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# *Case Study: The Investigation of Drug Induced Liver Injury: A Case Study in In-patient of Internal Medicine Ward*

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ABSTRACT

Adverse Drug Reactions (ADR's) caused by the use of drugs are still often founded in health services, especially those with the potential for Drug Induce Liver Injury. Therefore we need a measurement instrument to identify these events to prevent the hepatotoxic effects. In this case study, it was reported that a 22-year-old patient was admitted to a Surabaya city hospital in September 6, 2017 with complaints of nausea, vomiting, fever and decreased of appetite. On the laboratory examination found an increase in the total bilirubin value and Gamma Glutamyl Transferase. ALT significantly increased > 3x and ALP > 2x from the normal value. Based on the results of ultrasound and MRI, the impression of Gall Bladder Contracted and Cholecystitis Suspected were obtained with the conclusion that there was no obstruction of the biliary system and the normal abdominal organs. From the results of an in-depth investigation, the patient said that he regularly consumes Carrol Superpil to reduce back pain. After the clinical pharmacy assessment for the first Patient was DILI with a RUCAM score of 7 (probable DILI) due to the use of Carrol Superpil as well as the presence of Drug Related Problems in the patient, namely as Ceftriaxone which prescribed during the hospitalization which could affect ALT/ALP, it is recommended to replace antibiotics with Cefotaxime 3x1 gr.



## INTRODUCTION

Liver function disorders are still major health problems in both developed and developing countries (Matebesi, Z., & Timmerman, C., 2015). The Center for Data and Information (DATIN Info) of the Indonesia Republic Health Ministry (2015) stated that Indonesia is a country with a high incidence of liver disease. Allegedly the incidence increase is due to impermanent

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damage but can last for quite a long time. One of the causes of liver damage is drugs (Minjun et.al., 2015). In the United States there are about 2000 cases of acute liver failure that occur in each year and more than 50% are caused by drugs (N Chalasani and E Björnsson, 2010). Drugs that can induce the liver damage (hepatotoxic) or usually are referred to Drug Induced Liver Injury (DILI) (DA Perwitasari et.al., 2015). Liver damaged-inducing drugs are increasingly being recognized as a cause of acute and chronic liver disease (AC Paniagua and P Amariles, 2018). More than 1000 of drug products were withdrawn by the authorities in the United States because of their potential as hepatotoxic (Food and Drug Administration, 2016). Hepatotoxicity is an unwanted effect of a drug that can occur even when it is prescribed by a doctor (SA Alqahtani et.al, 2015).

DILI is often undiagnosed or clinically misdiagnosed since there are no specific serological tests as a marker of drug-induced liver damage (RJ Lu et.al., 2016). Therefore a measurement instrument is needed to identify the incidence of Adverse Drug Reaction (ADR's) due to the drugs administration that are potentially hepatotoxic (HL Tillmann et.al., 2019). There are several commonly used tools such as the Clinical Diagnostic Scale (CDS), Digestive Disease Week Japan 2004 (DDW-J) scale and the Roussel Uclaf Causality Method (RUCAM) (H Takikawa et.al., 2003). RUCAM is a DILI causality assessment method that most rational, comprehensive, and conventional with high accuracy and has been tested by several experts in the world. RUCAM has several advantages as follows; not influenced by gender, age or race, the parameters chosen are comprehensive, rational and objective and can be used by non-hepatologist clinicians (Yu et al., 2017). This article reviews a patient case in a hospital in Surabaya city who is suspected of having ADR's due to the use of drugs that have the DILI potential which was analyzed using the RUCAM score instrument

## CASE PRESENTATION

### 1. Subjective

The patient I (22 years old, 60 kg weighing) was admitted to the hospital (MRS) on September 6, 2017 with the complaints of nausea since 4 days before admission to the hospital (SMRS) accompanied by vomiting, fever, and decreased of appetite.

The results of the pharmacist's assessment did not show that the patient had a history of drug allergies and the previous diseases (Co-morbid). After a deep investigation, the patient said that he regularly took Carol Superpil, starting on October 25, 2017 and stopped taking the drug on November 3, 2017 (10 days) which the patient used to reduce back pain. The patient also has a psychosocial

history of consuming alcohol since 2015 and quitting since 7 months ago.

The patient's clinical condition can be seen in **Table I.**

**Table I.** The Patient's Clinical

| Clinical Condition | Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 6/11 /17 | 7/11 /17 | 8/11 /17 | 9/11 /17 | 10/11 /17 | 12/11 /17 | 13/11 /17 | 14/11 /17 |
| Nausea | √ | ↓ | ↓ | - | - | - | - | - |
| Stomach ache | √ | - | - | - | - | - | - | - |

## 2. Objective

An abdominal ultrasonography (USG) examination was performed on November 8, 2017 and obtained the impression of Contracted Gall Bladder and Suspended Cholecystitis with the conclusion that there is no the biliary system obstruction and the abdominal organs normal MRI.The laboratory supporting data can be seen in **Table II**. Based on the laboratory examination, it was shown that there were an increase in the total bilirubin and GGT values. ALT significantly increased > 3x and ALP > 2x from the MRS normal value on the first day until the third day. The doctor gave therapy with Curcuma Tablet 1 tablet/8 hours, Vitamin B6 1 tablet/12 hours and Ceftriaxone injection 1 g/12 hours which can be seen in **Table III.**

**Table II.** The Laboratory Supporting

| Laboratorium Parameter | Normal Value | Date | | |
|---|---|---|---|---|
| | | 6/11/17 | 9/11/17 | 14/11/17 |
| Creatinin | 0,5 – 1,5 mg/dL | 1 | | |
| BUN | 10 – 24 mg/dL | 8 | | |
| Albumin | 3,5 – 5,5 g/dL | 4,31 | 3,72 | |
| TP | | 7,94 | 6,60 | |
| Alkaline Phospatase | 34 -114 IU/L | 157 | 155 | 130 |
| Gamma Glutamyl Transferase | 7 – 50 U/L | 213 | 186 | 123 |
| Total Billirubin | 0,2 – 1 µmol/L | 5,23 | 7,1 | 2,6 |
| Billirubin Direct | 0 – 0,3 µmol/L | 3,48 | 5,4 | 1,8 |
| Billirubin Indirect | 0 – 0,8 µmol/L | | 1,7 | 0,8 |
| SGOT | 0 – 35 U/L | 387 | 103 | 38 |
| SGPT | 0 – 37 U/L | 935 | 431 | 147 |
| Globulin | 2,2 – 3,5 | | | |
| Anti HCV | (Negatif) | (Negatif) | | |
| HbSAg | 0-1 | 0,43 | | |
| IgM Anti HAV | | 0 | | |

## RESULT AND DISCUSSION

The Patient I, aged 23, was admitted to the hospital on 6/11/2017 with the complaints of nausea since 4 days ago, accompanied by vomiting, fever, decreased of appetite. The patient I admitted that he has no chronic disease history and has been taking Carol Superpill for the past 10 days for lowing back pain and difficulty in urinating.The patient also admitted of consuming alcohol since 2015 and stopped since 7 months ago. The doctor's initial diagnosis was suspected of cholecystitis.

On the laboratory examination on 6/11/2017, a drastic increase in ALT, ALP, Bilirubin, and GGT values were founded, while another marker of liver function, namely albumin, was at the normal values. The clinical pharmacy assessment for the patient based on the subjective data and the clinical laboratory is the assumption that this condition is a manifestation of Drug Induce Liver Injury (DILI) due to Carol Superpil.

**Table III.** The Patient's Therapy Profile

| Treatment | Signatura | Tanggal | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 6/11/17 | 7/11/17 | 8/11/17 | 9/11/17 | 10/11/17 | 11/11/17 | 12/11/17 | 13/11/17 | 14/11/17 |
| Curcuma Tablet | 1 tablet/8 hours | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Vitamin B6 | 2 tablet/12 hours | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Ceftriaxone Injection | 1g/12 hours | √ | √ | √ | √ | Switch to Cefotaxime 1 g/hours | √ | √ | √ | - |

According to Hys Law (Hyman Zimmerman, 1960) DILI is a condition in which there is an increase of Serum ALT >3 × Upper Limit Normal (ULN), serum total bilirubin >2 × ULN, in the cholestasis absence (increased serum alkaline phosphatase and no risk factors). Other causes besides of drugs is the increase of aminotransferases and bilirubin, such as viral hepatitis A, B, C, Acute Liver Disease. The steps for assessing DILI can be seen in **Figure 1.**

Based on the assessment results using the RUCAM score calculation, it can be seen in **Figure 2**, where the total score obtained is 7 with the meaning of "Probable DILI".

In this case, the value of R = 18, 44 was obtained therefore it was included in hepatocellular injury. Drugs that cause hepatocellular injury are shown in **Figure 3**. In this case, it is suspected that the drugs causing hepatocellular injury are NSAIDs because of the sodium salicylate which is contained in Carol Superpil and the indications for its use to treat back pain. Based on the pathogenesis, DILI can be divided into intrinsic and Idiosyncratic DILI. Intrinsic DILI is usually predictable and closely related to the drug dose magnitude. Unlike intrinsic DILI, idiosyncratic DILI is unpredictable, independent of dose, clinical manifestations can vary between each of the patients (Chalasani et al., 2014).

Most NSAIDs cause idiosyncratic DILI except aspirin (intrinsic DILI).

There are several pathogenesis underlying the occurrence of idiosyncratic DILI, including genetic polymorphisms that cause enzymes dysfunction and transport proteins involved in drug metabolism. In addition, HLA polymorphisms can cause the human body to produce an adaptive immune system in the liver in responding to drugs.

**Figure 1.** DILI Assasement (Yu, Y. et.al., 2017)

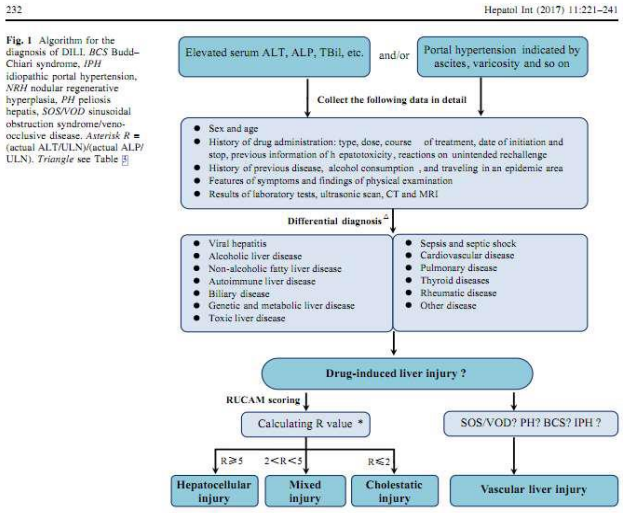
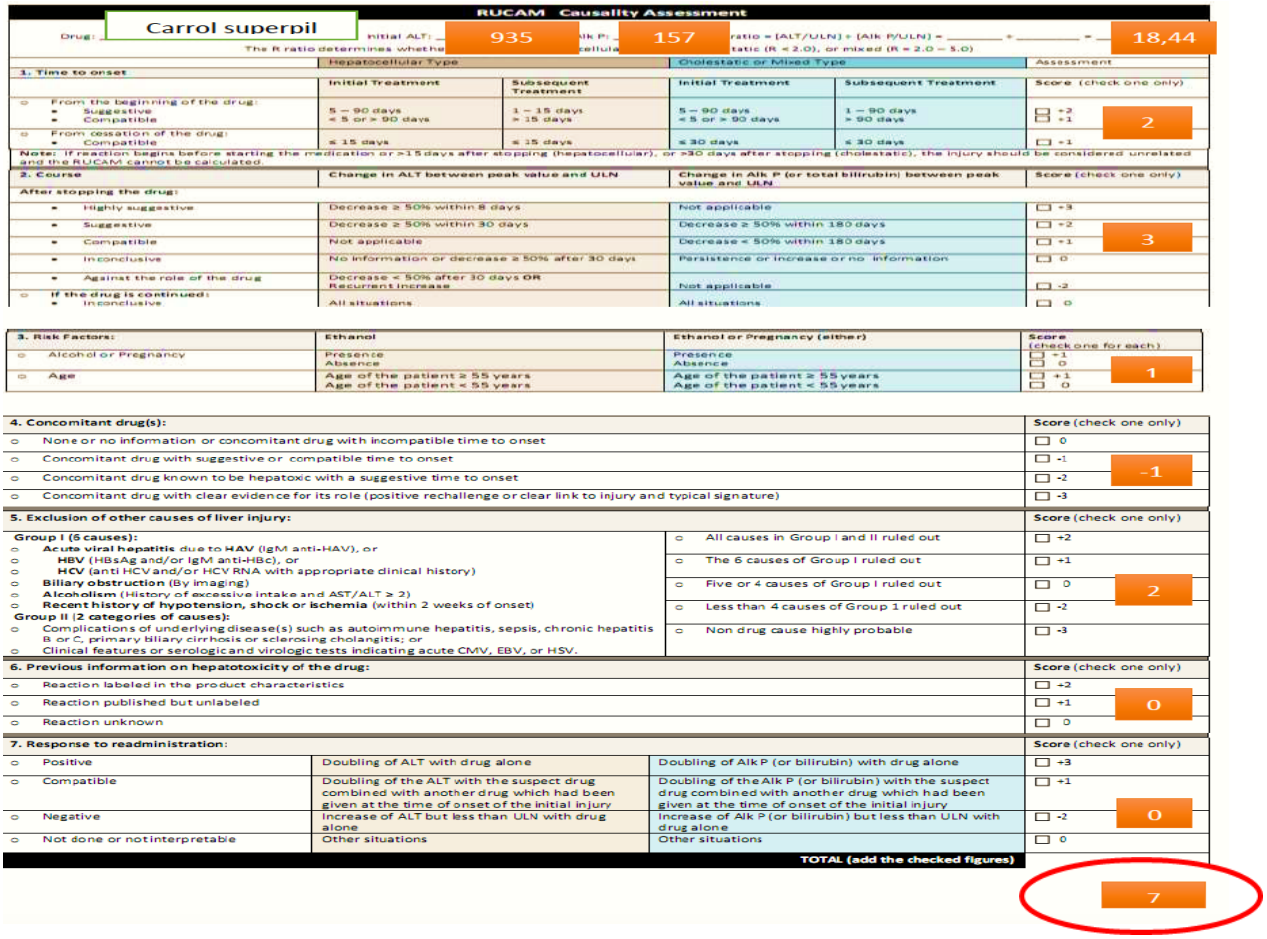



**Figure 2.** RUCAM Score Calculation (Chalasani, N. P. et.al., 2014)



Another possible mechanism is the reactive metabolites production from drugs that cause mitochondrial damage and induce oxidative stress, which ultimately leads to hepatocellular injury (Yu et al., 2017). Alcohol use, apart from its relationship with DILI, can cause liver cell damage where the alcohol metabolism product, namely acetaldehyde can cause Reactive Oxygen Species (ROS) overproduction which can trigger cell mitochondrial apoptosis. However, if it is associated to idiosyncratic DILI, the risk factors for alcohol are still debated because of the lack of evidence to prove the link between the two. In the Drug Induced Liver Injury Network (DILIN) study it was said that alcohol was negative trigger for DILI (Devarbhavi, 2012). The preferred management of DILI is the suspected discontinuation of precipitating drug should be carried out immediately where 95% of patients will experience spontaneous improvement because of their individual ability adapting to hepatotoxicity. As seen in the patients that ALT value gradually decreased to 147 and total bilirubin (TBil) to 2.6 on 14/11/2017. The patient's clinical condition began to improve where the patient is no longer complained of nausea, vomiting and his appetite began to increase. It was reported that the mean of recovery for the patients with hepatocellular injury was ± 3 weeks and for collestatic injury ± 4-6 weeks.

According to the data, within 3 months after the acute DILI onset , 42% of patients will still have an abnormal hepatic biochemical test and within 1 year 17% of patients will still have an abnormal hepatic biochemical test. Another Drug Related Problem (DRP's) that founded was the antibiotic Ceftriaxone prescribing where this antibiotic can affect the ALT parameter value, moreover it is recommended that another antibiotic which has no effect on ALT and bilirubin is cefotaxime 3x1 gr can be seen in **Table III**. The other prescribed drugs are appropriate, namely curcuma as a hepatoprotector and vitamin B6 to overcome B6 deficiency which is often found in the Acute Liver Injury cases

| Hepatocellular | Cholestatic | Mixed |
|---|---|---|
| Acetaminophen | Amoxicillin-clavulanic acid | Allopurinol |
| Allopurinol | Anabolic steroids | Azathioprine |
| Clindamycin | Captopril | Carbamazepine |
| Clopidogrel | Cefazolin | Chlorpromazine |
| Disulfiram | Chlorpromazine | Clindamycin |
| Fluoxetine | Cyproheptadine | Cyproheptadine |
| Flutamide | Enalapril | Doxycycline |
| Herbals | Estrogens | Methimazole |
| Imatinib | Griseofulvin | Mycophenolate mofetil |
| Interferon alpha and beta | Macrolides | Phenobarbital |
| Irbesartan | Methimazole | Phenytoin |
| Isoniazid | Oral contraceptives | Sulfonamides |
| Ketoconazole | Sulfonylureas | Trimethoprim-sulfamethoxazole |
| Lamotrigine | Terbinafine | Verapamil |
| Levofloxacin | Ticlopidine | |
| Lisinopril | Trimethoprim-sulfamethoxazole | |
| Losartan | Verapamil | |
| Methotrexate | | |
| Methyldopa | | |
| Minocycline | | |
| Mycophenolate mofetil | | |
| Nitrofurantoin | | |
| NSAIDs | | |
| Omeprazole | | |
| Pyrazinamide | | |
| Propylthiouracil | | |
| Rifampin | | |
| Valproic acid | | |

**Figure 3.** Kind of Drugs That Induced Liver Injury (Chalasani, N. P. et.al., 2014)

## CONCLUSION

Based on the case findings above, the clinical pharmacy assessment results for The Patient I was DILI with a RUCAM score = 7 (probable DILI) due to the use of Carrol Superpil as well as the presence of DRP in the patient, namely as ceftriaxone prescription during the hospitalization which could affect ALT/ALP moreover it is advisable to replace antibiotics with cefotaxime 1 gram/8 hours.

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## CONFLICT OF INTEREST

All author decleare there is no potential conflict of interest with the research, authorship, and/or publication of this article

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