Complications of Long Term Antibiotics Usage

Neha .K. Abraham¹, Sudha Muthusamy²*, Sambathkumar Ramanathan³

¹Department of pharmacy practice, ²Department of pharmacology, ³Department 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
- Pneumococcal pneumonia - 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 amoxicillin, piperacillin, carbenicillin and susceptible to vancomycin, tigecyclin 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 certain disease 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

<table>
<thead>
<tr>
<th>s.no</th>
<th>Disease condition</th>
<th>First line antibiotic preferred</th>
<th>Alternative therapy</th>
<th>Reference</th>
</tr>
</thead>
</table>
| 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 | Monotherapy with 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 (Locorten Vioform)  
*  
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        |
<table>
<thead>
<tr>
<th>Page</th>
<th>Condition</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Pharyngitis</td>
<td>Phenoxymethylpenicillin (Penicillin V)</td>
<td>Erythromycin</td>
<td>21, 22</td>
</tr>
<tr>
<td></td>
<td>Child &lt; 20 kg</td>
<td>250 mg, two or three times daily, for ten days</td>
<td>Child: 20 mg/kg/dose, twice daily or 10 mg/kg/dose, four times daily, for ten days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child ≥ 20 kg and Adults</td>
<td>500 mg, two or three times daily, for ten days</td>
<td>Adult: maximum 1 g/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>Amoxicillin</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child &lt; 30 kg</td>
<td>750 mg, once daily, OR 25 mg/kg, twice daily (maximum 1000 mg/day), for ten days</td>
<td>Amoxicillin clavulanate (if symptoms persist despite a treatment course of amoxicillin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child ≥ 30 kg and Adults</td>
<td>1000 mg, once daily, for ten days</td>
<td>Child: 10 mg/kg/dose (amoxicillin component), three times daily, for seven days (maximum 500 mg/dose amoxicillin component)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
<td>Adult: 500+125 mg, three times daily, for seven days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IM benzathine penicillin (stat)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child &lt; 30 kg</td>
<td>450 mg (600 000 U)</td>
<td>Fusidic acid eye gel</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Child ≥ 30 kg and Adults</td>
<td>900 mg (1 200 000 U)</td>
<td>Adult and child &gt; 2 years: 1 – 2 drops, every two hours for the first 24 hours then every 48 hrs</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sinusitis – acute</td>
<td>Amoxicillin</td>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child: 15 mg/kg/dose, three times daily, for seven days</td>
<td>Adult and child &gt; 12 years: 200 mg on day one, followed by 100 mg, once daily, on days two to seven</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amoxicillin clavulanate</td>
<td>Amoxicillin clavulanate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(if symptoms persist despite a treatment course of amoxicillin)</td>
<td>Child: 10 mg/kg/dose (amoxicillin component), three times daily, for seven days (maximum 500 mg/dose amoxicillin component)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult: 500+125 mg, three times daily, for seven days</td>
<td>Adult: 500 mg/kg/dose up to 2 g IV or IM</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Conjunctivitis</td>
<td>Chloramphenicol 0.5% eye drops</td>
<td>Fusidic acid eye gel</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Adult and child &gt; 2 years: 1 – 2 drops, every 48 hrs</td>
<td>Adult and child &gt; 2 years: 1 – 2 drops, every 48 hrs after symptoms have cleared</td>
<td>First 24</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Bacterial meningitis and suspected meningococcal sepsis</td>
<td>Benzylpenicillin (penicillin G)</td>
<td>Ceftiraxone</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Child &lt; one year: 300 mg IV or IM</td>
<td>Adult and child: 50 – 100 mg/kg up to 2 g IV or IM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child one to nine years: 600 mg IV or IM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adult and child &gt; ten years: 1.2 g IV or IM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Bites – human and animal</td>
<td>Amoxicillin clavulanate</td>
<td>Metronidazole</td>
<td>26, 27</td>
</tr>
<tr>
<td></td>
<td>Child: 10 mg/kg/dose (amoxicillin component), three times daily, for seven days (maximum 500 mg/dose, amoxicillin component)</td>
<td>Adult and child &gt; 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</td>
<td>Metronidazole + co-trimoxazole: an alternative for children aged under 12 years</td>
<td></td>
</tr>
</tbody>
</table>
| 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 |
<table>
<thead>
<tr>
<th></th>
<th>Condition</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Gonorrhea</td>
<td><strong>Ceftriaxone</strong>&lt;br&gt;Adult: 500 mg IM, stat (make up with 2 mL of 1% lignocaine or according to data sheet)&lt;br&gt;<strong>AND</strong>&lt;br&gt;<strong>Azithromycin</strong>&lt;br&gt;Adult: 1 g, stat (including in pregnancy and breastfeeding)</td>
</tr>
<tr>
<td>17</td>
<td>Urinary tract infection (UTI) – adult</td>
<td><strong>Trimethoprim</strong>&lt;br&gt;Adult: 300 mg, once daily, for three days (avoid during the first trimester of pregnancy)&lt;br&gt;&lt;br&gt;<strong>OR</strong>&lt;br&gt;<strong>Nitrofurantoin</strong>&lt;br&gt;Adult: 50 mg, four times daily, for five days (avoid at 36+ weeks in pregnancy, and in patients with creatinine clearance &lt; 60 mL/min)</td>
</tr>
<tr>
<td>18</td>
<td>Urinary tract infection (UTI) – child</td>
<td><strong>Co-trimoxazole</strong>&lt;br&gt;Child: 0.5 mL/kg/dose oral liquid (40+200 mg/ 5 mL), twice daily, for three days (maximum 20 mL/dose)</td>
</tr>
</tbody>
</table>
### Table 2. Long term antibiotics with complications

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

### References

34. Friedlander AL, Albert RK., Chronic macrolide therapy in inflammatory airways diseases, Chest., 2010, 5, 1202-12.
49. Lopez, D., Schluger, N., Tuberculosis following solid organ transplantation, Transpl Infect Dis., 2010, 12, 106–112.
51. Fraunfelder FW., Corneal toxicity from topical ocular and systemic medications, Cornea., 2006, 10, 1133-1138.
55. Fraunfelder FW., Corneal toxicity from topical ocular and systemic medications, Cornea., 2006, 10, 1139-1146.

*****