AMOXICILLIN: A BROAD SPECTRUM ANTIBIOTIC

SIMAR PREET KAUR¹, REKHA RAO², SANJU NANDA²

¹MM College of Pharmacy, MM University, Mullana, Ambala- 133001, Haryana, India, ²Department of Pharmaceutical Sciences, MD University, Rohtak-124001, Haryana, India

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ABSTRACT

Amoxicillin though originally introduced in the early 1970’s for oral use in U.K., has found a gradually regular place as broad spectrum antibacterial to treat the infections of various diseases. Amoxicillin has been found to be more effective against gram positive than gram negative microorganisms and demonstrated greater efficacy to penicillin and penicillin V. Moreover, it has been found comparable to other antibiotics, e.g. ampicillin, azithromycin, clarithromycin, cefuroxime and doxycycline in treatment of various infections/diseases. In the past decade, amoxicillin has been reported to be useful in the management of many indications and is used to treat infections of the middle ear (otitis media), tonsils (tonsillitis & tonsillopharyngitis), throat, larynx (laryngitis), pharynx (pharyngitis), bronchi (bronchitis), lungs (pneumonia), urinary tract (UTI), skin and to treat gonorrhoea. Recent studies suggested that it can be used as prophylaxis against bacterial endocarditis, in patients with prosthetic joint replacements and in dentistry. The renewed interest of the molecule has prompted a review of the salient facets of the drug.

Keywords: Amoxicillin, Antibiotic, Review

INTRODUCTION

Amoxicillin, an acid stable, semi-synthetic drug belongs to a class of antibiotics called the Penicillins (β-lactam antibiotics). It is shown to be effective against a wide range of infections caused by wide range of Gram +positive and Gram-negative bacteria in both human and animals¹⁴. It is a congener of ampicillin (a semi-synthetic amino-penicillin) differing from the parent drug only by hydroxylation of the phenyl side chain. It has found a niche in the treatment of ampicillin-responsive infections after oral administration⁴. Chemically amoxicillin is \((2S,5R,6R)\)-6-\([(2R)\)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid (Fig. 1). It is listed in a number of Pharmacopoeias. Amoxicillin monograph is available in United States, British and Indian pharmacopoeias⁷⁻⁹.

Fig. 1: It shows the chemical structure of Amoxicillin¹⁰

History and Challenges in Development

Historically, infectious diseases (IDs) have been the most important contributor to human morbidity and mortality until recent times, when non-communicable diseases begin to rival, and sometimes exceed, infections. Today, IDs still account for a large proportion of death and disability worldwide and in certain regions remain the most important cause of ill health¹¹. IDs are major public health issues for both developed and developing countries. Africa and India both suffer significant population losses each year from infectious and parasitic diseases. Approximately 5 million people in Africa and 2 million people in India – mostly children and young adults die each year because of these diseases. Africa and India’s 7 million infectious disease deaths account for 70% of infectious disease deaths worldwide and 13% of all deaths worldwide¹².

Fig. 2: It shows infectious disease mortality by Region, 1998

The World Health Organisation (WHO) in 2005 ranked infections as the leading global burden of disease and the leading cause of mortality in children. Acute respiratory infections are the leading infectious cause of death in all ages (fig. 3), worldwide¹³, ¹⁴. Current key community and hospital bacterial disease burdens include paediatric infections and multiple drug resistance in both Gram-positive and Gram-negative organisms¹³⁻¹⁵. An increasing prevalence of antibiotic resistance has led to the progressive decrease in the effectiveness of narrow-spectrum agents and to an increase in difficult-to-treat infections²⁶. More than ever, selection of the most appropriate antibiotic therapy has become a challenge for clinicians¹⁷.
In the 1960s, a limited range of non β-lactam antibacterials was available; most had certain limitations in terms of toxicity e.g. sulphonamides (rashes and renal toxicity); streptomycin and kanamycin (ototoxicity and nephrotoxicity); chloramphenicol (bone marrow aplasia); erythromycin (gastrointestinal side effects); tetracyclines (concentrate in developing bones and teeth) and colistin (neuro and nephro-toxicity). A number of beta-lactams, penicillins: penicillin G and V (gastric acid labile), ampicillin, methicillin (nephrotoxicity) and also cephalosporins: cephaloridine and cephalothin (nephrotoxicity) were reported. All of these agents were generally given as a four times daily dose and were associated with rashes and, rarely, anaphylaxis14.

At the end of the 1960s, challenging infections requiring treatment in hospitals included meningitis, endocarditis, neonatal infections, penicillin-resistant staphylococcal infections and infections caused by Gram-negative organisms. In primary care, infections of the urinary tract, respiratory tract and skin and soft tissues were a common cause of morbidity and sometimes mortality. Further problem areas emerging in the 1970s included mixed infections, antibiotic-resistant bacteria, new pathogens and infections in immunocompromised patients, those undergoing surgery, and infections in haemodialysis patients. There was a requirement for broad-spectrum antibiotics active against resistant organisms and in mixed infections14.

The 1970s saw the introduction of a number of important new antimicrobial agents, some of which were still associated with adverse events, such as co-trimoxazole (rashes and sulphonamide toxicity), tobramycin and amikacin (aminoglycoside toxicity) and metronidazole (neuropathy). Certain new beta-lactam antibiotics were also introduced including the cephalosporins – cefamandole, cefuroxime; the cephamycin, cefoxitin; and the penicillins – amoxicillin, flucloxacillin, mezlocillin, azlocillin and ticarcillin. All could be associated with rashes and, rarely, anaphylaxis14.

In 1972, amoxicillin was introduced in the UK, which maintained the broad-spectrum activity of ampicillin, but with increased bioavailability18, 19. As β-lactamase production by both gram-positive and gram-negative pathogens became a clinically relevant issue, efforts were made to develop an orally bioavailable, broad-spectrum penicillin that was also effective against these strains, resulting in the combination of amoxicillin and clavulanic acid (amoxicillin/clavulanate)18, 20. In 1981, SmithKline Beecham patented amoxicillin or amoxicillin/clavulanate potassium tablets, and first sold the antibiotic in 1998 under the trade names of amoxicillin, amoxyl, and trimox21.

At the close of the decade, a range of requirements for a new antibacterial still remained. These included activity against penicillinase-producing gram-positive and gram-negative organisms (including anaerobes), a broad spectrum of activity and good tolerability, including in children, availability as both an oral and injectable formulation, and activity in a range of indications including urinary tract infections (UTIs), respiratory tract infections (RTIs), skin and soft tissue infections (SSTIs), intra-abdominal infections and septicemia. This set the scene for the development of an antibacterial agent that would fulfill these requirements14.

Although there are currently new antibacterial compounds in development, most are at a pre-clinical stage. It is necessary, therefore, to make the best use of currently available agents. The development of higher dosing regimens and pharmacokinetically enhanced formulations have allowed amoxicillin (alone and in combination) to continue to play an important role in the treatment of a range of infections, particularly those of the respiratory tract in both adults and children worldwide14.

Development of Amoxicillin

Penicillins contain β-lactam ring as basic nucleus & this ring can be added to increase their acid stability and their β-lactamase resistance11.

Adding an electron withdrawing group onto the 6-position (located on the β-lactam ring) amide group can increase its acid stability by making the amide oxygen less nucleophilic as in amoxicillin. This ensures that the amide oxygen will not attack the β-lactam ring’s carbonyl group to open it12.

In the 1950s, the entire β-lactam family of antibiotics consisted of two compounds with a limited spectrum of activity– penicillin G and penicillin V. There was considerable interest in developing new penicillins by modifying the side chain of the molecule (Fig. 4). One method was to provide the side chain precursors in the fermentation broth. The range and diversity of compounds that could be produced in this way, however, were limited14, 15.

Fig. 4: It shows the basic structure of Penicillin14

The next approach, by scientists at Beecham Research Laboratories (BRL), was to produce p-aminobenzylpenicillin since its side chain could be modified later when required. Broth fermentation was again the method used, but in the absence of sufficient side chain precursors the resulting molecule, 6-aminopenicillanic acid (6-APA) identified in 1957, was without a side chain. 6-APA was used to produce synthetic β-lactams, notably the β-lactamase stable methicillin, launched in 196014, 22, 23.

A further objective at that time was to identify broad spectrum penicillin. This was realised in 1961 with the synthesis of ampicillin and, later in 1970, with amoxicillin. Amoxicillin is very closely related to ampicillin with the same spectrum of activity and potency but is much better absorbed when given orally, achieving blood concentrations approximately twice as high as those obtained with ampicillin (Fig 5)14.

Fig. 5: It shows the Amoxicillin and Ampicillin serum concentrations in fasting subjects following 500 mg dose24

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Physico-chemical properties

Amoxicillin is white or almost white (amoxicillin trihydrate-off white crystalline, and amoxicillin-sodium white or slight pink, amorphous very hygroscopic) powders, with slight sulphurous odour, compatible with citrate, phosphate and borate buffers. Amoxicillin sodium is very soluble in water, sparingly soluble in anhydrous ethanol, very slightly soluble in acetone, while Amoxicillin trihydrate is slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkalai hydroxides.

Degradation of amoxicillin trihydrate as well as sodium, in sealed and open comtainers were found to show two step degradation at various temperatures. Under controlled humidity conditions, both the amoxicillin trihydrate and amoxicillin sodium showed first order degradation.

Liquid chromatographic method: US Pharmacopeia has recommended liquid chromatographic (LC) method for analysis of pure amoxicillin and assay of amoxicillin in pharmaceutical dosage form (tablet, capsule, oral suspension and injection). The methods recommended the use of a mobile phase of acetonitrile:solvent mixture [6.8 g of monobasic potassium phosphate in 100 ml of water, pH to about 5.0±0.1 adjusted with 4.5% NaOH (96:4)] at a flow rate of 1.5 ml/min, using octadecyl silane chemically bonded to porous silica or ceramic micro-particles (3-10µm) or a monolithic silica rod packing L-ion a stainless steel column 25 cm x 4.0 mm, with detector 230 nm. Indian Pharmacopoeia has also suggested a similar LC method using columns with octadecyl silane chemically bonded to porous silica or ceramic microparticles (5 µm) packing LC.

Potentiometric titration method: Indian Pharmacopoeia (1996), recommended that a solution of drug in buffer (about 50 mg, dissolved in 10 ml of alkaline borate buffer, pH 9.0 and 0.2 ml of acetanhydride and stirred for 3 minutes. Added 10 ml of 1M sodium hydroxide and allowed to stand for 15 minutes. Added 10 ml of 1M nitric acid and 20 ml of acetate buffer pH 4.6) titrated with 0.02 M mercuric nitrate, determining the end-point potentiometrically with a platinum or mercury indicator electrode and a mercury-mercurochloride salt reference electrode and disregarding any preliminary inflection in the titration curve. Subtract the percentage content of degradation products from the calculated percentage content of total penicillins to calculate the percentage content of amoxicillin sodium.

In case of trihydrate, given drug buffer solution (about 0.25 g, add 25 ml of alkaline borate buffer pH 9.0 and 0.5 ml of acetic anhydride, stir for 3 minutes, add 10 ml of acetate buffer pH 4.6) can be used for assay.

Other methods of analysis

The extensive literature survey showed that, there are several methods which can be used for assaying amoxicillin in formulated substances, formulation products and biological fluids. Literature survey revealed Ultraviolet spectroscopy to assay amoxicillin in formulated products. Ultraviolet of a derivative i.e. degradation of amoxicillin at pH 5.2 in the presence of cupric ion gives a product absorb at 320 nm, measurement of which was used as official assay method in British Pharmacopoeia, 1973. Ultraviolet of a derivative method can also be used to assay amoxicillin in urine, but may be interfered by penicilloic acid and other metabolites. A newly developed green bientzemetic UV-spectrophotometric method for the determination of amoxicillin in pharmaceutical preparations has been based on two enzymatic reactions in which, d-4-hydroxy phenylglycine side chain of amoxicillin was selectivelycleaved off by penicil acylase and subsequently, reacted with 2-oxoglutarate, by the catalysis of d-phenyl glycine aminotransferase, to yield 4-hydroxy benzoyl formate with high UV absorption. Then amount of amoxicillin was determined as a change in absorbance at 335 nm. Several Colorimetric methods have been postulated for the determination of amoxicillin, mainly in formulated products of which, a well established hydroxylamine method was one alternative assay method in USP XX. It involved reaction of β-lactam carbonyl with hydroxylamine at pH 7 to give hydroxamic acid which reacted with ferric ions to form purple colour in strong acid measured at 480 nm. Amin et al, 1994 reported a selective colorimetric method for the determination of amoxicillin in pure form and in pharmaceutical preparations, based on the reaction of amoxicillin with 4-nitrophenol (I), 2,4-dinitrophenol (II), 3,5-dinitrobenzoic acid (III) or 3,5-dinitrosalicylic acid (IV) in alkaline medium. The method is selective for the determination of amoxicillin in the presence of its degradation products, other antibiotics and different amino acids normally encountered in dosage forms. Amoxicillin has also been quantized in drug substances or formulations by polaroagraphy of a 6.2 pH solution, an acid hydrolysis or a bromine oxidation product. A product formed by alkaline hydrolysis, heating with formamide or ammonia ethanolamine at pH 5 can be detected by a method based on potrolysis with limit of 10µg/ml for amoxicillin in plasma. A Flow injection method has been used in which amoxicillin hydrolysed by immobilised β-lactamase, the penicilloic acid reacted with iodine and the 4blue starch-iodine colour measured. The quenching of fluorescence of mercurochrome has been used to assay amoxicillin & this measurement was made at pH 10 (Fluorescence method). A spectrophotometric method based on degradation to a fluorescent product, measured after extraction into an organic solvent can be used which is capable of assaying amoxicillin in plasma or urine down to about 1µg/ml. Nagaralli et al, 2002 reported a sensitive spectrofluorometric method for amoxicillin based on the measurement of absorbances of tris-(o-phenanthroline) iron(II) [method A] and tris (bipyridyl) iron(II) [method B] complexes at 510 and at 522 nm, respectively. Microbiological assay by agar plate diffusion method with a sensitive strain of organism (Sarcina lutea or Bacillus subtilis) has been reported to assay amoxicillin in biofluids. However it is lengthy and not very sensitive method. An enzyme linked immunosorbent assay (ELISA) has been developed & used to assay in lung secretions which was capable of measuring amoxicillin down to 10ng/ml. High Performance Liquid Chromatography methods are commonly used to assay amoxicillin and its metabolites in biological fluids, nearly all reversed phase as for assay of drug substance and formulation methods. But the use of ion pairing is more common estimation method for biological fluids where separation from endogenous components may be aided by this technique. A recent report by Fernandez-Torres et al,2010 showed that, an accurate and sensitive reversed-phase high-performance liquid chromatography –diode array–fluorescence (RP-HPLC –DAD–FLD)
Amoxicillin is well absorbed (at different rate and extent from various regions of gut) from GIT. It enjoys widespread clinical use, doses54‐58. The Apparent volume of distribution of amoxicillin is be 1.5‐3 times greater than those of ampicillin after equivalent oral doses38, azithromycin42, clarithromycin44‐46, cefuroxime47‐49 administration of many indications and is used to treat infections of various micro‐organisms with MIC ranges 0.06 µg/ml‐4 µg/ml for most of micro‐organisms except Staphylococcus epidermidis and Staphylococcus aureus which require higher MICs up to 64µg/ml and ≥256 µg/ml respectively. The absolute time bound amoxicillin concentrations remained > MIC value of 0.06 µg/ml was 13 hours in healthy subjects35, 59.

In a study, responses of bacteria were exposed to amoxicillin and ampicillin at continuously decreasing levels with half‐life values (like in‐vivo). For Escherichia coli, the kill rates were higher with amoxicillin than with ampicillin with exponential bactericidal response. With an antibiotic half‐life of 1 hr, the amoxicillin first order inactivation rate was 3.54 hr⁻¹ and the viable cell half‐life was 0.196 hr; the respective values for ampicillin were 2.341 hr⁻¹ and 0.296 hr. With an antibiotic half‐life of 5 hrs, the inactivation rate was 0.704 hr⁻¹ corresponding to a viable cell half‐life of 0.985 hr for amoxicillin compared to 0.380 hr⁻¹ and 1.937 h respectively for ampicillin. For Staphylococcus aureus, the rates of kill were similar with both agents, but, amoxicillin had a longer bacteriostatic phase which was not seen with ampicillin. This led to a longer lasting antibacterial effect and reduction to a lower total count with amoxicillin60.

Clinical studies

*H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence: Randomized, double‐blind clinical studies performed in the United States in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within 1 year) evaluated the efficacy of Lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14‐day therapy, or in combination with amoxicillin capsules as dual 14‐day therapy, for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of 2 different eradication regimens were established:

**Triple Therapy:** Amoxicillin 1 gram twice daily/clarithromycin 500 mg twice daily/Lansoprazole 30 mg twice daily.

**Dual Therapy:** Amoxicillin 1 gram three times daily/clarithromycin 500 mg three times daily/Lansoprazole 30 mg three times daily.

All treatments were for 14 days. *H. pylori* eradication was defined as 2 negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

Triplet therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Table 1: Shows Helicobacter pylori eradication rates – triple therapy (amoxicillin/clarithromycin/lansoprazole)61

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent of Patients Cured</th>
<th>Triple Therapy</th>
<th>Triple Therapy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(95% Confidence Interval)</td>
<td>Evaluatable Analysis</td>
<td>Intent‐to‐Treat Analysis</td>
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<tr>
<td></td>
<td>(Number of Patients)</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Study 1</td>
<td>92/75.3 - 93.5</td>
<td>86</td>
<td>73.3 - 93.5 (n = 48)</td>
</tr>
<tr>
<td>Study 2</td>
<td>86/73.7 - 90.8</td>
<td>83</td>
<td>72.0 - 90.8 (n = 66)</td>
</tr>
</tbody>
</table>

a This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within 1 year) and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLO test (Delta West Ltd, Bentley, Australia). histology, and/or culture.
Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within 1 year). All dropouts were included as failures of therapy.

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### Table 2: Shows Helicobacter pylori eradication rates – dual therapy (amoxicillin/lansoprazole)\(^a\)\(^b\)

<table>
<thead>
<tr>
<th>Percent of Patients Cured [95% Confidence Interval] (Number of Patients) Study</th>
<th>Dual Therapy</th>
<th>Dual Therapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Evaluable Analysis</td>
<td>Intent-to-Treat Analysis</td>
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<tr>
<td>Study 1</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>[62.5 - 87.2]</td>
<td>[56.8 - 81.2]</td>
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<tr>
<td></td>
<td>(n = 51)</td>
<td>(n = 60)</td>
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<tr>
<td>Study 2</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>[51.9 - 77.5]</td>
<td>[48.5 - 72.9]</td>
</tr>
<tr>
<td></td>
<td>(n = 58)</td>
<td>(n = 67)</td>
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</table>

\(^a\)This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within 1 year) and *H. pylori* infection at baseline as defined above and at least 2 of 3 positive endoscopic tests from CLO test, histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

\(^b\)Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within 1 year). All dropouts were included as failures of therapy.

\((P < 0.05)\) versus lansoprazole alone. \((P < 0.05)\) versus lansoprazole/amoxicillin and clarithromycin dual therapy.

## Adverse Effects

A pharmacovigilance study conducted for documenting side effects of drugs within the WHO Programme for International Drug Monitoring from January 1988 up to June 2005, the GIF database collected 37, 906 reports, of which 1095 were related to amoxicillin alone and 1088 to amoxicillin in combination (amoxicillin/clavulanic acid). The percentage of skin reactions was higher for both amoxicillin alone (82%) and amoxicillin in combination (76%); on the contrary, the percentage of gastrointestinal, hepatic and haematological reactions was higher for amoxicillin combination (13%, 4% and 2%, respectively) than for amoxicillin alone (7%, 1% and 1%, respectively). Amoxicillin combination seems to be associated with a higher risk of Stevens-Johnson syndrome, purpura and hepatitis than amoxicillin alone. In particular, the reporting rate of hepatitis is on average 9-fold higher for amoxicillin combination than for amoxicillin\(^c\). The adverse effects associated with amoxicillin are categorised in Table 3.

### Table 3: Shows adverse events associated with Amoxicillin treatments (Reproduced from ref: 2, 35, 56, 61 and 62)

<table>
<thead>
<tr>
<th>Organ/System</th>
<th>Severity</th>
<th>Very Common (1in10 or more)</th>
<th>Common (1in100 to 1in10)</th>
<th>Uncommon (1in1000 to 1in100)</th>
<th>Rare (1in10000 to 1in1000)</th>
<th>Very Rare (Below 1in10000)</th>
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<tbody>
<tr>
<td>Gastrointestinal Tract (GIT)</td>
<td>Diarrhoea</td>
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<td></td>
<td>Nausea, Vomiting, Lower gastro-intestinal irritation reactions (mild and transitory diarrhoea &amp; pruritus ani)</td>
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<td></td>
<td>Indigestion</td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissues</td>
<td>Allergic skin reactions (a morbilliform exanthema)</td>
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<tr>
<td></td>
<td>&quot;fifth day rash&quot; (depends on size of the dose &amp; the patient's condition)</td>
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<td></td>
<td>Typical type I allergic reactions like skin rash, pruritis, urticaria and purpura; angio-oedema and anaphylaxis (less frequent).</td>
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<td></td>
<td>Erythema multiform</td>
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<td></td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis</td>
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<tr>
<td>Hepatobiliary Tract</td>
<td>A moderate rise in AST and/or ALT values (significance unknown)</td>
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<td>Hepatitis and cholestatic jaundice &amp; Hepatic effects, predominant in males &amp; elderly patients, particularly, over 65 yrs, but very rare in children (incidence increases by exceeding courses of treatment to 14 days)</td>
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<tr>
<td>Nervous System</td>
<td>Dizziness, headache</td>
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<td>Blood and Lymphatic</td>
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<td></td>
<td>Reversible Leucopenia</td>
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<td></td>
<td>Reversible agranulocytosis and haemolytic anaemia, prolongation</td>
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\(^c\)\((P < 0.05)\) versus clarithromycin/amoxicillin dual therapy.
Usual
B. a)
Infestations
Infections and Urogenital Tract Interstitial nephritis and Disorders Immune System Drug b a
Ear/Nose/Throat Mild/Moderate 500 mg every 12 Hours or 250 mg every 8 hours
Severe 875 mg every 12 Hours or 500 mg every 8 hours
Lower Respiratory Tract Mild/Moderate or Severe 875 mg every 12 Hours or 500 mg every 8 hours
Skin/Skin Structure Mild/Moderate 500 mg every 12 Hours or 250 mg every 8 hours
Severe 875 mg every 12 Hours or 500 mg every 8 hours
Genitourinary Tract Mild/Moderate 500 mg every 12 Hours or 250 mg every 8 hours
Severe 875 mg every 12 Hours or 500 mg every 8 hours
Gonorrhea Acute, uncomplicated ano-genital & urethral infections in males & females 3 grams as single oral dose
Pre-pubertal children: 50 mg/kg, combined with 25 mg/kg probenecid as a single dose.
Note: since probenecid is contraindicated in children under 2 years, do not use this regimen in these cases
Duodenal ulcer, (H. pylori - associated) ▲ Triple antibiotic therapy: 1000 mg amoxicillin with 500 mg clarithromycin and 30 mg lansoprazole two times a day at twelve-hour intervals for 14 days
▲ Dual antibiotic therapy: 1000 mg amoxicillin with 30 mg lansoprazole three times a day at 8-hour intervals for 14 days
Bacterial endocarditis (prophylaxis) ▲ 3 grams 1 hour before the procedure, then 1.5 grams 6 hours after the initial dose

Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.

The children’s dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations.

Drug interactions
A. Food-Drug Interactions:
B. Fatty meal significantly interfere with amoxicillin, the time above MIC (T>MIC) was prolonged by administration with food. Mean unbound T>MIC of 0.06 µg/ml (minimum required for the inhibition of S. pyogenes) increased from 11.0 hours under fasting conditions to 12.2 hours with a low-fat meal and 14.6 hours with a high-fat meal35.

C. Drug-Drug Interactions:
a) Clavulanic acid/ Potassium clavulanate: Clavulanic acid (β-lactamase inhibitor) increases the effect of amoxicillin and inhibits the development of resistant in β-lactamase producing microorganisms36, 37.

b) Clarithromycin and Lansoprazole: Clinical trials involving the use of combination therapies (e.g. triple therapy in combination with clarithromycin and lansoprazole, or double with lansoprazole alone against H. pylori-related duodenal ulcer disease) no adverse effect peculiar to these combinations were observed35, 56.

c) Probenecid: Concurrent amoxicillin use with this product or other inhibitors of the renal acid secretory system increases and prolongs blood amoxicillin concentrations34, 54.

d) Allopurinol: may increase the possibility of skin rash35, 56.
e) **Anticoagulants:** Abnormal prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin and oral anticoagulants.35, 56.

f) **Methotrexate:** Amoxicillin decrease the renal clearance of methotrexate leads to renal impairments/toxicity.63.

g) **Others:** Tetracyclines, chloramphenicol and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin. Whether amoxicillin decreases the effectiveness of oral contraceptives has not been fully elucidated.35, 56.

**Dosage Forms and Regimen**

Amoxicillin available in the dosage form of tablets (200mg-875mg), chewable tablets (125-500mg), dispersible tablets (750mg), capsules (250mg-500mg), oral suspension and dry powder for oral suspension/drops (50mg/ml-400 mg/ml) strengths for oral administration & injection & dry powder for injection (250mg-1000mg) strengths for intramuscular and intravenous injection/infusion, for treatments of infections and for prophylaxis use. Dosage regimen for various disease conditions, given in table-4.

**CONCLUSION**

Amoxicillin with its comparable clinical efficacy to other antibacterials and favourable dosage, pharmacokinetic profile and tolerability is an excellent candidate to treat various infectious diseases. As it is less effective against gram negative organisms and bacterial resistance develop to the drug candidate, it is the one area where major development is required. Progression in work is also required to investigate new routes of administration and dosage forms with more efficacies to reduce the dose and associated side effects.

**REFERENCES**


