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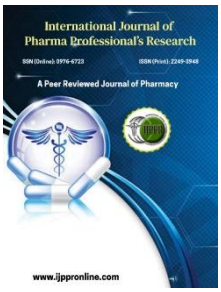

To determine drug interactions between the medicines given to Dengue Patients

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Keywords:
Dengue Hemorrhagic Fever; DSS- Dengue Shock Syndrome; DDIs- Drug-Drug Interactions

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ABSTRACT:
Dengue fever is a viral disease transmitted by infected mosquitoes, primarily Aedes aegypti and Aedes albopictus. Symptoms include fever, headache, joint and muscle pain, nausea, vomiting, and a rash. In severe cases, it can lead to complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can be fatal. The pathogenesis of dengue is a complex process involving viral replication, an immune response, and the potential for excessive inflammation and plasma leakage. Understanding the pathogenesis of dengue is crucial for the development of effective prevention and treatment strategies. Dengue virus is further divided into four distinct serotypes, known as DENV-1, DENV-2, DENV-3, and DENV-4, and infection with one serotype does not provide immunity against the other serotypes. There are currently no vaccines that can protect against all four serotypes of DENV.

Introduction:

Dengue fever is a viral illness transmitted by the bite of an infected mosquito. It is prevalent in tropical and subtropical regions of the world, particularly in areas with a high density of the Aedes mosquito, which is the primary vector for dengue.

Symptoms of dengue fever can range from mild to severe and usually begin [1-3] days after the bite of an infected mosquito. They may include high fever, severe headache, joint and muscle pain, nausea, vomiting, and a rash. Some people may also experience severe abdominal pain, difficulty breathing, and bleeding from the nose or gums. [4] Dengue hemorrhagic fever, which can be fatal, can develop from dengue fever in severe cases.

To **prevent** from dengue fever, it is important to take precautions to avoid mosquito bites, such as using insect repellent, wearing long-sleeved shirts and pants, and sleeping under a mosquito net. It is also important to eliminate mosquito breeding sites by removing standing water from around the

home. In some cases, vaccines are available to help prevent dengue fever.

Dengue fever is a viral illness transmitted by mosquitoes that affects millions of people worldwide each year. Fever, headache, muscle and joint pain, and a rash are among the symptoms of the disease. In severe cases, it can lead to complications such as dengue hemorrhagic fever and dengue shock syndrome, which can be fatal. [5-7]

1.1. Dengue Pathogenesis:

Dengue is a viral infection caused by the dengue virus (DENV), which is transmitted to humans through the bite of infected mosquitoes, primarily Aedes aegypti and Aedes albopictus.

Once the virus enters the body, it replicates in the lymphoid tissue, primarily in the lymph nodes. The virus then spreads to the bloodstream, where it infects and replicates in the monocytes and macrophages, leading to viremia (the presence of virus in the blood).

During the viremia stage, the virus can infect and damage multiple organs, including the liver, spleen, and heart. The infected cells release pro-inflammatory cytokines and chemokines, leading to the recruitment of immune cells to the site of infection. This results in an immune response, which can lead to the development of fever, rash, and other symptoms of dengue fever. [8]

As the immune response progresses, the virus is cleared from the bloodstream, and the symptoms of dengue fever subside. However, in some cases, the immune response can become overactive, leading to an excessive release of pro-inflammatory cytokines and chemokines. This can result in increased vascular permeability, leading to plasma leakage and the development of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). [9]

In DHF and DSS, plasma leakage can lead to the loss of fluids and electrolytes from the bloodstream, leading to dehydration and hypotension. This can progress to shock and organ failure, which can be fatal if not treated promptly.

Overall, the pathogenesis of dengue is a complex process involving viral replication, an immune response, and the potential for excessive inflammation and plasma leakage. Understanding the pathogenesis of dengue is crucial for the development of effective prevention and treatment strategies. [10]

After a usual incubation period of 5-7 days, dengue starts quickly and progresses through three stages: **febrile, critical, and convalescent.**

- In Febrile Phase fever typically lasts 2–7 days and can be biphasic.
- The critical phase of dengue begins at defervescence and typically lasts 24–48 hours.
- As plasma leakage subsides, the patient enters the convalescent phase and begins to reabsorb extravasated intravenous fluids and pleural and abdominal effusions.

1.2. Dengue Virus Serotype:

Dengue virus (DENV) is a single-stranded RNA virus belonging to the Flavivirus genus, which also includes other important human pathogens such as West Nile virus and yellow fever virus. DENV is further divided into four distinct serotypes, known as:

DENV-1,
DENV-2,
DENV-3, and
DENV-4.

Each serotype is antigenically distinct, meaning that it has unique surface proteins that are recognized by the immune system. As a result, infection with one serotype does not provide immunity against the other serotypes. In fact, infection with one serotype can increase the risk of severe disease upon subsequent infection with another serotype. Antibody-dependent

enhancement (ADE) is the term used to describe this phenomenon.

All four serotypes of DENV are found in tropical and subtropical regions throughout the world, with the highest incidence of dengue fever and dengue hemorrhagic fever occurring in Southeast Asia, the Western Pacific, and Latin America. The distribution of the serotypes can vary depending on the location and time period. For example, DENV-1 is the most common serotype in Southeast Asia, while DENV-2 is more common in the Western Pacific and Latin America.

There are currently no vaccines that can protect against all four serotypes of DENV. The current dengue vaccine, Dengvaxia, provides protection against all four serotypes; however, its efficacy is lower in people who have not previously been infected with dengue virus. Therefore, ongoing research is needed to develop a more effective vaccine that can provide cross-protection against all four serotypes.

In conclusion, dengue virus is a complex and dynamic virus that is divided into four distinct serotypes, each with unique antigenic properties. Understanding the serotypes of dengue is important for the development of effective prevention and treatment strategies, as well as the management of outbreaks of dengue fever and dengue hemorrhagic fever. [11]

1.3. Treatment prescribing patterns:

As of right now, dengue fever has no particular treatment. Instead, management of the disease typically involves relieving symptoms through the use of pain relievers, fluids, and rest. In addition, it's important to prevent secondary infections by keeping the patient's wound clean and dry.

When it comes to prescribing patterns for dengue fever, studies have shown that there is significant variation depending on the country, region, and healthcare setting. For example, in a study conducted in Pakistan, researchers found that most patients with dengue fever were treated with antipyretics, analgesics, and fluids. However, in some cases, antibiotics and steroids were also prescribed, despite there being no evidence to support their use.[12-15]

Another study conducted in India found that the most commonly prescribed medications for dengue fever were paracetamol and ibuprofen for fever and pain management, respectively. Antihistamines were also frequently prescribed, even though they are not recommended for the treatment of dengue fever. [7]

In general, the current best practice for dengue fever is to manage the symptoms as much as possible and to prevent secondary infections, for example, by keeping the patient's wound clean and dry.

Additionally, it is important to note that the prescribing pattern for dengue fever should be based on the latest clinical guidelines, which are continuously updated as new research emerges.

In conclusion, prescribing patterns for dengue fever vary greatly depending on the country, region, and healthcare setting. However, the current best practise for dengue fever is to manage the symptoms and prevent secondary infections. Additionally, healthcare providers should always be updating themselves on the current clinical guidelines for dengue fever treatment. [16]

METHODOLOGY:

The methodology section outlines the details of a prospective observational study conducted at the Rohilkhand Medical College and Hospital in Bareilly, India over a period of two months. The study included both outpatient and inpatient populations below the age of 65 who were prescribed two or more drugs. Data was collected from case sheets and direct patient interviews, while prescriptions involving alternative systems of medicine and patients above 65 years of age were excluded.

DDIs were detected using the drug interaction checker within (www.drug.com) and (www.medscape.com). The detected DDIs were classified in 3 categories, serious, monitor and minor in total no. of drugs prescribed.

DDI identification: The pre-processed data is analysed to identify potential DDIs. This is typically done using software tools that have knowledge bases of known DDIs and algorithms to identify potential interactions based on the prescribed drugs, dosages, and other relevant factors.[17-19]

Data analysis: The validated DDIs are analysed to understand the frequency, severity, and risk factors associated with the interactions. This can be done using statistical methods such as descriptive statistics and multivariate analysis.

Through prescription analysis, this study aimed to determine the risk factors associated with potential DDIs and calculate the frequency of potential DDIs in a teaching hospital's inpatient population.

Methodology: This study is a prospective observational study conducted at a tertiary care hospital in Bareilly, India, over a period of two months. The inclusion criteria were out-patients and in-patients below the age of 65 with a prescription containing two or more drugs, while the exclusion criteria were prescriptions with less than two drugs, patients over the age of 65, and prescriptions from alternative systems of medicine. The data was collected from case sheets and direct patient interviews.

Result: This case study analyzed 40 prescriptions from a hospital and found a total of 227 drugs prescribed, ranging from 2 to 5 drugs per patient. Out of these, 42 drug-drug interactions (DDIs) were identified, with 22 prescriptions having at least one DDI. Two of the identified DDIs were classified as serious, while 21 were classified as monitor closely and 19 were minor. The serious DDI involved the combination of pantoprazole and fluconazole, which can lead to an increased risk of bone fractures, osteoporosis, and hypomagnesemia. Another serious DDI was found between fluconazole and itraconazole, which can increase the QTc interval and should be avoided or an alternate drug should be used.

PLAN OF WORK

Sr. no.	Plan Of Work	Duration
1	Framing of title of the project work	2 Days
2	Literature survey	10 Days
3	Obtaining institutional clearance.	3 Days
4	Collection of prescription from OPD	2 Months
5	To identify the interaction among the prescribed medicines.	
6	To identify the type and severity of DDIs	
7	To make the database of the interaction identified.	7 Days
8	Submission of report.	10 Days

The possible DDIs in the various prescriptions are stated under below table:

SR. No.	PRESCRIPTION	PRSCRIBED BRAND	DRUG COM	DRUG INTER

	DETAIL	ED DRUG	POSITION	ACTIONS
01	**Pt. Name :Raja** Age : 41 Sex : M	Inj. Pentop OD Inj. Emset BD Inj. Fevestin TDS Tab Aciloc 150 BD	Pantaprazole Ondensetrone Acetaminophen Ranitidine 150mg	NA
02	**Pt. Name :Punam** Age :17 Sex :F	Inj. Monocef 1g OD Tab Aciloc 150 BD Tab Acedep SP BD	Ceftriaxone Ranitidine 150mg Aceclofenac (100mg) Paracetamol (325mg) Serratiopeptidase (10mg)	NA
03	**Pt. Name : Suhani** Age : 17 Sex :F	Inj. Monocef OD Tab. Aciloc 150 BD Tab.Neurokind Plus OD	Ceftriaxone Ranitidine 150mg Multivit.	NA
04	**Pt.Name :Manoj** Age : 23 Sex :M	Tab.monrab DSR OD Tab Limcee 500 OD Tab. calpol 500 TDS	Domperidone (30mg) Rabeprazole (20mg) Ascorbic Acid IP Acetaminophen	NA
05	**Pt.Name: Ashok Kumar** Age : 23 Sex :M	Tab. Zifi 200 BD Cap. Coolest DP OD Tab. Dolo 500 SOS Tab Limcee 500 OD Cap. Becasule OD	Cifixime Domperidone (30mg) Pantoprazole (40mg) Paracetamol Ascorbic Acid IP Vi t. B complex.	NA
06	**Pt. Name : sukhilal** Age : 45	Tab. Evicef 200 BD Tab Paracip TDS Cap. Neurokin	Cifixime Acetaminophen Multivitamin	NA

	Sex :M	d gold OD		
07	**Pt. Name : Riya** Age : 23 Sex : F	Inj. Romiset Inj. Emeset Tab. Acedep SP Tab AtoZ	Romiplostim (250mcg) Ondansetron (2mg/ml) Aceclofenac (100mg) Paracetamol (325mg) Serratiopeptidase (10mg) Multivitamin.	NA
08	**Pt. Name : Riya** Age : 23 Sex : F	Daclor 500 OD Zeerodol SP BD Rabekind 20 OD	Chloramphenicol Aceclofenac (100mg) Paracetamol (325mg) Serratiopeptidase (10mg)	NA
			Rabeprazole (20mg)	
09	**Pt. Name : Reena devi** Age : 35 Sex : F	Mahacef 200 BD Tab. Neurobion Forte OD Dolo 650 SOS Tab. Forcan 150 OD	Cefixime (200mg) Thiamine Mononitrate Riboflavin Pyridoxine Hydrochloride Cyanocobalamin Nicotinamide Calcium Pantothenate Paracetamol (650mg) Fluconazole (150mg)	**Moderate** The blood levels of pantoprazole can rise when fluconazole is taken. Diarrhea, abdominal pain, nauseousness, vomiting, and flatulence may become more common as a result. Additionally, while receiving long-term treatment, you may be more vulnera

				ble to bone fractures, osteoporosis, and hypomagnesemia (low blood magnesium),
10	**Pt. Name : Sukhdev** Age : 27 Sex : M	Tab.monrab DSR OD Tab. Caripill BD Tab.Ceftas 200 BD Tab Aciloc 150 BD	Domperidone (30mg) Rabeprazole (20mg) Carica Papaya leaf extract Cefixime (200mg) Reneti dine 150mg	

5. METHODOLOGY

5.1. Study design

It is a prospective observational study.

5.2. Study site

The study work was conducted at "TERTIARY CARE HOSPITAL (ROHILKHAND MEDICAL COLLEGE AND HOSPITAL, BAREILLY) DISTRICT BAREILLY".

5.3. Study period

The whole study was completed in two months.

5.4. Inclusion criteria

- Out-door patients & Indoor Patients.
- Age group below 65 years.
- Prescription with two or more drug prescribed for patients.

5.5. Exclusion criteria

- Prescription with less than 2 drugs prescribed.
- Age group more than 65 years.
- Ayurveda, Siddha, & other prescription involving alternative system of medicine.

5.6. Source of data

The data was collected from the case sheet of outdoor patients as well as indoor/hospitalized patients and direct patient interview from ROHILKHAND MEDICAL COLLEGE AND HOSPITAL BAREILLY.

METHODOLOGY

The data was collected from case sheets of out-door patients as well as in-door Patient or hospitalized patient in medicine as well as pediatrics ward & direct patient interview from ROHILKHAND MEDICAL COLLEGE AND HOSPITAL. Demographic information (age & sex) main diagnosis, number of drugs and details of comorbidities were obtained from the clinical record. All medications that were prescribed, including routine and pre-re-nata (means as required) medications were screened for DDIs.

DDIs were detected using the drug interaction checker within (www.drug.com) and (www.medscape.com). The detected DDIs were classified in 3 categories, serious, monitor and minor in total no. of drugs prescribed.

DDI identification: The pre-processed data is analysed to identify potential DDIs. This is typically done using software tools that have knowledge bases of known DDIs and algorithms to identify potential interactions based on the

prescribed drugs, dosages, and other relevant factors.

Data analysis: The validated DDIs are analysed to understand the frequency, severity, and risk factors associated with the interactions. This can be done using statistical methods such as descriptive statistics and multivariate analysis.[20-24]

Through prescription analysis, this study aimed to determine the risk factors associated with potential DDIs and calculate the frequency of potential DDIs in a teaching hospital's inpatient population.

RESULT

Total number of drug interactions:

Severity of DDIs	Number of DDIs	DDIs present in the number of prescription
Serious DDIs	2	2
Monitored	21	18
Minor DDIs	19	15

6.2. DISCUSSION

In this case study the collective data was found that the drug-drug interaction in between the drugs or medicine prescribed in the prescription by the registered medical practitioner. We collect the 40 prescription via Rohilkhand Medical College and Hospital. Out of 40 enrolled patients in the study sample was 26 male, 14 female age between 18 to 65. The total no of drug was prescribed 227, ranging between 2 to 5 per patient. Overall 42 DDIs were identified in the study sample.

In all these prescription the drug-drug interaction was found in 22 prescriptions and remains 18 prescription were free from any interaction. In which 2 prescriptions was found serious and monitor closely were 18 prescriptions.

Overall 42 DDI were found in the total 22 prescriptions in which 2 DDIs from 2 prescriptions were serious DDIs , 21 DDIs from 18 Prescriptions were monitor closely DDIs and 19 DDIs from 15 Prescriptions were minor DDIs.

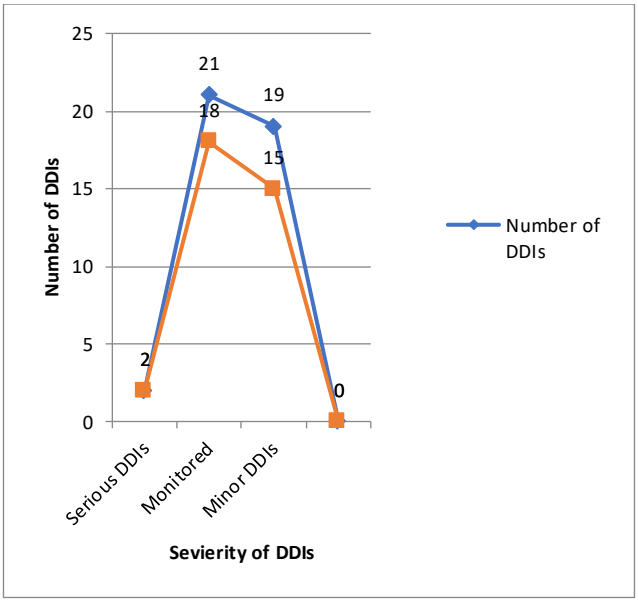

Figure 1: Graph showing analyzed data of severity of disease in the number of prescriptions.

One of the moderate DDI was:

- **Pantoprazole + fluconazole:**
  The blood levels of pantoprazole can rise when fluconazole is taken. Diarrhea, abdominal pain, nauseousness, vomiting, and flatulence may become more common as a result. Additionally, while receiving long-term treatment, you may be more vulnerable to bone fractures, osteoporosis, and hypomagnesemia (low blood magnesium)

One of the Serious DDI amongst Prescription was:

- **fluconazole + itraconazole:**
  - fluconazole and itraconazole both increase QTc interval.
  Avoid or Use Alternate Drug.
  - fluconazole will increase the level or effect of itraconazole by affecting hepatic/intestinal enzyme CYP3A4 metabolism.[25-26]

7. CONCLUSION

Finally, this case study examined 40 prescriptions written by outside Rohilkhand Medical College and Hospital patients. 24 prescriptions had at least one of the 42 drug-drug interactions (DDIs) that

were found. The remaining DDIs were categorised as minor, while two of the DDIs required strict monitoring and were classed as serious. Between fluconazole and itraconazole, the most frequent significant drug-drug interaction was discovered. Our findings emphasise the need of taking into account potential DDIs when prescribing medications and the requirement for increased knowledge among medical practitioners in order to avoid and manage unwanted interactions.

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