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DRUG INDUCED MEDICAL SYNDROMES

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ABSTRACT

The drug induced syndromes related hospitalization in emergency and intensive care units (ICU) is very high, enhances the patient duration of hospital stay and cost of the therapy. Iatrogenic disease is an ever enduring concern for patients, healthcare professionals and health administrators. Most of these Drug induced diseases are largely preventable if strict vigilance and proper periodic clinical and diagnostic monitoring are undertaken. This overview article delivers the information concerning the different drug induced syndromes with its causative agents, clinical manifestation and therapy.

KEYWORDS: Drug induced diseases, iatrogenic diseases.

INTRODUCTION

The word "Syndrome" comes from the Greek word sundrom, which means concurrence of symptoms, or from word sundromos, which means running together. A syndrome is a set of medical signs and symptoms that are correlated with each other and, often, with a particular disease or disorder.[1]

A drug-induced disease is the unintended effect of a drug, which results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or require hospitalization. With the multitude of drugs prescribed to a single patient adverse drug reactions are bound to occur. Iatrogenic (of a disease or symptoms) induced in a patient by the treatment or comments of a physician. One of the basic principles in treatment stated by Hippocrates is "First do no harm". Stories of medical remedies causing more harm than good have been recorded from time immemorial. An iatrogenic disorder occurs when the deleterious effects of the therapeutic or diagnostic regimen causes pathology independent of the condition for which the regimen is advised. It would be impossible to provide the benefits of modern medicine if reasonable steps in diagnosis and treatment were withheld because of possible risks. Diagnostic procedures (mechanical and radiological), therapeutic regimen (drugs, surgery, other invasive procedures), hospitalization and treating doctor himself can bring about iatrogenic disorders.[2]

Atypical haemolytic uremic syndrome (aHUS)

Extremely rare disease characterized by low levels of circulating red blood cells due to their destruction (haemolytic anaemia), low platelet count (thrombocytopenia) due to their consumption and inability of the kidneys to process waste products from the blood and excrete them into the urine (acute kidney failure), a condition known as uraemia. aHUS is considered a form of thrombotic microangiopathy (TMA). TMA is broken down into two main forms – thrombotic thrombocytopenia purpura and haemolytic uremic syndrome.

Causative agents: Mitomycin-C, Cyclosporine, Quinine, Cocaine, Clopidogrel.

Symptoms: Upper respiratory infection or gastroenteritis. Vague feelings of illness, fatigue, irritability, and lethargy. The three main findings of aHUS are haemolytic anaemia, thrombocytopenia, and acute kidney failure.

Management: Humanized anti-C5 monoclonal antibody Eculizumab is used to bind to the complement protein 5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. It has now been approved for atypical haemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy.[3]

Burning Mouth syndrome

Burning Mouth Syndrome (BMS) is a painful, complex condition often described as a burning, scalding, or tingling feeling in the mouth that may occur every day for months or longer. Dry mouth or an altered taste in the mouth may accompany the pain. BMS is most commonly found in adults over the age of 60.

Causative agents: Antihypertensives, Antiretrovirals, Antiseizure drugs.

Symptoms: Burning or scalded sensation that most commonly affects tongue, lips, gums, palate, throat or whole mouth, Sensation of dry mouth with increased thirst. Taste changes, such as a bitter or metallic taste, loss of taste.

Management: Oral rinses or lidocaine. Clonazepam, TCAS, gabapentin, SSRIs, Trazodone. Topical capsaicin has been used as a desensitizing.[4]

Blue-Gray Syndrome: Blue grey syndrome is an amiodarone related hyperpigmentation considered as a skin storage disease secondary to drug deposition.

Causative agents: Amiodarone.

Symptoms: Blue-gray skin pigmentation, dyspnea, cough and fever.

Management: Discontinuation of the causative agent. Careful and regular long term follow-up is mandatory.[5]

Cushing's syndrome: Rare condition characterized by the hypersecretion of the adrenocorticotropic hormone (ACTH) due to a pituitary adenoma that ultimately causes endogenous hypercortisolism by stimulating the adrenal glands.

Causative agents: Glucocorticoids.

Symptoms: Upper body obesity, moon face, hirsutism, and facial plethora, thin arms and legs, severe fatigue and muscle weakness, High blood pressure, High blood sugar, osteoporosis and infections.

Management: Medications to control excessive production of cortisol at the adrenal gland include Metapyrone, Ketoconazole, Aminoglutethamide and Mitotane. Pasireotide works by decreasing ACTH production from a pituitary tumour.[6]

Churg Strauss syndrome: Churg-Strauss syndrome (CSS) is a necrotizing systemic vasculitis which affects the small- to medium-sized blood vessels and is characterized by asthma, eosinophilia and extravascular eosinophilic granulomas.

Causative agents: Montelukast, Zafirlukast.

Symptoms: Asthma is the most common sign of Churg-Strauss syndrome. The disorder can also cause a variety of other problems, such as hay fever, rash, gastrointestinal bleeding, and pain and numbness in your hands and feet.

Management: Corticosteroids, cyclophosphamide. In severe cases, anti-TNF blocking agents such as Infliximab or Etanercept, is used. Recombinant IFN-alpha can be a effective when given on a short-term basis.[7,8]

Drug Rash with Eosinophilia and Systemic symptoms Syndrome (DRESS): DRESS syndrome reflects a serious hypersensitivity reaction to drugs and has been classified under a delayed type IV b hypersensitivity reaction, where T helper type II cells play a significant role.

Causative agents: Anticonvulsants, Sulfonamides, Dapsone, Allopurinol, Minocycline, Gold, Hydroxychloroquine (HXQ) Sulfate, Isoniazid, Rifampicin, Ethambutol and Pyrazinamide.

Symptoms: Symptoms generally include fever, an often itchy rash which may be morbilliform or consist mainly of macules or plaques, facial edema, enlarged and sometimes painful lymph nodes, and other symptoms due to inflammation-based internal organ involvement, most commonly liver, less commonly kidney, lung, and heart, and rarely pancreas or other organs.

Management: Immediate discontinuance of the offending drug. The mainstay treatment of severe cases is systemic glucocorticoids, relying on the anti-inflammatory actions of these drugs to suppress the eosinophil- and T cell-induced tissue damage caused by the disorder. Less severe cases of this disorder may be better treated with topical steroids. Interferon-α is also useful for long-lasting DRESS.[9]

Ebstein's anomaly: Ebstein anomaly is a rare congenital heart defect. The tricuspid valve separates the right lower heart chamber (right ventricle) from the right upper heart chamber (right atrium). In Ebstein anomaly, the positioning of the tricuspid valve and how it functions to separate the two chambers is abnormal.

Causative agent: Lithium.

Symptoms: Bluish skin, failure to thrive, breathing problems and a fast heartbeat.

Management: Atrial fibrillation with pre-excitation, treatment includes procainamide, flecainide, propafenone, dofetilide, and Ibutilide. Intravenous amiodarone may also convert atrial fibrillation and/or slow the ventricular response.[10]

Floppy iris syndrome: Characterized by a flaccid iris which billows in response to ordinary intraocular fluid currents, a propensity for this floppy iris to prolapse towards the area of cataract extraction during surgery, and progressive intraoperative pupil constriction despite standard procedures to prevent this.

Causative agent: Tamsulosin.

Symptoms: Poor dilation of the pupil, both pre-operatively and intraoperatively. Iris billowing and floppiness, Iris prolapse through the incision sites, progressive constriction of the pupil (miosis) during surgery.

Management: Atropine Sulfate 1% pupilloplegic 2-3 days prior to surgery, may improve pupillary dilation.[11]

Fanconi's syndrome: Fanconi syndrome is a disorder of the kidney tubules in which certain substances normally absorbed into the bloodstream by the kidneys are released into the urine instead.

Causative agents: Cisplatin, Ifosfamide, Tenofovir, Sodium Valproate, Aminoglycosides, Outdated Tetracyclines.

Symptoms: Excessive thirst, excessive urination, vomiting, failure to thrive, slow growth, low muscle tone, muscle weakness, kidney disease, bone disease, hypophosphatemia, hypokalemia.

Management: Blood (acidosis) may be neutralized by sodium bicarbonate. Potassium supplements to treat hypokalaemia. Bone disease requires treatment with phosphates and vitamin D supplements. Kidney transplantation may be lifesaving if a child with the disorder develops kidney failure.[12]

Gray baby syndrome: Gray Syndrome is a potentially fatal complication that develops in new-born infants (usually preterm babies), due to an overdose of the antimicrobial medicine chloramphenicol.

Causative agents: Chloramphenicol.

Symptoms: Blue-coloured lips, nails; pale blue-grey body appearance, hypothermia and high blood pressure; irregular breathing, feeding difficulties, poor muscle tone, Vomiting, diarrhoea (green, watery stools), and distended abdomen.

Management: Immediate discontinuation of chloramphenicol medication. Blood transfusion to remove the toxic levels of chloramphenicol in blood. This is achieved through exchange blood transfusions. Phenobarbital and third generation cephalosporin effectively can be given at recommended doses.[13]

Guillain-Barre syndrome: Guillain–Barré syndrome (GBS) is an acute onset, usually monophasic immune-mediated disorder of the peripheral nervous system.

Causative agents: Neural tissue antirabies vaccine.

Symptoms: Tingling and weakness in feet and legs and spreading to upper body and arms. As Guillain-Barre progresses, muscle weakness can evolve into paralysis. Difficulty with eye or facial movements, including speaking, chewing or swallowing.

Management: Immunomodulatory therapy, such as plasmapheresis or the administration of intravenous immunoglobulins (IVIGs).[14]

Hand - Foot Syndrome (Palmar – Plantar Erythrodysaesthesia / HFS): Erythrodysaesthesia is a relatively common adverse effect of chemotherapeutic drugs.

Causative agents: 5-Fluorouracil, Doxorubicin, Docetaxel, Idarubicin, and Cytarabine.

Symptoms: Erythema, tenderness, tingling, numbness, dry rash and desquamation over the palms and soles.

Management: Therapies include dose modification, pyridoxine, regional cooling, and oral corticosteroids.[15]

Loffler's syndrome: It is a disease in which eosinophils accumulate in the lung in response to a parasitic infection.

Causative agents: Daptomycin, Sulfasalazine, Minocycline, Mesalamine.

Symptoms: Irritable bowel syndrome, abdominal pain and cramping, skin rashes and fatigue. The Loffler's syndrome itself will cause breathlessness, coughing as well as a fever.

Management: For drug-induced pulmonary eosinophilia, discontinue administration of the offending drug. When a parasitic infection is documented, appropriate use of anthelmintic drugs is indicated. In severe cases of simple pulmonary or drug-induced eosinophilia, systemic corticosteroids are highly effective.[16]

Nicolau Syndrome (Livedoid Dermatitis/NS): Nicolau Syndrome is a rare adverse drug reaction with unknown pathogenesis at the site of intramuscular drug injection.

Causative agents: Nonsteroidal anti-Inflammatory Drugs, Corticosteroids and Penicillin.

Symptoms: Extreme pain around the injection site, with overlying skin rapidly becoming erythematous, violaceous, or blanched and sometimes with reticular pattern. The reaction eventually leads to variable degrees of necrosis to the skin and underlying tissue. The wound eventually heals, can lead to atrophic, disfiguring scarring.

Management: Pain controlled with analgesics. Hyperbaric oxygen treatment given with the assumption of microarterial thrombi as well as heparin and pentoxyphylline. Vasospasm may be relieved by the

phosphodiesterase inhibiting action of Pentoxyphylline. Topical corticosteroids are effective for acute tissue inflammation. Debridement of the affected skin, subcutaneous tissue and muscle and flap reconstruction are ideal surgical measures.[17]

Neuroleptic Malignant Syndrome (NMS): Neuroleptic malignant syndrome (NMS) is a life-threatening emergency that is often seen as a complication of antipsychotic agents. Incidence of NMS ranges from 0.2% to 3.2%.

Causative agents: Butyrophenones, Phenothiazines, Thioxanthenes, Hydroxyzine, Reserpine;, Amitriptyline, Amoxapine, Desipramine, Maprotiline, Phenelzine, Tranylcypromine, Diazepam, Lorazepam, Carbamazepine, Phenytoin, Amantadine, Bromocriptine, Levodopa, Lithium.

Symptoms: High fever, irregular pulse, tachycardia, tachypnea, muscle rigidity, altered mental status, autonomic nervous system dysfunction resulting in high or low blood pressure, dyskinesia, dysphagia, festinating gait, oculogyric crisis and opisthotonos are seen in patients.

Management: Strong suspension of NMS neuroleptics should be done immediately. Supportive measures are of great importance especially rehydration and cooling. Bromocriptine and Dantrolene given in divided doses orally or parenterally up to 60mg per day.[18]

Purple Glove Syndrome (PGS): Purple Glove Syndrome is caused by intravenous administration of phenytoin resulting in soft tissue injury at the site of injection leading to oedema and purplish-black discoloration of the hand.

Causative agent: Phenytoin.

Symptoms: Intense pain, purplish black discoloration and edema at the site of injection.

Management: The management of PGS is mainly conservative, which includes limb elevation and physiotherapy. Use of low concentration local anesthetic for brachial plexus block has an added advantage of preserving motor function to facilitate physiotherapy in addition to providing adequate analgesia and relief of vasospasm.[19]

Radiation recall reaction: is a severe skin reaction that occurs when certain chemotherapy drugs are administered during or soon after radiation treatment. The rash appears like a severe sun burn.

Causative agents: Dactinomycin, Doxorubicin, Daunorubicin, Epirubicin, Idarubicin.

Symptoms: range from mild rash, dry desquamation and/or pruritus, to symptoms that are increasingly painful and may include swelling/edema, vesicles, maculopapular eruptions, and papules.

Management: Topical or systemic corticosteroids or nonsteroidal anti-inflammatory drugs are used to reduce inflammation. Antihistamines can also be used for symptomatic relief.[20]

Reye's syndrome: It is a rare but serious condition that causes swelling in the liver and brain. Reye's syndrome most often affects children and teenagers recovering from a viral infection, most commonly the chickenpox.

Causative agent: Aspirin.

Symptoms: Vomiting, personality changes, confusion, seizures, and loss of consciousness.

Management: For the treatment of fever or pain related to the flu, chickenpox or another viral illness, acetaminophen or Ibuprofen as a safer alternative to aspirin. Intravenous (IV) fluids. Diuretics to stop swelling. Medications to prevent bleeding. Vitamin K, plasma and platelets in instances of liver bleeding.[21]

Red Man Syndrome (Red-Neck Syndrome /RMS): is an anaphylactoid reaction from antibiotic use consisting of a pruritic erythematous rash to the face, neck, and upper torso. Involvement of the extremities may occur but to a lesser degree.

Causative agents: Vancomycin, Ciprofloxacin, Amphotericin B, Rifampicin and Teicoplanin.

Symptoms: Sensation of burning and itching, agitation, dizziness, headache, chill, fever and perioral paraesthesia.

Management: When a patient develops RMS, the IV antibiotic infusion should be stopped immediately. It can be managed with diphenhydramine 50 mg by mouth or intravenously and ranitidine 50 mg intravenously. Most episodes will resolve within 20 minutes. Normal saline IV boluses are used to treat hypotension. If vancomycin must be continued, patients should be premedicated with diphenhydramine 50 mg I.V. 1 hour before each dose.[22]

Rabbit's Syndrome (RS): is an antipsychotic induced dyskinesia of the mouth, characterized by fine, rapid, involuntary perioral motion that resembles the chewing motion of a rabbit.

Causative agents: Methotrimipramine, Benzatropine, chlorpromazine, Lithium, Sulpiride, Thioridazine, Haloperidol, Biperidine, Amitriptyline, Paroxetine, Risperidone, Clozapine, Olanzapine, Aripiprazole.

Symptoms: involuntary movements of the mouth which are fine, rhythmic and rapid, along the vertical axis, and without involvement of the tongue.

Management: Anticholinergic agents such as Benzatropine, Biperidine, Procyclidine and Trihexyphenidyl. Disappears few days after starting with anticholinergic agent, but there are chances of recurrence on stopping anticholinergic medications.[23]

Shoulder hand syndrome: Neuropathic pain disorder that develop as an exaggerated response to a traumatic lesion or nerve damage, that generally affects the extremities, or as the consequence of a distant process such as a stroke, spinal lesion or myocardial infarction. It rarely appears without an apparent cause. CRPS of upper limbs after stroke is frequently today called shoulder-hand syndrome (SHS).

Causative agent: Isoniazid.

Symptoms: Extreme pain including burning, stabbing, grinding, and throbbing. The pain is out of proportion to the severity of the initial injury. Moving or touching the limb is often intolerable.

Management: Bisphosphonates have the potential to reduce pain associated with bone loss, calcitonin, and ketamine a strong anaesthetic, may alleviate pain. Steroid medications, such as prednisone, may reduce inflammation and improve mobility in the affected limb. Antidepressants, such as amitriptyline, and anticonvulsants, such as gabapentin (Neurontin), are used to treat pain that originates from a damaged nerve (neuropathic pain).[24]

Sjogren's syndrome: is a disorder of immune system.

Causative agents: TCAs, Antihistamines.

Symptoms: Accompanies other immune system disorders, such as rheumatoid arthritis and lupus. In Sjogren's syndrome, the mucous membranes and moisture-secreting glands of eyes and mouth are usually affected first. Dry eyes. Eyes might burn, itch or feel gritty — as if there's sand in them. Dry mouth as might feel like it's full of cotton, making it difficult to swallow or speak.

Management: Eye drops such as cyclosporine decrease eye inflammation. Drugs such as pilocarpine and cevimeline can increase the production of saliva, and sometimes tears. NSAIDs for Arthritis.[25]

Serotonin Syndrome: Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system (CNS). It is seen with therapeutic medication use, inadvertent interactions between drugs, and intentional self-poisoning. It includes mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.

Causative agents: L-tryptophan, Amphetamine, Lithium, Dextromethorphan, Meperidine, Fluoxetine, Duloxetine Trazodone, Venlafaxine, Buspirone, Isocarboxazid, phenelzine, tranylcypromine, Selegiline, tramadol.

Symptoms: Mental status changes can include anxiety, agitated delirium, restlessness, and disorientation. Autonomic manifestations can include diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhoea. Neuromuscular hyperactivity manifest as tremor, muscle rigidity, myoclonus, hyperreflexia.

Management: Syndrome usually resolves within 24 hours after the withdrawal of the causative drug. If serotonin syndrome has occurred as a result of an acute overdose activated charcoal may be beneficial soon after the ingestion. Hyperthermia should be treated with external cooling measures such as ice, mist, fans, and a cooling blanket. Rigidity, seizures, and agitation are treated with benzodiazepines. Severe symptoms have been successfully treated with Cyproheptadine 4-8 mg PO every 1-4 hours or 0.25mg/kg/day divided every 1-4 hours in children.[26]

Severe Dapsone Hypersensitivity Syndrome: Dapsone is widely used for Hansen's disease, can cause fatal severe form of adverse reaction with multiorgan involvement. Dapsone Hypersensitivity Syndrome (DHS) that occurs during first 2 to 8 weeks of initiating the treatment. The incidence of DHS ranges from 0.5% to 3%.

Causative agent: Dapsone.

Symptoms: Characterized by sudden onset of papular or exfoliative rash, accompanied by fever, malaise and weakness, followed by jaundice and tenderness of liver, lymphadenopathy and mononucleosis.

Management: Patients can be treated with corticosteroids both orally (Prednisolone 40 mg/d) and topically (Beclomethasone dipropionate ointment 0.025%, 2 times a day). Cetirizine and Hydroxyzine are also given.[27]

Stevens-Johnson syndrome (SJS): It is an immune-complex–mediated hypersensitivity reaction that is a severe expression of erythema multiform. It's usually a reaction to a medication or an infection.

Causative agents: Ibuprofen, Allopurinol, Chloroquine, Penicillamine, Sulfasalazine, Carbamazepine, Ethosuximide, Phenobarbital, Phenytoin, Valproic Acid, Amoxicillin, Imipenem, Ciprofloxacin, Clindamycin, Doxycycline, Erythromycin, Sulfadiazine, Sulfamethoxazole- Trimethoprim, Dapsone,

Fluconazole, Nystatin, Nevirapine, Abacavir, Efavirenz, Tamoxifen, Verapamil, Enalapril, Acetazolamide.

Symptoms: flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters, and the affected skin dies, sheds and then heals.

Management: Discontinue any medications that may be causing it. Fluid replacement. Start with steroids, antibiotics to control infection. Wound care by removing any dead skin and place medicated dressing over the affected areas.[28]

Sweet Syndrome: is a recurrent and rare skin disease caused by the release of cytokines, with diverse possible etiologic causes.

Causative agents: Abacavir, All-Trans Retinoic Acid, Bortezomib, Carbamazepine, Celecoxib, Clozapine, Diclofenac, Diazepam, Furosemide, Hydralazine, Imatinib, Lenalidomide, Minocycline, Nitrofurantoin, Norfloxacin, Ofloxacin, Pegfilgastrin, Propylthiouracil, Quinupristin, Dalfopristin, Trimethoprim-Sulfamethoxazole.

Symptoms: Rapid onset of fever, leucocytosis, painful erythematous and edematous papules, plaques and nodules infiltrated by neutrophils.

Management: Causative drugs should be suspended and systemic corticosteroids can be given to the patient for the management of lesions.[29]

Toxic Epidermal Necrolysis (Lyell Syndrome/TEN): is a rare, potentially life-threatening mucocutaneous disease, usually provoked by the administration of a drug and characterized by acute necrosis of the epidermis. An immunologic response to immunocomplexes formed by metabolites of the causal drug and the common tissue antigens is thought to be responsible for this disorder.

Causative agents: Sulfonamides, Pyrazolones, Barbiturates, Ibuprofen, Allopurinol and Carbamazepine.

Symptoms: Fever, general malaise, and other flu-like symptoms, bullous and erosive lesions involve oral, ocular, and genital mucosae; and vast areas of the skin with extensive dermoepidermal detachments.

Management: Prompt identification and withdrawal of the causative drug, systemic Steroids, high-dose intravenous immunoglobulin Cyclosporine, and Cyclophosphamide.[30]

CONCLUSION

Drug-induced disease is usually predictable and arises not out of ignorance but from failure to assess correctly the risks of a changing picture of disease, age, diet, or interactions with other treatment. Further, ADR related hospitalization in emergency and intensive care units (ICU) is very high, experts says that additional care is required for the better patient care and also to improve the quality of life. Iatrogenic disease or drug induced disease (DID) is an ever enduring concern for patients, healthcare professionals and health administrators.

REFERENCES

1. Medical Syndrome [internet]. [Cited 2011 Dec 27]; Available from: URL: http://www. medindia. net/patients /patientinfo/ syndrome/home.asp.
2. The Editors. The practice of medicine: Iatrogenic disorders. In: Fauci SAS, Braunwald E, Kasper DL and Hauser SL editors. Harrison's Priniciples of Internal Medicine. 15th ed. New York : McGraw Hill, 2001; 3.
3. Atypical Hemolytic Uremic Syndrome: A Brief Review Kuixing Zhang,[1] Yuxin Lu,[1] Kevin T. Harley,[2] and Minh-Ha Tran[1], 2017 Jun 1; 9(2): 7053.
4. Burning mouth syndrome : A review Rajendra G Patil, Udita Singh, Ganapathi Moger, Simi Thankappan Year : 2017 | Volume : 29 | Issue : 1 | Page : 25-29.
5. Ammoury A, Michaud S, Carle Paul C, Squarcioni CP, Alvarez F, Lamant L et al. Photo distribution of blue-gray hyperpigmentation after amiodarone treatment molecular characterization of amiodarone in the skin. Arch Dermatol, 2008; 144(1): 92-6.
6. Cushing's disease: a multidisciplinary overview of the clinical features, diagnosis, a treatment A Buliman, et al J Med Life, 2016 Jan-Mar; 9(1): 12–18.
7. Knoell DL, Lucas J, Allen JN. Churg-Strauss syndrome associated with zafirlukast. Chest., 1998 Jul; 114(1): 332–334.
8. Hellmich B, Gross WL. Recent progress in the pharmacotherapy of Churg-Strauss syndrome. Expert Opin Pharmacotherapy, 2004; 5: 25–35.
9. Volpe A, Marchetta A, Caramaschi P, Biasi D, Bambara LM, Arcaro G. Hydroxychloroquine-induced DRESS syndrome. Clin Rheumatol, 2008; 27: 537–9.
10. C. Cherry, S. DeBord, N. Moustapha-NadlerEbstein's anomaly: a complex congenital heart defect AORN J, 2009; 89: 1098-1110.
11. Pärssinen, O.; Leppänen, E.; Keski-Rahkonen, P.; Mauriala, T.; Dugué, B.; Lehtonen, M. (2006). "Influence of Tamsulosin on the Iris and Its Implications for Cataract Surgery". *Investigative Ophthalmology & Visual Science*, 47(9): 3766–3771.
12. Izzedine H, Launay-Vacher V, Isnard-Bagnis C, Deray G. Drug-induced Fanconi's syndrome, *Am J Kidney Dis*, 2003; 41: 292-309.
13. Mulhall A, Louvois JD, Hurley R. Chloramphenicol toxicity in neonates: its incidence and prevention. Br Med J, 1983; 287(6403): 1424-1427.
14. Green DM, Ropper AH. Mild Guillain–Barré syndrome. Arch Neurol, 2001; 58: 1098–101.

15. Saini KS, Attili SV, Saini ML, Batra U, Lakshmaiah KC, Acharya R et al. Capecitabine-induced hand-foot syndrome J Indian Acad Clin Med, 2007; 8(2): 144-5.
16. *Kovalszki, Anna; Weller, Peter F. (December 2016). "Eosinophilia". Primary care., 43(4): 607–617.*
17. Lie C, Leung F, Chow SP. Nicolau syndrome following intramuscular diclofenac administration: a case report. J Orthop Surg, 2006; 14(1): 104-7.
18. Bottoni TN. Neuroleptic malignant syndrome: a brief review. Hospital Physician, 2002 Mar: 58-63.
19. Singh G, Cherian VT, Thomas BP. Low-concentration, continuous brachial plexus block in the management of Purple Glove Syndrome: a case report. J Med Case Reports, 2010; 4(48): 1-4.
20. Azria D, Magne N, Zouhair A, et al. Radiation recall: a well recognized but neglected phenomenon. Cancer Treat Rev., 2005; 31: 555–570.
21. James N. Atkins, M.D, Edward F. Haponik, M.D. Reye's syndrome in the adult patient. The American Journal of Medicine, October 1979; 67(4): 672–678.
22. Sivagnanam S, Deleu D. Red man syndrome. Crit Care, 2003; 7(2): 119-20.
23. Dell'Osso MC, Fagiolini A, Ducci F, Masalehdan A, Ciapparelli A, Frank E. Newer antipsychotics and the rabbit syndrome. Clin Pract Epidemiol Ment Health, 2007; 3(6): 1-6.
24. Schwartzman RJ, Erwin KL, Alexander GM (May 2009). "The natural history of complex regional pain syndrome". *The Clinical Journal of Pain*., 25(4): 273–80.
25. Brito-Zerón, P; Baldini, C; Bootsma, H; Bowman, SJ; Jonsson, R; Mariette, X; Sivils, K; Theander, E; Tzioufas, A; Ramos-Casals, M (7 July 2016). "Sjögren syndrome". *Nature Reviews. Disease Primers*, 2: 16047.
26. Brent J. Monoamine Oxidase Inhibitors and the Serotonin Syndrome. In: Haddad LM, Shannon MW, Winchester JF, eds. Clinical Management of Poisoning and Drug Overdose. 3rd ed. Philadelphia, PA: W.B. Saunders Company, 1998: 459-463.
27. Sener O, Doganci L, Safali M, Besirbellioglu B, Bulucu F, Pahsa A. Severe dapsone hypersensitivity syndrome. J Investig Allergol Clin Immunol, 2006; 16(4): 268-70.
28. Jeung YJ, Lee JY, Oh MJ, Choi DC, Lee BJ. Comparison of the causes and clinical features of drug rash with eosinophilia and systemic symptoms and stevens - johnson syndrome. Allergy Asthma Immunol Res., 2010; 2(2): 123-6.
29. Lund JJ, Stratman EJ, Jose D, Xia L, Wilson D, Moizuddin M. Drug-Induced Bullous Sweet Syndrome with Multiple Autoimmune Features. Autoimmune Diseases, 2010; 2010: 1-4.
30. Harr T, French LE. Toxic epidermal necrolysis an Stevens -Johnson syndrome. Orphanet J Rare Dis., 2010; 5(39): 1-11.