International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.12, pp 180-188, 2017

Complications of Long Term Antibiotics Usage

Neha .K. Abraham[1], Sudha Muthusamy[2]*, Sambathkumar Ramanathan[3]

[1]Department of pharmacy practice, [2]Department of pharmacology, [3]Department of pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam- 638183, Tamilnadu, India.

Abstract : Antibiotics are drugs that either kill or inhibit the growth of bacteria: bactericidal and bacteriostatic respectively. Antibiotics may account up to 30% of a hospital's drug. Various strategies have been used to implement guidelines and antimicrobial-control programs to limit the emergence and spread of antimicrobial-resistant organisms. Turkey uses 42.2% of antibiotics and was rated as the first country, using most of the antibiotics. Cephalosporins are the class of antibiotic which are mostly used to treat infections. The choice of antibiotics may also vary depending on the presenting microorganism. As the complications of these antibiotic therapies are increasing nowadays, the dose calculation is needed for infective treatment. Alternative therapy or discontinuation of therapy can be done in case of severe complications which cannot be reversed.
Key Words : Antibiotics, antimicrobial agent.

Introduction

Antibiotics are the class of drugs that can cure disease and are mainly effective in treatment of many bacterial, fungal and viral infections. The majority of common antibiotics that are used today were revealed in the ''Golden Age" of antibiotics. Bacteria may reproduce with increased environmental pressure and multiple antibiotic resistance organisms such as *Escherichia coli* and *Staphylococcus aureus* has been observed. More than 70% of the bacteria that cause hospital-acquired infections are resistant to at least one of the drugs most commonly used to treat them. The hospital's budget includes 30% of antibiotics [1–3]. For the past 20 years it was seen that, inappropriate usage of certain antibiotics was found to be a major problem and a reason for high costs and also the selection and wrong duration of antibiotics may causes the spreading of drug-resistant microorganisms. Various criteria have been used to apply guidelines and antimicrobial-control programs to limit the growth and spreading of antimicrobial-resistant organisms [4, 5].

To prevent such conditions we need specific selective therapy of antibiotics used for treating specific infections. Newer antibiotics are invented, for further improvement of particular disease conditions with limited complications and adverse effects. Newer aminoglycosides, tetracyclines, beta lactamases, cephalosporins, macrolides, etc., are established. They aim to have minimum complications with maximum effectiveness. Most commonly the recent studies develop intravenous antibiotics for use in hospitals. With rising outpatient antibiotic resistance in respiratory system disorders and urinary infections, new oral antibiotics for outpatient use be urgently needed. The rate of bacterial diarrheal infection among children younger more than 5 years was high. ***E. coli*** was predominant isolate and impeneim was the most effective antibiotics on bacterial isolates [6,7].

Duration of Treatment of Antibiotics

In most instances the optimum duration of antibiotic was unknown. The duration varies from a single dose to many months depending on the infection. For more complicated infections a shorter durations and a higher dose therapy is recommended. For certain infections with lower complications a minimum duration is recommended and some examples are shown below.

Recommended Minimum Durations of Treatment

(Duration of treatment for some infectious conditions)

- Tuberculosis 4 - 6 months
- Empyema/lung abscess 4 - 6 weeks
- Atypical pneumonia - 2 - 3 weeks
- Pneumococcalpneumonia - 5 days
- Pneumococcal meningitis - 7 days
- Endocarditis - 4 weeks
- Osteomyelitis - 4 weeks

Antibiotic Resistance

Antibiotic resistance is the ability of bacteria to repel or withstand the effects of an antibiotic. Development of resistance is a microorganism's protective mechanism for surviving in the environment. Though antibiotics do not technically cause resistance, they allow it to happen by creating a situation where a preexisting variant bacterium can flourish and grow. Recent studies found that there is an increased bacterial sensitivity in milk[8, 9].Antibiotic resistance can spread from bacteria to bacteria**,** patient to patient and from animals to patients. Resistance patterns vary from country to country, from hospital to hospital in the same country, from unit to unit in the same hospital. Antibiotic resistance occurs through any of the following mechanisms: Spontaneous deoxyribonucleic acid (DNA) mutation, transformation, and plasmid transfer. Spontaneous DNA mutation: Bacteria are prokaryotes with relatively few genes. Any population of bacteria may have one variant bacterium with unusual traits such as the ability to be resistant to an antibiotic. After treatment with antibiotics, this one bacterium remains, multiplies, and eventually becomes the predominant bacteria. Recent studies showed that cellulitis patients develop resistance to amoxicilin, piperacillin, carbenicillin and susceptible to vancomycin ,tygecyclin and meropenem [10, 11]. Transformation is a form of microbial reproduction; one bacterium takes up DNA from another bacterium. If the DNA contains a gene for antibiotic resistance, it can be transferred from one bacterium to another by this method. Plasmid transfer is another method of acquiring resistance [12].

Certain Disease Conditions Involving Long Term Antibiotic Therapy

There are some disease conditions, for which antibiotics are used for long term and may develop resistance or some other problems, due to which we need to undergo an alternative therapy which is shown in table 1.

Complications of Long Term Therapy with Antibiotics

On usage of long term antibiotics for certaindisease conditions, some complications may occur which are detailed in table 2. These are peculiar complications which may occur for particularly antibiotic usage.

Conclusion

Antibiotics therapies were indicated for several bacterial infective conditions. The antibiotic therapy is needed to prevent secondary infections also. There are certain guidelines to prevent the unnecessary use of antibiotics. As the complications of these therapies are increasing nowadays the dose calculation is needed for infective treatment. Alternative therapy or discontinuation of therapy can be done in case of severe complications which cannot be reversed.

Table 1: Disease condition in which 1st line antibiotics preferred and alternative therapy for it

s.no	Disease condition	First line antibiotic preferred	Alternative therapy	Reference
1	**COPD – acute exacerbations**	**Amoxicillin** **Adult:** 500 mg, three times daily, for five days	**Doxycycline** **Adult:** 200 mg, on day one (loading dose), followed by 100 mg, once daily, on days two to five	13
2	**Pertussis (Whooping cough)**	**Azithromycin** (first-line for children, alternative for adults) **Child < 45 kg:** 10 mg/kg/dose, once daily, on day one, followed by 5 mg/kg/dose, once daily, on days two to five **Adult** and **Child > 45 kg:** 500 mg on day one, followed by 250 mg, once daily, on days two to five **Erythromycin** (first-line for adults, alternative for children aged over one year) **Child:** 10 mg/kg/dose, four times daily, for 14 days **Adult:** 400 mg, four times daily, for 14 days	**None**	14, 15
3	**Pneumonia – adult**	**Amoxicillin** **Adult:** 500 mg – 1 g, three times daily, for five to seven days	Monotherapywith **roxithromycin**or**doxycycline** is acceptable for people with a history of penicillin allergy.	16
4	**Pneumonia – child**	**Amoxicillin** **Child:** 25 – 30 mg/kg/dose, three times daily, for five to seven days (maximum 500 mg/dose age three months to five years, 1000 mg/dose age > five years)	**Erythromycin** **Child:** 10 – 12.5 mg/kg/dose, four times daily, for seven days	17
5	**Otitis externa – acute**	**Clioquinol + flumethasone**(LocortenVioform)* **Adult** and **child > 2 years:** 2 to 3 drops, twice daily, for 7 days ***OR*** **Dexamethasone + framycetin + gramicidin** (Sofradex)* **Adult** and **child:** 2 to 3 drops, three to four times daily, for 7 days	**Acetic acid 2%** (Vosol)* may be sufficient in mild cases. **Ciprofloxacin + hydrocortisone** (Ciproxin HC)* if *Pseudomonas* suspected. **Flucloxacillin**if there is spreading cellulitis or the patient is systemically unwell; also consider referral to hospital.	18, 19
6	**Otitis media**	**Amoxicillin** **Child:** 15 mg/kg/dose, three times daily, for five days (seven to ten days if age < two years, underlying medical condition or perforated ear drum)	**Co-trimoxazole** **Child > 6 weeks:** 0.5 mL/kg/dose oral liquid (40+200 mg/5 mL), twice daily, for five to seven days (maximum 20 mL/dose)	20

7	**Pharyngitis**	**Phenoxymethylpenicillin**(Penicillin V) **Child < 20 kg:** 250 mg, two or three times daily, for ten days **Child ≥ 20 kg** and **Adults:** 500 mg, two or three times daily, for ten days ***OR*** **Amoxicillin** **Child < 30 kg:** 750 mg, once daily, OR 25 mg/kg, twice daily (maximum 1000 mg/day), for ten days **Child ≥ 30 kg** and **Adults:** 1000 mg, once daily, for ten days ***OR*** **IM benzathine penicillin (stat)** **Child < 30 kg:** 450 mg (600 000 U) **Child ≥ 30 kg** and **Adults:** 900 mg (1 200 000 U)	**Erythromycin** **Child:** 20 mg/kg/dose, twice daily or 10 mg/kg/dose, four times daily, for ten days (maximum 1 g/day) **Adult:** 400 mg, twice daily, for ten days	21, 22
8	**Sinusitis – acute**	**Amoxicillin** **Child:** 15 mg/kg/dose, three times daily, for seven days	**Doxycycline** **Adult** and **child > 12 years:** 200 mg on day one, followed by 100 mg, once daily, on days two to seven **Amoxicillin clavulanate**(if symptoms persist despite a treatment course of amoxicillin) **Child:** 10 mg/kg/dose (amoxicillin component), three times daily, for seven days (maximum 500 mg/dose amoxicillin component) **Adult:** 500+125 mg, three times daily, for seven days	23
9	**Conjunctivitis**	**Chloramphenicol 0.5% eye drops** **Adult** and **child > 2 years:** 1 – 2 drops, every two hours, for the first 24 hours then every 48 hrs	**Fusidic acid eye gel** **Adult** and **child > 1 year:** apply to the eye, twice daily until 48 hours after symptoms have cleared	24
10	**Bacterial meningitis and suspected meningococcal sepsis**	**Benzylpenicillin**(penicillin G) **Child < one year:** 300 mg IV or IM **Child one to nine years:** 600 mg IV or IM **Adult** and **child > ten years:** 1.2 g IV or IM	**Ceftriaxone** **Adult** and **child:** 50 – 100 mg/kg up to 2 g IV or IM	25
11	**Bites – human and animal**	**Amoxicillin clavulanate** **Child:** 10 mg/kg/dose (amoxicillin component), three times daily, for seven days (maximum 500 mg/dose, amoxicillin component) **Adult:** 500+125 mg, three times daily, for seven days	**Adult** and **child > 12 years: Metronidazole** 400 mg, three times daily, **+ doxycycline** 200 mg on day one, followed by 100 mg, once daily, on days two to seven **Metronidazole + co-trimoxazole**is an alternative for children aged under 12 years	26, 27

			(doxycycline contraindicated)	
12	**Cellulitis**	**Flucloxacillin** **Child:** 12.5 mg/kg/dose, four times daily, for seven days **Adult:** 500 mg, four times daily, for five to seven days **Cephalexin** **Child:** 12.5 mg/kg/dose, four times daily, for seven to ten days (maximum 500 mg/dose) **Adult:** 500 mg, four times daily, for seven days	**Cephalexin** **Adult:** 500 mg, four times daily, for seven days **Erythromycin** **Child < 12 years:** 20 mg/kg/dose, twice daily, or 10 mg/kg/dose, four times daily, for seven to ten days (maximum 1 g/day) **Adult:** 800 mg, twice daily, or 400 mg, four times daily, for seven days **Co-trimoxazole**(if MRSA present): **Child > 6 weeks:** 0.5 mL/kg/dose oral liquid (40+200 mg/5 mL), twice daily, for five to seven days (maximum 20 mL/dose)	28
13	**Diabetic foot infections**	**Amoxicillin clavulanate** **Adult:** 500+125 mg, three times daily, for five to seven days	**Cephalexin** 500 mg, four times daily, + **metronidazole** 400 mg, twice to three times daily, for five to seven days ***OR*** (for patients with penicillin hypersensitivity) **Co-trimoxazole**160+800 mg (two tablets), twice daily, + **clindamycin*** 300 mg, three times daily, for five to seven days	29
14	**Impetigo**	**Topical** (localised area of infection): **Hydrogen peroxide 1%** cream apply two to three times daily, for five days ***OR*** **Povidone-iodine 10% ointment** Apply three times daily, for five days **Oral** (extensive/multiple lesions): **Flucloxacillin** **Child:** 12.5 mg/kg/dose four times daily, for five days (maximum 500 mg/dose) **Adult:** 500 mg, four times daily, for five days	**Topical** (localised area of infection): **Fusidic acid 2%** cream or ointment Apply three times daily, for five days If topical treatment fails, use oral treatment as above. **Oral** **Cephalexin** (if flucloxacillin not tolerated) **Child:** 12–25 mg/kg/dose, twice daily, for five days **Adult:** 500 mg, four times daily or 1 g, twice daily, for five days	30
15	**Campylobacter enterocolitis**	**Erythromycin** **Child:** 10 mg/kg/dose, four times daily, for five days **Adult:** 400 mg, four times daily, for five days	**Ciprofloxacin** **Adult:** 500 mg, twice daily, for five days (not recommended for children)	31

16	**Gonorrhoea**	**Ceftriaxone** **Adult:** 500 mg IM, stat (make up with 2 mL of 1% lignocaine or according to data sheet) ***AND*** **Azithromycin** **Adult:** 1 g, stat (including in pregnancy and breastfeeding)	**Ciprofloxacin** 500 mg, stat + **azithromycin** 1 g, stat, only if the isolate is known to be ciprofloxacin sensitive. Resistance rates vary by location.	32
17	**Urinary tract infection (UTI) – adult**	**Trimethoprim** **Adult:** 300 mg, once daily, for three days (avoid during the first trimester of pregnancy) ***OR*** **Nitrofurantoin** **Adult:** 50 mg, four times daily, for five days (avoid at 36+ weeks in pregnancy, and in patients with creatinine clearance < 60 mL/min)	**Norfloxacin** **Adult:** 400 mg, twice daily for three days – but should be reserved for isolates resistant to initial empiric choices and avoided during pregnancy	33, 34
18	**Urinary tract infection (UTI) – child**	**Co-trimoxazole** **Child:** 0.5 mL/kg/dose oral liquid (40+200 mg/ 5 mL), twice daily, for three days (maximum 20 mL/dose)	**Cefaclor** **Child:** 8 – 10 mg/kg/dose, three times daily, for three days (maximum 500 mg/dose) **Amoxicillin clavulanate** **Child:** 10 mg/kg/dose (amoxicillin component), three times daily, for three days (maximum 500 mg/dose,amoxicillin component)	35, 36

Table 2. Long term antibiotics with complications

s.no	Antibiotics	Complications	Reference
1	**Ceftaroline**	Hemolyticanemia	37
2	**Colistin**	Neurotoxicity, Renal impairement	38
4	**Daptomycin**	Myopathy, esinophilic pneumonia	39
5	**Ertapenem**	Thrombophlebitis	40
6	**Linezolid**	Bone marrow suppression, optic neuritis, serotonin syndrome	41
7	**Trimethoprim**	Nephrotoxicity, myelosuppression, hepatotoxicity	42, 43
8	**Amphotericin B**	Anemia, pulmonary toxicity	44
9	**Voriconazole**	Jaundice, loss of eye sight	45, 46
10	**AKT4**	Hepatotoxicity	47, 48
11	**Aminoglycosides**	Ototoxicity, corneal epithelial changes, superficial punctate lesions, vortex keratopathy produced by subconjunctival gentamicin and conjunctival inclusions.	49, 50, 51
12	**Fluroquinolones**	Hepatic failure, esinophilia, respiratory distress syndrome, peripheral neuropathy	52, 53, 54, 55
13	**Amoxicillin**	Hepatitis, hepatotoxicity	53
14	**Doxycycline**	Hepatotoxicity, toxic epidermal necrolysis	54
15	**Azithromycin**	Liver failure, corneal erosion	54
17	**Cephalexin**	Interstitial nephritis, renal failure	52
18	**Cotrimoxazole**	Ototoxicity, aseptic meningitis	50
20	**Clindamycin**	Jaundice, liver failure	55
21	**Nitrofurantoin**	Hepatitis, haemolytic anemia	55

References

1. Avorn J, Soumerai SB, Taylor W., Reduction of incorrect antibiotic dosing through a structured educational order form, Arch Intern Med.,1988, 8, 1720–1724.
2. Baum C, Kennedy DK, Knapp DE., Drug utilization in the United States,Clin Infect Dis., 1985,3, 451–453.
3. Salama S, Roststein C, Mandell L., A multi-disciplinary hospital-based antimicrobial use program: impact on hospital pharmacy expenditures and drug use, Can J Infect Dis., 1996, 7, 104–109.
4. Duncan RA., Controlling use of antimicrobial agents, Infect Control HospEpidemiol.,1997, 18, 260–266.
5. John JF, Fishman NO., Programmatic role of the infectious diseases physician in controlling antimicrobial costs in the hospital, Clin Infect Dis., 1997, 2, 471–485.
6. C.J. Currie, E. Berni, S. Jenkins-Jones.,Antibiotic treatment failure in four common infections in UK primary care,Br. Med. J., 2014, 11, 5493.
7. AmeanA.Yasir., Assessment of Children under than Five Ages toward theDiarrheal Cases with Antibacterial Effect of bacteria isolatesinBabylon Province, International Journal of ChemTech Research., 2017, 10, 734-741**.**
8. R. Davidson, R. Cavalcanti, J.L.,Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia, N. Eng. J. Med., 2002, 10,747–750.
9. Arnold, S. and Straus, S., Interventions toimprove antibiotic prescribing practices in ambulatory care,Cochrane Database Syst Rev., 1998, 4, 3539.
10. R. Pant, S. Nirwal and N. Rai., Prevalence of antibiotic resistant bacteria and analysis of microbial quality of raw milk samples collected from different regions of Dehradun, International Journal of PharmTech Research.,2013, 5, 804-810.
11. Ayanruoh, S., Waseem, M., Quee, F., Humphrey, A. and Reynolds, T., Impact of rapidstreptococcal test on antibiotic use in a pediatricemergencydepartment,PediatrEmerg Care., 2009,25, 748–750.
12. Donna Partogi,DinaArwinaDalimunthe, Cut PutriHazlianda., Bacterial patterns, resistance and susceptibility to antibioticin patients with cellulitis., 2017, 10, 19-23**.**

13. Butler, C., Rollnick, S., Pill, R., Maggs-Rapport, F. and Stott, N.,Understanding the culture of prescribing: qualitative study of general practitioners'and patients' perceptions of antibiotics for sore throats,BMJ., 1998, 3, 637– 640.
14. Australian Medicines Handbook, Adelaide; Australian Medicines Handbook Pty Ltd, 2011.
15. British Infection Association and Health Protection Agency, Management of infection guidance for primary care for consultation and local adaptation.Public Health England,
16. 2012.
17. Ellis-Pegler R, Thomas M., Approaches to the management of common infections in general practice, Auckland; Diagnostic Medlab, 2003, 4, 123-130.
18. Lang S., Guide to pathogens and antibiotic treatment,Auckland; Diagnostic Medlab., 2004, 7, 342-356.
19. Lang S, Morris A, Taylor S, Arroll B.,Management of common infections in general practice: Part 1, NZ FamPhy., 2004, 3, 176-8.
20. Lang S, Morris A, Taylor S, Arroll B., Management of common infections in general practice: Part 2, NZ Fam Phys.,2004, 4, 258-60.
21. Michael M, Hodson E, Craig J., Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children, Cochrane Database Syst Rev., 2010, 1, 3966.
22. New Zealand Formulary, 2010, 7, 365-367.
23. NICE Clinical Knowledge Summaries, 2012, 7, 456-467.
24. Starship Children's Health. Clinical guidelines, 2016, 8, 128-129.
25. The National Heart Foundation of New Zealand,Guidelines for rheumatic fever., 2008, 2, 122-127.
26. The New Zealand Sexual Health Society (NZSHS), Best practice guidelines.,2015, 5, 12-17.
27. Owens Jr RC, Donskey CJ, Gaynes RP, Loo VG, Muto CA., Antimicrobial-associated risk factors for Clostridium difficile infection,Clin Infect Dis., 2008, 1, 19-31.
28. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M., Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin, Am J RespirCrit Care Med., 1998, 157, 1829-1832.
29. Hashiba M, Baba S., Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis,ActaOtolaryngol Suppl., 1996, 5, 73-78.
30. Cervin A, Kalm O, Sandkull P, Lindberg S., One-year low-dose erythromycin treatment of persistent chronic sinusitis after sinus surgery: clinical outcome and effects on mucociliary parameters and nasal nitric oxide,Otolaryngol Head Neck Surg., 2002, 12, 481-9.
31. Cymbala AA, Edmonds LC, Bauer MA., The disease-modifying effects of twiceweekly oral azithromycin in patients with bronchiectasis,TreatRespir Med., 2005, 4, 117-22.
32. Serisier DJ, Martin ML., Long-term, low-dose erythromycin in bronchiectasis subjects with frequent infective exacerbations,Respir Med.,2011, 10, 946-9.
33. Wong C, Jayaram L, Karalus N, Eaton T., Azithromycin for prevention of exacerbations in noncystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial,Lancet., 2012, 3, 660-7.
34. LabroMT.,Cellular and molecular effects of macrolides on leukocyte function,Curr Pharm Des., 2004, 10, 3067-80.
35. Friedlander AL, Albert RK., Chronic macrolide therapy in inflammatory airways diseases, Chest., 2010, 5, 1202-12.
36. Rubin BK, Henke MO.,Immunomodulatory activity and effectiveness of macrolides in chronic airway disease, Chest., 2004, 2, 70-8.
37. Sakata KK, Larsen BT, Boland JM, PalenB,Muhm JR., Nitrofurantoin-Induced Granulomatous Interstitial Pneumonia,Int J SurgPathol., 2014, 22, 352-7.
38. American Geriatrics Society Beers Criteria Update Expert, P., American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults, J Am Geriatr Soc., 2012, 6, 616-631.
39. Zeller V, Lhotellier L, Marmor S, Leclerc P, Krain A, Graff W., One-stage exchange arthroplasty for chronic periprosthetic hip infection: results of a large prospective cohort study, J Bone Joint Surg Am.,2014, 9, 1.
40. van Buchem FL, Peeters MF, van't Hof MA., Acute otitis media: a new treatment strategy,Br Med J.,1985, 2, 1033–1037.
41. Carlin SA, Marchant CD, Shurin PA, Johnson CE, Super DM, Rehmus JM., Host factors and early therapeutic response in acute otitis media, J Pediatr., 1991, 11, 178–183.

42. Blumberg, H.M., Burman, W.J., Chaisson, R.E., American thoracic society/centers for disease control and prevention/ infectious diseases society of America: treatment of tuberculosis,Am. J RespirCrit Care Med.,2003, 16, 603–662.
43. Chang, K.C., Leung, C.C., Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter, Eur. Respir., 2007, 2, 347–351.
44. YewW.W, TamC.M.,Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection,MMWR., 2001, 5, 733–735.
45. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease, British Thoracic Society, Thorax., 2010, 6, 559–570.
46. Hu, Y, Coates, A.R, Mitchison, D.A., Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of Mycobacterium tuberculosis,Antimicro Agents Chemother., 2003, 4, 653.
47. Jasmer, R.M., Saukkonen, J.J, Blumberg, H.M., Shortcourserifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial, Ann Intern Med., 2002, 13, 640–647.
48. Joint Tuberculosis Committee of the British Thoracic Society, Chemotherapy and management of tuberculosis in the United Kingdom: recommendations, Thorax., 1998, 5, 536–48.
49. Lopez, D., Schluger, N., Tuberculosis following solid organ transplantation,TransplInfect Dis.,2010, 12, 106–112.
50. Marr, J., Moffet, H., Kunin, C., Guidelines for improving the use of antimicrobial agents in hospitals: a statement by the Infectious Diseases Society of America, J. Infect. Dis., 1988, 15, 869–876.
51. Fraunfelder FW., Corneal toxicity from topical ocular and systemic medications, Cornea., 2006, 10, 1133-1138.
52. Hollander DA, AldaveAJ., Drug-induced corneal complications, CurrOpinOphthalmol., 2004, 6, 541-8.
53. D'Amico DJ, Kenyon KR., Drug-induced lipidoses of the cornea and conjunctiva,IntOphthalmol., 1981, 4, 67-76.
54. D Amico DJ, Kenyon KR., Drug-induced lipidoses of the cornea and conjunctiva, IntOphthalmol., 1981, 4, 67-76.
55. Fraunfelder FW., Corneal toxicity from topical ocular and systemic medications, Cornea., 2006, 10, 1139-1146.
56. Gibson JM, Fielder AR, Garner A, Millac P., Severe ocular side effects of perhexilene maleate: case repor, Br J Ophthalmol., 1984, 8, 553-60.
57. Gokulgandhi MR, Vadlapudi AD, Mitra AK., Ocular toxicity from systemically administered xenobiotics, Expert Opin Drug MetabToxicol., 2012, 10, 1277-1291.

*****