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Diagnostic Value of Procalcitonin Levels Compared to Leukocyte and CRP Levels in Detecting Acute Perforated Appendicitis in Children at Saiful Anwar Hospital Malang

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Abstract: *Appendicitis is an acute abdominal case in children often found in surgical clinical practice. Specific and accurate diagnostic methods for predicting acute and perforated appendicitis in children have not been established and is a challenge. Examinations such as CT scans have disadvantages such as radiation risk and unavailability of these facilities in several health service centers, while Ultrasound is not realiable since it is operator dependent and 46% of cases of appendix cannot be evaluated due to individual variations. The most commonly used diagnostic parameters are leukocyte examination, CRP and Procalcitonin as the recently used parameter, where the levels are detected in acute appendicitis and have an increase in perforated cases. Therefore, this study examined the significance of leukocytes, CRP and Procalcitonin in predicting the incidence of acute and perforated appendicitis.*

The purpose of the study was to determine the specificity, sensitivity, cut-off of leukocyte levels, CRP and procalcitonin in predicting acute perforated appendicitis. The research method used observational cohort study conducted to children aged 2-18 years with lower right abdominal pain and suspected appendicitis at Syaiful Anwar Hospital Malang for 1 year. The examinations of leukocytes, CRP, and Procalcitonin were carried out before surgery. Data analysis was performed using the Mann Whitney Uand Chi Square tests. For the cut-off evaluation, the homogeneous data were entered into the ROC curve to obtain sensitivity, cut-off specificity of leukocytes, CRP and Procalcitonin evaluations.

From June, 2016 to June 2017, it was obtained 45 patients consisting of 10 acute appendicitis and 35 perforated appendicitis patients who met the inclusion criteria. Based on gender distribution, it was obtained 16 female patients and 29 male patients. Gender differences did not differ significantly in perforated incidents. Based on the distribution test for leukocytes, CRP and Procalcitonin, It showed that there was no significant results. It was obtained accuracy of 68.6% for leukocytes with a sensitivity of 68.6%, specificity of 70% and cut off value of 14,930. CRP had an accuracy of 95.1% with a cut off value of 6,375,while Procalcitonin had the accuracy of 97.7% with a cut off value of 0.35. The sensitivity and specificity for CRP and procalcitonin have the same values of 91.4% and 90%, respectively.

It can be concluded that procalcitonin was not a significant parameter in predicting the incidence of perforated appendicitis. The results indicated that thesensitivity and specificity of leukocyte were the lowest, while the sensitivity and specificity of CRP and procalcitonin were similar, but the accuracy of procalcitonin was better compared to CRP and leukocytes. The cut off value was obtained from a wide range of data, so that it was difficult to use itin making clinical decisions. More sample data are needed to be applied clinically. Further studies need to consider the use of other more potent proinflammatory biomarkers other than procalcitonin, leukocytes and CRP to evaluate the incidence of acute and perforated appendicitis in pediatric surgical patients.

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I. Background

Appendicitis is inflammation of the vermiform appendix and is the most common cause indicated by emergency abdominal surgery in general surgical clinics.[1]An evidence-based study defines perforated appendicitis in pediatric patients as the presence of holes in the appendix wall or the presence of fecalith in the abdomen.[2] Appendicitis in pediatric patients with acute abdomen can be systematically identified using valid Clinical Prediction Rules (CPRs), such as Pediatric Apendisitis Score(PAS) and Alvarado Scoring (Migration, Anorexia, Nausea/vomiting, Tenderness in the right lower quadrant, Rebound pain, Elevation in temperature, Leukocytosis, Shift to the left, commonly abbreviated as MANTRELS).[3] However, further examination is still needed to make the diagnosis and to find out whether the appendicitis has perforated.

The duration of appendicities symptoms is very important in establishing the diagnosis and management because perforation can occur within 48-72 hours.[4] Appendix perforation often occurs in children due to the shorter omentum, the longer appendix with thinner walls, and lack of body endurance.[5] Perforation

increases the risk of abdominal abscesses and small-bowel obstruction prolonging the length of hospital stay. Complications that often occur in children such as intestinal obstruction causing the managements such as laparoscopic appendextomy which is milder in physical stress are a relative contraindication because carbon monoxide insufflation is not optimal.

The performance of radiological modalities such as abdominal Ultrasound and CT scan remains inadequate to be used as screening for acute abdominal conditions in children despite having a good sensitivity[6,7,8]. Abdominal CT scan has the risk of causing radiation exposure, especially in children with long life expectancy and rapidly developing cells. Thus, the use of abdominal CT scan to detect the presence of acute perforated appendicitis is not recommended.[9]Ultrasound is a radiological action that depends on the expertise of the operator. The effectiveness of ultrasound is also confused if the patient has thick belly fat. In the states of the retrosecal appendix, perforated appendix, the gas-filled appendix, false negative condition can occur.[10] This is supported by a study conducted by Reddan et.al. (2016) where 46% of appendicitis cases were not visualized onUltrasound[5,6].

Traditional clinical signs of infection and routine laboratory tests such as CRP or leukocytes are less accurate in diagnostics and sometimes misleading because in conditions where sterile inflammation or viral infection occurs, its level will increase. According to Sulistyo (2008) peripheral blood leukocyte levels, CRP, and plain film of the abdomen have diagnostic value in establishing

a diagnosis of acute appendicitis. In Saiful Anwar Hospital (RSSA), leukocyte and CRP12 levels are routinely examined in pediatric surgical patients with suspected appendicitis.[12] In severe acute appendicitis, classical proinflammatory cytokines such as TNF-α, IL-1β, or IL-6 increase only momentarily or intermittently, if they increase.[9]Given these diagnostic and therapeutic dilemmas, more rigorous examination is very important. The low specificity of markers currently available further increases awareness of the need for more specific perforated acute appendicitis markers.[11]

Further research studies that the state of acute and perforated appendicitis is fundamentally different from the immune response that occurs. Inflammation of appendicitis occurs because of the proinflammatory response of local cytokines associated with systemic proinflammatory cytokines. IL-6 promoter of single nucleotide polymorphisms, IL-1, IL-10 and LPS are minimally detected in patients with uncomplicated appendicitis and have higher levels in cases of complicated or perforated appendicitis. Where a higher increase in IL-6 results in more intense thrombosis of local tissue and inflammation due to the ability of IL-6 to stimulate degranulation of neutrophils and inhibit apoptosis. Increased levels of IL-6 and IL-10 can stimulate production from biomarkers such as Procalcitonin.[5,7]

Procalcitonin (PCT) is one of the inflammatory markers that has recently been studied for the initial diagnosis of acute abdomen.[14] PCT is a precursor of calcitonin found in C cells of the thyroid gland, lung and intestine.[15] Assicot (1993) reported that there was an increase in the level of procalcitonin in patients with bacterial, fungal and sepsis infections. Many studies confirm that procalcitonin is an inflammatory biomarker in host responses to microbial and pathological infections that require surgical management such as ileus and pancreatitis.[16]Some studies also proved the correlation between increased levels of procalcitonin and the severity of infection.[14]In patients with sepsis, procalcitonin levels increase by more than a few hundred nanograms per ml.[16]. Qualitative assessment has been developed so that procalcitonin levels can help diagnose acute appendicitis in children.[9]Nonetheless, the quantitative standard for the functioning of procalcitonin levels as a marker of acute perforated appendicitis in pediatric surgical patients has not been established.

In the case of acute perforated appendicitis where markers such as CRP cannot support the specificity and sensitivity of infection to the vermiform appendix, quantitative assessment of procalcitonin levels is suspected to help establish an accurate and immediate diagnosis. Wang et. al (2011) stated through a study conducted in 2011 that procalcitonin levels were better in helping diagnose complications of acute appendicitis.[13]

With the ELFA examination method, the application of measuring procalcitonin can be easily carried out at the laboratory. Thus, the use of long, expensive, and operator dependent imaging supports such as ultrasound, CT and MRI can be avoided. As a result, complications of acute appendicitis due to late diagnosis and management such as perforated, gangrenous or abscess conditions can be minimized. Therefore, the author decided to use procalcitonin levels as a marker of acute perforated appendicitis in pediatric surgical patients compared to the use of leukocyte and CRP in the emergency department of Saiful Anwar Hospital.

II. Research Method&Data Analysis

Patients who present to the Emergency Department (ED) of Saiful Anwar Hospital and were diagnosed with appendicitis and fulfilled the inclusion criteria were treated according to applicable medical standards after signing the informed consent for medical treatment and the study was conducted to the patients' family. The identity of the patients will be kept secret, replaced by the order code. Anamnesis, physical examination,

laboratory tests were conducted according to medical standards and the data were taken. All medical treatmentswere carried out in accordance with applicable standard procedures.

Procalcitonin, leukocyte & CRP levels were measured before surgery and matched with surgical durante findings (acute nonperforated appendicitis, perforated appendicitis). Data were processed statistically to determine the range of procalcitionin levels that reflect each condition of appendicitis and the cut off value that distinguishes between nonperforated appendicitis and perforated appendicitis.

Before the analysis, the collected data were checked for completeness and correctness. The data were then coded, tabulated, and inserted into the computer. The data included the levels of procalcitonin, leukocytes and CRP. Data comparisons were made between leukocytes, CRP and procalcitonin. The accuracy of the procalcitonin test with the cut-off point was analyzed by comparing it to the surgical durante findings (nonperforated appendicitis, acute perforated appendicitis). The diagnostic ability of the procalcitonin serological test was considered good if the accuracy and other diagnostic parameters were ≥80%.

The cut-off point for serum procalcitonin levels for cases of non perforated appendicitis versus perforated appendicitis was analyzed using receiver operating characteristic (ROC). Before ROC analysis, the value of procalcitonin level measurement wasconverted into a continuous scale and was returned as the value of procalcitonin test result that was commonly used after the cut-off point was found. Determination of the cut-off point was based on the most optimal value of sensitivity and specificity based on ROC analysis. Data analysis used the SPSS computer software.

III. Result

Based on the study conducted from July, 2016 to July, 2017, it was obtained 45 patients consisting of 10 patients with acute perforated appendicitis and 35 patients with acute appendicitis. Blood sampling is carried out before the surgery.

Based on gender distribution, it was obtained 16 female patients (35.6%) and 29 male patients (64.4%) with p value = 0.739 (p> 0.05). Thus, it can be concluded that there were no significant differences between female and male patients. Frequency distribution by age obtained p value = 0.222 (p> 0.05), so that the distribution by age was not significantly different.

Table 1Comparison of appendicitis data by gender

Gender	Appendicitis		Total
	AA	APA	
Female	4 (40%)	12 (34.3%)	16 (35.6%)
Male	6 (60%)	23 (65.7%)	29 (64.4%)
Total	10 (100%)	35 (100%)	45 (100%)

Description : AA, acute appendicitis; APA, acute perforated appendicitis; p = 0.739

The duration of appendicitis symptoms is very important in establishing the diagnosis and management because perforation can occur in 48-72 hours.[4]Perforated appendix often occurs due to the shorter omentum, the longer appendix with thinner walls, and lack of the body's resistance.[5] Perforation increases the risk of abdominal abscesses and small bowel obstruction which prolongs the length of hospital stay. In a study conducted on 45 patients, there was an increase in leukocytes in acute (100%) and perforated conditions (88.9%). Leukocyte levels in the acute appendicitis were not significantly different from the perforated appendicitis.

Table 2 Frequency Distribution of Leukocyte in Cases of Acute and Perforated Appendicitis

Age	Appendicitis		Total
	AA	APA	
Normal	0 (0%)	6 (17.1%)	6 (13.3%)
Increase	10 (100%)	29 (88.9%)	39 (86.7%)
Total	10 (100%)	35 (100%)	45 (100%)

Description: AA, acure appendicitis; APA, acute perforated appendicities; p = 0.160

From the ROC curve, the accuracy obtained from leukocyte levels to distinguish acute and perforated conditions was 68.6%. With specificity and sensitivity of 70% and 68.6%, respectively, The cut off value of leukocyte levels obtained to distinguish acute and perforated conditions is 14930.

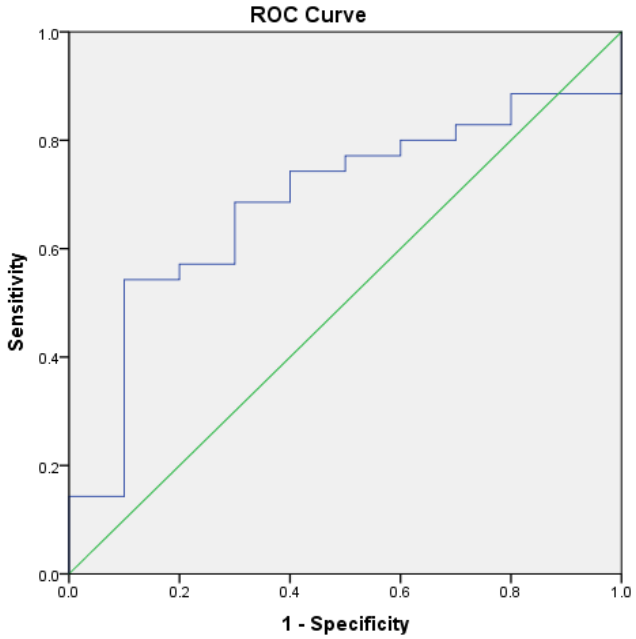

Figure 1 ROC Curve of Leukocyte Levels of Appendicitis Patients at Saiful Anwar Hospital Malang

Description: Area under curve = 0.686; sensitivity = 68.6%; specificity = 70%
Increased CRP was found in 90% of patients with acute appendicitis and 94.3% in patients with acute perforated appendicitis in Saiful Anwar Hospital Malang with p value = 0.632 (p> 0.05), so that the increase in CRP in acute and perforated appendicitis was not significantly different.

Table 3 Frequency Distribution of CRP levels in Cases of Acute and Perforated Appendicitis

Age	Appendicitis		Total
	AA	APA	
Normal	1 (10%)	2(5.7%)	3 (6.7%)
Increase	9 (90%)	33(94.3%)	42 (93.3%)
Total	10 (100%)	35 (100%)	45 (100%)

Description: AA, acute appendicitis; APA, acute perforated appendicitis; p = 0.632

The accuracy obtained from CRP levels to distinguish acute and perforated conditions was 95.1%. With specificity and sensitivity of 90% and 91.4%, respectively, The cut off value of CRP levels obtained to distinguish acute and perforated conditions is 6,375. CRP levels are like leukocytes, have a fairly large range in the condition of acute appendicitis with levels of 0.03 mg/dl - 11.13 mg/dl and in perforated conditions of 2.03 mg/dl - 38.06 mg/dl.

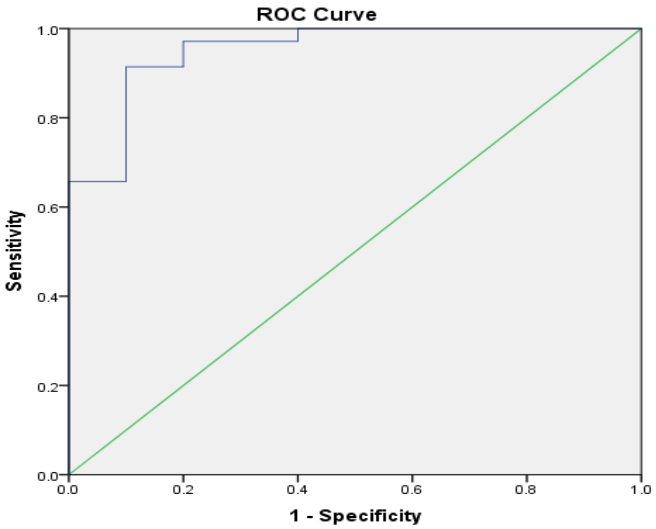

Figure 2 ROC Curve of CRP Levels in Acute and Perforated Appendicitis Patients at Saiful Anwar Hospital Malang

Description: Area under curve = 0.951; sensitivity = 91.4%; specificity = 90%

Bacterial inflammation increases PCT levels to> 2 ng/ml, while in cases of viral infection, PCT levels are < 0.5 ng/ml. Based on the ROC curve, it was obtained that the area under curve was 97.7% with a sensitivity of 90% and a specificity of 91.4%. Meanwhile, the cut off value for the procalcitonin levels is 0.35.

Table 4 Frequency Distribution of Procalcitonin Levels in Acute and Perforated Appendicitis at Saiful Anwar Hospital Malang

Age	Appendicitis		Total
	AA	APA	
Normal	5 (50%)	7 (20%)	12 (26.7%)
Increase	5 (50%)	28 (80%)	33 (73.3%)
Total	10 (100%)	35 (100%)	45 (100%)

Description: AA, acute appendicitis; APA, acute perforated; p = 0.058

Serum PCT levels due to severe bacterial infection followed by a systemic response can reach 100 ug/L. The dramatic increase in PCT during acute infection is uniquely not followed by an increase in parallel levels of calcitonin or a decrease in serum calcium levels.[15] The half-life of serum PCT is 25-35 hours and does not change significantly in kidney failure. Therefore, serum PCT levels can be used for diagnostic purposes in patients whose kidney function is damaged.[45]

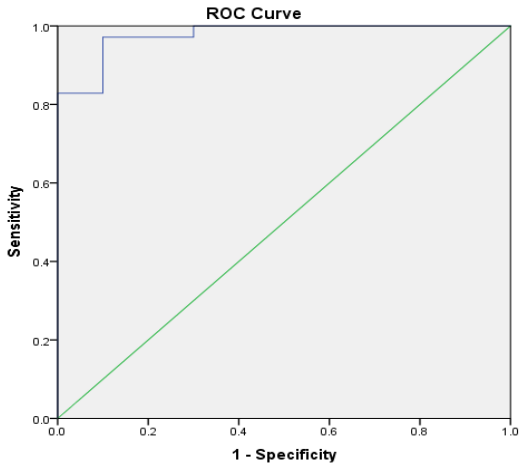

Figure 3 ROC Curve of Procalcitonin Levels in Acute and Perforated Appendicitis Patients at Saiful Anwar Hospital

IV. Discussion

Appendicitis is inflammation of the vermiform appendix and is the most common cause of emergency abdominal surgery indicated in general surgical clinics.[1] An evidence-based study defines perforated appendicitis in pediatric patients as the presence of holes in the appendix wall or the presence of fecalith in the abdomen.[2] Perforation increases the risk of abdominal abscesses and small bowel obstruction which prolongs the length of hospital stay. Thus, the initial diagnosis of acute abdomen is the main goal of the practice of surgery, where the possibility of surgery with laparoscopic measures that are milder in physical stress compared to conventional appendectomy surgery techniques can be considered in the acute condition.

According to Sulistyo (2008), peripheral blood leukocyte levels, CRP, and plain film of abdomen have a high diagnostic value in establishing the diagnosis of acute appendicitis. In Saiful Anwar Hospital, leukocyte and CRP levels are routinely examined to pediatric surgery patients with suspected appendicitis.[12] Wang et. al (2011) stated through a study conducted in 2011 that procalcitonin levels were better in helping diagnose complications of acute appendicitis.[13]

Procalcitonin (PCT) is one of the inflammatory markers that has recently been studied for the initial diagnosis of acute abdomen.[14]PCT is a precursor of calcitonin found in C cells of the thyroid gland, lung and intestine.[15] Assicot (1993) reported that there was an increase in the level of procalcitonin in patients with bacterial, fungal and sepsis infections. Many studies confirm that procalcitonin is an inflammatory biomarker in host responses to microbial and pathological infections that require surgical management such as ileus and pancreatitis.[16]Some studies also proved the correlation between increased levels of procalcitonin and the severity of infection.[14]In patients with sepsis, procalcitonin levels increase by more than a few hundred nanograms per ml.[16]. Qualitative assessment has been developed so that procalcitonin levels can help diagnose acute appendicitis in children.[9]

Based on the study conducted from July, 2016 to July, 2017, it was obtained 45 patients consisting of 10 patients with acute perforated appendicitis and 35 patients with acute appendicitis. Based on gender distribution, it was obtained 16 (35.6%) female patients and 29 (64.4%) male patients. Appendicitis is the most common cause of emergency abdomen in children aged two years and above with a ratio of male: female = 1.2: 1. The incidence of appendicitis in children in the United States ranges from 70,000 with details of 1-2 cases per 10,000 children aged 0-4 years and 25 cases per 10,000 children aged 10-17 years.[23]The average age of appendicitis incident is 6-10 years.[24] While the available epidemiological data shows the consistency of the age of pediatric appendicitis patients at Saiful Anwar Hospital Malang ranging from 6 to 12 years.

In a study conducted on 45 patients, it was obtained an increase in leukocytes in acute (100%) and perforated conditions (88.9%). Leukocyte levels in acute appendicitis were not significantly different from the perforated conditions. An increase in the number of leukocytes occurs in about 90% of cases of appendicitis. In nonperforated appendicitis, the number of leukocytes increases to around 10,000-18,000/mm^3. Non-perforated appendicitis patients with the number of leukocytesof more than 18,000/$mm^3$are rarely found. Some other experts provide a limit of 11,000-14,000/mm^3 for acute appendicitis, and more than 18,000/mm^3 for perforated appendicitis.

From the ROC curve, the accuracy obtained from leukocyte levels to distinguish acute and perforated conditions was 68.6%. With specificity and sensitivity of 70% and 68.6%, respectively, the cut off value of leukocyte levels obtained to distinguish acute and perforated conditions is 14930. These leukocyte levels have a fairly large range in the condition of acute appendicitis with levels of 8890 mg/dl - 26030 mg/dl and in perforated conditions of 6530 mg/dl - 32660 mg/dl. The time span between the initial onset of appendicitis and treatment can affect leukocyte levels

Increased CRP was found in 90% acute appendicitis patients and in 94.3% acute perforated appendicitis patients at Saiful Anwar Hospital Malang. The accuracy obtained from CRP levels to distinguish acute and perforated conditions was 95.1%. With specificity and sensitivity of 90% and 91.4%, respectively.

The cut off value of CRP levels obtained to distinguish acute and perforated conditions was 6,375. CRP levels were like leukocytes, they had a fairly large range in the condition of acute appendicitis with levels of 0.03 mg/dl - 11.13 mg/dl and in perforated conditions of 2.03 mg/dl - 38.06 mg/dl. The time span between the initial onset of appendicitis and treatment can affect CRP levels because CRP was found during acute inflammation as a non-specific inflammatory mediator. CRP increased 1,000-2,000 times from 4-6 hours (other literature is 6-12 hours) after the onset of inflammation. This dramatic increase in CRP places it as the focus of attention in the acute phase of inflammation. Peak CRP levels occurred on the third day of the onset of inflammation and slowly decreased.

In healthy humans, blood procalcitonin levels are lower than the clinical examination detection limit (0.01 ug/L). Bacterial inflammation increased PCT levels to> 2 ng/ml while in cases of viral infection, PCT levels were <0.5 ng/ml. Increased PCT levels took place quickly in 2 hours after the initial pro-inflammatory stimulus due to the release of lung and intestinal cells. The level reached its peak after 12-48 hours, then decreased slowly within 48-72 hours.[15]

Serum PCT levels due to severe bacterial infection followed by a systemic response can reach 100 ug/L. The dramatic increase in PCT during acute infection was uniquely not followed by an increase in parallel levels of calcitonin or a decrease in serum calcium level.[15]The half-life of serum PCT was 25-35 hours and did change significantly in kidney failure. Therefore, serum PCT levels can be used for diagnostic purposes in patients whose kidney function is damaged.[45]

Bacterial inflammation increased PCT levels to> 2 ng / ml while in cases of viral infection, PCT levels were <0.5 ng/ml. Based on the ROC curve, the area under curve was 97.7% with a sensitivity of 90% and a specificity of 91.4%. Meanwhile, it was obtained that the cut off value for the procalcitonin levels was 0.35.
In another study conducted on 31 patients, procalcitonin examination in appendicitis patients had a sensitivity of 100%, specificity of 83%, and higher accuracy value (65.4%) compared to CRP examination (54.88%) with sensitivity of 84.2% and specificity of 83%.[55] The findings of this study were not different from the findings of other studies conducted at Saiful Anwar Hospital Malang where the values of accuracy, sensitivity and specificity of procalcitonin were higher compared to leukocytes and CRP.

V. Conclusion

The results showed that the parameters of procalcitonin levels were not significant as single diagnostic value in predicting the diagnosis of acute perforated appendicitis in children compared with leukocytes and CRP. Although its specificity and sensitivity were almost the same as CRP, PCT was better in terms of accuracy. The cut off value for PCT was 0.35 for predictions of the incidence of acute perforated appendicitis in children at Saiful Anwar Hospital.

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