cavity**: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
  5. **Cervical lymphadenopathy (>1.5-cm diameter)**, usually unilateral

- Exclusion of other diseases with similar findings
Clinical features and diagnosis

- **Fever**
  - Acute
  - Subacute
  - Convalescent

- **Arthritis**
  - Myocarditis
  - Aneurysms

- **Cardiovascular**
  - Red palms/soles
  - Desquamation
  - Nail changes

- **Skin**

- **Lips & Conjunctiva**

- **Cervical Lymphadenopathy**

- **Thrombocytosis**

- **Weeks**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
Kawasaki disease

Strawberry Tongue

Figure 191.2: Kawasaki disease. Strawberry tongue in patient with mucocutaneous lymph node syndrome.
(Courtesy of Tetsuaki Kawasaki, MD. From Kurlitis S: Clinical pediatric dermatology, ed 2, Philadelphia, 1993, Saunders.)
Kawasaki disease

Congestion of bulbar conjunctiva
Kawasaki disease

Indurative edema of the hand

Figure 191.5: Kawasaki disease. Indurative edema of the hands in a patient with mucocutaneous lymph node syndrome.
(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S: Clinical pediatric dermatology, ed 2, Philadelphia, 1993, Saunders.)
Kawasaki disease

BCG redness: common in <2 yr (infant with incomplete KD)

Courtesy of Assoc. Rekwan sittiwangkul
Incomplete Kawasaki disease

- Some of the classic features of KD but **not enough to meet the case definition**
- More likely to be infants and older children
- Consider in all children with unexplained fever for ≥5 days associated with 2 or 3 of the principal clinical features
- **Echocardiography is useful**: coronary arteries meet Japanese Ministry of Health criteria for aneurysms, Z-score
- Supplemental laboratory criteria
Treatment of Kawasaki disease

Aspirin
Dose of aspirin during the acute phase of illness

• **Anti-inflammatory (high doses):** 80 to 100 mg/kg/day divided in 4 doses or **moderate doses** 30 to 50 mg/kg/day

Duration of high/moderate-dose aspirin vary

• **reduce the aspirin dose after the child has been afebrile for 48 to 72 hours**
• **continue high-dose aspirin until day 14 of illness and ≥48 to 72 hours after fever cessation**
Treatment of Kawasaki disease

When high-dose aspirin discontinue
- begin low-dose aspirin for antiplatelet: 3–5 mg/kg/day maintain until no evidence of coronary changes by 6 to 8 weeks after onset of illness
- Risk for Reye syndrome if active infection with varicella or influenza
- Should receive annual influenza vaccine
Treatment of Kawasaki disease

**IVIG**
Initial therapy: **IVIG 2 g/kg in a single infusion together with aspirin**
- Institute within the first 10 days of illness if possible, within 7 days of illness
- Postponing administration of live-virus vaccines (measles, varicella) for at least 11 months
Prognosis of Kawasaki disease

• Low mortality rate 0.1-0.3%
• Uncommon recurrence of KD
• Long-term morbidity relates to the degree of coronary artery (CA) involvement
Infective endocarditis

Large vegetation at aortic and mitral valves
Infective endocarditis

- Complicated problem
- 0.5 – 1 per 1,000 admission
- SNH & QSHC, KKU
  0.8 per 1,000 admission 68% CHD, 18% RHD (decreased from 46%) 1992-2011
- Underlying CHD, transient bacteremia
  IVDU, venous catheter related
- **Bacteria**: viridians streptococci, staphylococci
  gram negative, enterococci, pneumococci, hemophilus
- **Fungus**
Transient Bacteremia

- Tooth extractions (no gingivitis) 34%
- **Tooth extractions (gingivitis)** 75%
- Chewing mint candy 20%
- Brushing teeth 40%
- Urethral surgery 57%
- Bronchoscopy 15%
A child with heart disease

?? Infective endocarditis

1. Unexplained fever
2. Pneumonia
3. Neurological deficit
4. Hematuria
5. Embolization
Classical findings of IE

1. Fever
2. Change in cardiac examination
   *** New cardiac murmur
3. Splenomegaly
4. Emboli
Modified Duke Criteria

2 major criteria or
1 major criteria & 3 minor criteria or
5 minor criteria
Modified Duke Criteria

- **Major criteria**
  - Positive blood culture
  - Evidence of endocarditis on ECHO

- **Minor criteria**
  - Predisposing condition
  - Fever, Embolic-vascular signs
  - Immune complex phenomena
  - Single positive blood culture/serologic evidence of infection
  - Other ECHO signs
Embolic-vascular signs

http://simple cardio.blogspot.com/2012/06/peripheral-signs-of-infective.html
Appropriate antibiotic
* proper blood culture (1-3 ml, 5-7 ml)

Indication for surgery
1. Cardiac arrhythmia
2. Embolization/Size of vegetation
3. Continued positive blood culture
4. Heart failure
IE prophylaxis before dental procedures

1. **Prosthetic** cardiac valves, including transcatheter-implanted prostheses and homografts
2. **Prosthetic material** used for cardiac valve repair, such as annuloplasty rings and chords
3. **Previous IE**
4. **Unrepaired cyanotic congenital heart disease or repaired CHD, with residual** shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device
5. **Cardiac transplant with valve regurgitation** caused by a structurally abnormal valve**
# Prophylactic Regimens for Dental Procedures

<table>
<thead>
<tr>
<th>Route</th>
<th>Agent</th>
<th>Single Dose 30–60 min Before Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Children</td>
</tr>
<tr>
<td>Oral</td>
<td>Amoxicillin</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>Unable to take oral medications</td>
<td>Ampicillin or Cefazolin or ceftriaxone</td>
<td>50 mg/kg (IM, IV)</td>
</tr>
<tr>
<td>Allergic to penicillin or ampicillin—oral</td>
<td>Cephalexin*†or Clindamycin, or Azithromycin or Clarithromycin</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>Allergic to penicillin or ampicillin and unable to take oral medication</td>
<td>Cefazolin or ceftriaxone Clindamycin</td>
<td>50 mg/kg (IM, IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 g (IM, IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 g (IM, IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 g (IM, IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg</td>
</tr>
</tbody>
</table>
Myocarditis is an inflammatory disease of the myocardium, structural and functional abnormalities secondary to cell injury and death.

Myocarditis accounted for 0.05% of pediatric discharges in the United States.

Myocarditis is an important cause of cardiovascular morbidity and mortality in the pediatric population.

Based on the severity of illness, myocarditis can be classified into 3 clinical categories: acute, fulminant, and chronic.
Sudden cardiac death in adolescents found myocarditis to be the cause in up to 17% of cases.

27% of cases of dilated cardiomyopathy were secondary to viral myocarditis.

The most commonly reported epidemics of myocarditis have been caused by Coxsackie viruses. During outbreaks of this virus in Europe in 1965, 5% to 12% of patients infected with Coxsackie B virus cardiac manifestations of their disease.

Over the last several decades there has been a shift in the primary viral pathogens to parvovirus B19 and human herpes virus 6.
Three phases of viral associated myocarditis

- **Phase 1** involves *direct injury to the myocardium* by viral entry and proliferation of the host innate immune system and cytokine release.
- **Phase 2** is characterized by *activation of the acquired immune system* and antigen specific responses involving T cells, B cells, and antibody production. Due to *cross-reaction* between myocardial specific antigens and viral proteins.
- **Phase 3** is characterized by either *resolution* of inflammation and viral infection, or *progression* towards a chronic dilated cardiomyopathy.
Three phases of viral associated myocarditis

Phase 1
- Viral entry and activation of innate immune response
- Genetic predisposition
- Viral uptake mediated by CAR and DAF
- Active viral replication
- Viral-mediated cardiomyocytolysis
- Viral protease-induced apoptosis
- Cardiac autoantibodies present
- Innate immune responses including expression of interferons, interleukins, TNF-α, induction of cytokine mRNA

Phase 2
- Activation of acquired immune response
- Activation of adaptive immunity
- Cytokine and chemokine release
- T-cell-mediated clearance of virus-infected cells
- T-cell-mediated myocardial injury/necrosis and production of interleukins and interferons
- Cardiac autoantibodies present

Phase 3
- Recovery or disease progression
- Resolution
- Clearance of virus
- Normalization of LV systolic function
- Dilated cardiomyopathy
- Delayed or ineffective viral clearance with chronic inflammation
- Myocyte degeneration, interstitial fibrosis, hypertrophy
- Global remodelling
- Chronically reduced LV ejection fraction

R.K. Singh et al. / Progress in Pediatric Cardiology 43 (2016) 23–30
Clinical Presentations

- **Clinical Presentations**: asymptomatic individuals to cardiogenic shock and sudden death
- **History**: respiratory tract infections and gastroenteritis
- **Presenting symptoms**: shortness of breath (69%), vomiting (48%), poor feeding (40%), upper respiratory symptoms (39%), fever (36%), and lethargy (36%)
- **Physical examinations**: signs of cardiac dysfunction, heart failure causing pulmonary venous congestion, S3 or S4 gallop, murmurs associated with mitral valve and tricuspid valve insufficiency
- **Chest pain can be present or absent in myocarditis.**
The gold standard for diagnosis of myocarditis is endomyocardial biopsy (EB): variable and low sensitivity in pediatric patients, only 20% to 40% have confirmation on EB.

The diagnosis of myocarditis is usually based on the clinical picture with support of noninvasive tests to reach the final diagnosis.

- **Electrocardiogram (EKG):** Sinus tachycardia with low-voltage QRS complexes and inverted T waves
- **Chest radiographs:** cardiomegaly and pulmonary venous congestion
Diagnostic Evaluation

**Echocardiogram**: myocardial function, pericardial effusion and could be a lifesaving diagnosis

**Cardiac computed tomography (CT) and cardiac MRI (CMRI)**

**The Lake-Louise Criteria (LLC) in CMR** The patterns of late gadolinium enhancement in various forms of myocarditis

**Serum markers of inflammation**: Creatine kinase level, troponin level
ECHO in acute myocarditis
Cardiac MRI in myocarditis
Pathophysiology of Congestive heart failure

\[ CO = HR \times SV \]
Management of cardiogenic shock

- Suggestive clinical & para-clinical signs
- Ventilation optimization (reduce afterload)
- Preload and afterload optimization
- Treatment of curable disease & arrhythmia
- Medication therapy:
  1st line Dobutamine (milrinone is alternative)
  2nd line Noradrenaline (levosimendan)
  3rd line Vasopressin/ECMO

The usual dose of IVIG for myocarditis is 2 g/kg/dose once.

A systematic review of all pediatric and adult studies concluded there is currently insufficient evidence in the literature to support the routine use of IVIG for treatment of acute myocarditis.

The usual dose of corticosteroids for myocarditis is 0.5–2 mg/kg/day divided 1–4 times per day.

A Cochrane Database review of eight randomized clinical trials (RCTs) with a total of 719 pediatric and adult myocarditis showed no difference in mortality between the corticosteroid and control groups.

The corticosteroid group did have an improved left ventricular ejection fraction (LVEF) and CK-MB levels.

VA ECMO (Extracorporeal membrane oxygenator)

VA ECMO

Centrifugal pump

Oxygenator
ECMO in PICU
Thank you for your attention

Contact Address:
Assistant professor. Yuttapong Wongswadiwat
Department of Pediatrics, Faculty of Medicine, KhonKaen University, THAILAND
Email: wyutta@kku.ac.th