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(54) Title: FORMULATIONS OF AMOXICILLIN AND CLAVULANATE POTASSIUM AND METHODS FOR USING SAME

(57) Abstract: The invention is directed to a composition containing amoxicillin and clavulanate potassium where the clavulanate potassium is present in an amount equal to or less than about 21,5 mg/5 mL.



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5 **FORMULATIONS OF AMOXICILLIN AND CLAVULANATE AND
METHODS FOR USE OF SAME**

RELATED APPLICATIONS

10 [0001] This application claims priority from provisional application Serial
No. 61/648,579 filed May 17, 2012.

FIELD OF THE INVENTION

15 [0002] The invention is for a composition comprised of amoxicillin and
clavulanate potassium and a method of use of same.

BACKGROUND OF THE INVENTION

20 [0003] Amoxicillin is well known as a treatment for various bacterial infections
and its use as an antibiotic, alone or in combination with other compositions and
medications has been documented. For instance, amoxicillin is used to treat skin
infections, dental infections, ear infections, respiratory tract infections, urinary
tract infections, and gonorrhea. However, treatment of certain bacterial
infections has been made more difficult by resistance. In particular, many gram
negative bacteria produce an enzyme, β -lactamase, that attacks the β -lactam
ring of β -lactam antibiotics and renders them ineffective. To counteract this
25 effect, β -lactamase inhibitors have been developed that can bind to β -lactamase
and prevent it from attacking the antibiotic. The antibiotic and the inhibitor are
preferably administered together. For example the β -lactam antibiotic amoxicillin
can be administered with the β -lactamase inhibitor clavulanate potassium. This
additional clavulanate potassium is not needed in non-beta lactamase mediated
30 resistance treatments.

 [0004] To deal with resistant bacteria, the amount of amoxicillin has
increased in dosage as certain bacteria have become resistant to the amoxicillin.
For instance, *Streptococcus pneumoniae* have become resistant to amoxicillin

such that the prescribed treatment dosage has increased from 400 mg/5 mL per day to over 600 mg/5 mL per day over the last decade. The amount of the clavulanate potassium has similarly increased or remained constant, in ratio with the increase in amoxicillin. Further the actual combined taken dosage for the patient, of the combined amoxicillin and clavulanate potassium has in fact doubled over the last few years.

[0005] A combination of amoxicillin and clavulanate potassium is a treatment of choice for *otitis media* (middle ear infection), *pharyngitis* (sore throat), *sinusitis* (sinus infection), *tonsillitis*, *tonsillopharyngitis*, infections of the genital organs (vagina, uterus, fallopian tubes/ovaries) and the urinary tract (kidneys, ureters, bladder and urethra), *cellulitis* (infection of the dermis and subcutaneous tissue), *erysipelas* (superficial form of cellulitis), *folliculitis* (inflammation of the hair follicles), *furuncles*, *carbuncles*, *abscesses*, *impetigo* (large vesicles or honey-crusted sores), infected ulcers and infected burns, *tracheobronchitis*, *bronchitis*, *pneumoniae*, *gonorrhea*, acute uncomplicated sexually transmitted diseases. The combination of amoxicillin and clavulanate potassium is considered the gold standard for antibiotic treatment, against which most new products on the market are compared. Resistant bacteria is on the rise in the population, it is believed, due to resistant organisms.

[0006] Concerns about the development of antimicrobial resistance have led to recommendations to withhold antibiotics from patients unless symptoms persist or worsen, which is sometimes referred to as a "watchful waiting strategy", which can prolong the symptoms for the patient.

[0007] Notably, due to vaccination there has been a selective reduction of treatable *S. pneumoniae* compared to resistant *Haemophilus influenzae* as causative agents. The resistance building up to amoxicillin has led to the increase of the dosage and/or dosage unit of amoxicillin in certain antibiotic compositions. Correspondingly, the other active pharmaceutical ingredients in such antibiotic compositions has also increased, typically based on ratios.

[0008] Certain current formulations of amoxicillin and clavulanate potassium have a high concentration of clavulanate potassium. However

clavulanate potassium has the potential to cause rare serious side effects such as jaundice and hepatitis (see, for example, Joint Formulary Committee. British National Formulary, 47th edition. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2004). Other minor systemic reactions include headache, rash, mycosis, vaginitis, and agitation. The following infrequent and rare adverse reactions have been reported for ampicillin-class antibiotics: hepatitis; cholestatic jaundice; hemorrhagic/pseudomembranous colitis; angioedema; Stevens-Johnson syndrome; hypersensitivity vasculitis; tooth discoloration; and seizure. The most common side effect diarrhea.

Nausea, vomiting, and upset stomach are also common. In rare cases it can cause immediate and delayed allergic reactions - specifically, skin rashes, fever, and anaphylactic shock.

[0009] More frequently, patients taking clavulanate potassium may experience diarrhea (Reed, M. D. (1998) Clinical pharmacokinetics of amoxicillin and clavulanate potassium. *Pediatric Infectious Disease Journal* 17, 957-62), which can lead to dehydration and further sickness. Although advantageous from the standpoint of efficacy, use of amoxicillin and clavulanate potassium is also associated with a relatively high incidence of diarrhea. This diarrhea is infrequently severe enough to require discontinuing treatment, but it may occasion delays in a patient's returning to work if an adult or day care and school if a child. While not being bound by theory, it is possible that the occurrence of diarrhea is related to the clavulanate potassium component of the drug combination. Formulations of amoxicillin-clavulanate potassium have used varying ratios of the two components; over time, the trend has been to increase the dosage of amoxicillin, mainly to achieve higher efficacy rates against *S. pneumoniae*.

[0010] Amoxicillin-clavulanate potassium ratios have thus ranged from 4:1 to 14:1. The currently available amoxicillin-clavulanate potassium suspension for pediatric use contains 600 mg of amoxicillin and 42.9 mg of clavulanate potassium per 5 mL (a ratio of 14:1). The currently recommended adult dosage ranges from about 500 mg/250 mg through about 4,000 mg/250 mg per day with

a common dose being about 1700 mg/250 mg per day. The currently recommended pediatric dosage, 90/6.4 mg/kg/day administered in two divided doses for 10 days, results in a dose of clavulanate potassium almost twice as high as the dose recommended for adults (6.4 mg/kg/day vs. 3.5 mg/kg/day).

5 [0011] Clavulanate potassium may also cause vomiting, diarrhea, diaper rash in children, and oral moniliasis, which while not as serious as the other side effects, are debilitating to the patient and his/her caregivers. Adult or geriatric patients may be affected by vomiting and diarrhea resulting in lost work days. The pediatric patient with diarrhea and/or vomiting cannot return to school or day
10 care until typically twenty-four (24) hours after the last episode of diarrhea or vomiting. Such constraints affect the parents and care giver of the pediatric patient in that they typically must use vacation days to stay home with the vomiting child, or work from home with a reduced productive outcome. Given the data that approximately twenty percent (20%) of all pediatric patients taking the
15 current dosage of amoxicillin and clavulanate potassium experience some diarrhea and/or vomiting, this translates to twenty percent (20%) of children not able to return to school or day care and consequently twenty percent (20%) of parents or care givers staying home with the affected pediatric patient.

[0012] Indeed, the guidelines for treatment of acute otitis media by the
20 American Academy of Pediatrics recently discussed the side effects of clavulanate potassium as including diarrhea, diaper dermatitis, rashes and allergic reactions. In "*The Diagnosis and Management of Acute Otitis Media*" by Allan S. Lieberthal, *et al.* (published online February 25, 2013 in *Pediatrics*, the official journal of the American Academy of Pediatrics), the recommendations to primary
25 care clinicians for the management of children from 6 months through 12 years of age with uncomplicated acute otitis media (AOM) remains amoxicillin alone, though the article states "Amoxicillin-clavulanate has a broader spectrum than amoxicillin and may be a better initial antibiotic. However, because of cost and adverse effects, the subcommittee has chosen amoxicillin as first-line AOM
30 treatment." Thus, the side effects of the clavulanate potassium seem to affect the treatment recommendations. It is thus discovered and sought in the present

invention to minimize the amount of clavulanate potassium necessary for treatment of antibiotics to be very useful.

[0013] While not wishing to be bound by theory, it is possible that clavulanate potassium has the property of binding irreversibly to β -lactamase.

5 (Reed, M. D. (1998). Clinical pharmacokinetics of amoxicillin and clavulanate potassium. *Pediatric Infectious Disease Journal* 17, 957-62), thus enhancing the effectiveness of amoxicillin. If so, then this might explain the rapidly declining need for clavulanate potassium in the course of a combined treatment with amoxicillin and clavulanate potassium. After an initial loading dose of clavulanate
10 potassium is provided, it is contemplated in the invention that either the same amount or much less may be needed. Continuing to administer the same composition of amoxicillin and clavulanate potassium over the treatment regimen period, as the currently prescribed method, may result in too much clavulanate potassium being taken in subsequent doses.

15 [0014] Clearly for the working population it is particularly important to use the minimal, yet effective, amount of clavulanate potassium so as to reduce the risk of diarrhea and vomiting. We have discovered that overall less clavulanate potassium is required for the entire treatment regimen, which can either be (a) a lower dose through the regimen, (b) high dose of clavulanate
20 potassium at the beginning of treatment to bind to β -lactamase and then less throughout the regimen, or (c) a combination thereof and varying dosages throughout the treatment regimen. Thus, either the same smaller amount, or less, clavulanate potassium may be required as treatment progresses. However in current treatments amoxicillin and clavulanate potassium are administered in a
25 set combined dosage form administered at the same level at a ratio of about 4:1-14:1 over a period of days (typically ten (10) days). Although various amoxicillin and clavulanate potassium regimens are available, the need for minimizing clavulanate potassium has not been adequately addressed. Until recently, the thrust behind reformulations of amoxicillin-clavulanate potassium has been
30 adequate coverage of *S. pneumoniae*. Currently, focus has shifted to adequate coverage of *H. influenzae*. However, minimizing adverse events and side effects

has not been given precedence over the efficacy of the dosage formulation to address *S. pneumoniae*, *H. influenzae* and other bacteria.

[0015] For instance, in a study published in the New England Journal of Medicine in January 2011, the table below (Table 1) shows the higher rates of diarrhea, vomiting and diaper dermatitis in children taking amoxicillin-clavulanate potassium versus those taking a placebo.

Table 3. Complications and Adverse Events According to Study Group and Treatment Received at the Time of Occurrence.^a

Adverse Event	Amoxicillin-Clavulanate Group (N=144)			Placebo Group (N=147)		
	During Receipt of Amoxicillin-Clavulanate	During Receipt of Rescue Therapy	Total	During Receipt of Placebo	During Receipt of Rescue Therapy	Total
	number of children (percent)					
Mastoiditis [†]	0	0	0	1 (1)	0	1 (1)
Perforation of tympanic membrane	1 (1)	0	1 (1)	6 (4)	1 (1)	7 (5)
Protocol-defined diarrhea [‡]	34 (24)	2 (1)	36 (25)	11 (7)	11 (7)	22 (15) [§]
Diaper-area dermatitis	67 (47)	6 (4)	73 (51)	24 (16)	27 (18)	51 (35) [§]
Oral thrush	7 (5)	0	7 (5)	0	1 (1)	1 (1)
Vomiting	12 (8)	0	12 (8)	11 (7)	1 (1)	12 (8)
Rash ^{**}	1 (1)	0	1 (1)	1 (1)	1 (1)	2 (1)

^a In each study group, one child was not followed beyond enrollment. Comparisons were adjusted for study site, history or no history of recurrent acute otitis media, and exposure or no exposure to other children.

[†] Mastoiditis developed on day 5 in an 11-month-old child with unilateral acute otitis media and a score on the Acute Otitis Media Severity of Symptoms (AOM-SSS) scale of 14 at entry and of 7 on day 5. A culture of middle-ear aspirate yielded serotype 19A *Streptococcus pneumoniae* with a penicillin minimum inhibitory concentration of 2 µg per milliliter. The child was hospitalized for 41 hours and treated initially with parenteral antibiotics and subsequently with oral antibiotics; he recovered uneventfully.

[‡] Diarrhea was defined in the protocol as three or more watery stools in 1 day or two watery stools daily for at least 2 days. Treatment was discontinued because of diarrhea in six children in the amoxicillin-clavulanate group and one child in the placebo group, in whom *Clostridium difficile* enteritis developed.

[§] P=0.05 for the difference between the amoxicillin-clavulanate group and the placebo group.

^{||} P=0.008 for the difference between the amoxicillin-clavulanate group and the placebo group.

^{||} In the amoxicillin-clavulanate group, treatment was discontinued in one child because of vomiting.

^{**} In each group, treatment was discontinued in one child because of rash.

[0016] Thus, a need exists for an amoxicillin-clavulanate potassium composition, and treatment method, which reduces the side effects of diarrhea and vomiting while still maintaining the high efficacy of the antibiotic combination. One of the objectives of the invention is to maintain high efficacy while improving safety profile, namely reducing the common and disruptive side effects of diarrhea and vomiting in working, pediatric and geriatric patients.

[0017] Various formulations and dosing modalities currently exist for the combination of amoxicillin-clavulanate potassium. Tablets and suspensions are also available. Delayed release tablet formulations have been developed (see for example U.S. Pat. Nos. 5,910,322, 6,299,903, 6,544,558,

6,756,057, 6,783,773, 6,977,086, 7,122,204, 7,534,781, and publications 2006,0121106, 2008/0300569, and 2011/0020408).

[0018] However, these systems provide combination doses of amoxicillin-clavulanate potassium that do not address the need for a reduced set amount of
5 clavulanate potassium (whether constant throughout the treatment or in a reduced set amount when compared to current conventional and known amounts) throughout the treatment regimen, including reducing the amount as treatment progresses. There is a need for a dosage, and a method that provides a means of reducing the overall amount of clavulanate potassium for the
10 treatment regimen, when compared to current conventional and known dosage amounts.

[0019] Thus, a need exists for a composition having amoxicillin-clavulanate potassium without elevating the possibility of the severe side effects of jaundice and hepatitis and the more common and disruptive side effects of
15 diarrhea and vomiting.

[0020] These and other needs are met by the present invention including a composition and a method for treating bacterial infections. Other advantages of the present invention will become apparent from the following description and appended claims.

20

SUMMARY OF THE INVENTION

[0021] This invention provides a composition including an amount of amoxicillin and an amount no greater than about 21.5 mg/5 mL of clavulanate potassium.

25 [0022] Also part of this invention is a composition including an amount of amoxicillin and an amount of clavulanate potassium in at a ratio of at least about 28:1, preferably in a range of about 28:1 through about 56:1.

[0023] A further embodiment of this invention is a method of use of a composition including an amount of amoxicillin and an amount no greater than
30 about 21.5 mg/5 mL of clavulanate potassium, where the composition is administered over a period of days.

[0024] A further embodiment of this invention is a method of use of a composition including an amount of amoxicillin and an amount of clavulanate potassium in at a ratio of at least about 28:1, preferably in a range of about 28:1 through about 56:1, where the composition is administered over a period of days.

5

DETAILED DESCRIPTION OF THE INVENTION

10 [0025] The invention includes a composition comprised of amoxicillin and clavulanate potassium where the amount of clavulanate potassium is less than about 21.5 mg/5 mL. A multiple day dosage method is included.

[0026] Another embodiment of the invention is a composition comprised of amoxicillin and clavulanate potassium in a ratio of at least about 28:1. A
15 multiple day dosage method is included.

[0027] For purposes of this invention, the following terms have the meanings given below unless otherwise indicated.

[0028] "Unit Dose" means a discrete dose of a composition of this invention given once, in a single administration.

20 [0029] "Dose" or "dosage" may mean either a single administration of a composition or can mean several administrations of the same composition depending on context. For example if the composition is given twice a day, a dose could be taken to mean two administrations of the same composition, in suitably measured amounts. Thus the same "dose" may be given two or three
25 times (or more if necessary) in the treatment regimen before progressing to the subsequent dose, which would be of a composition having a different given amount of medication. However as defined above a unit dose means a single dose given a single time, i.e. in one administration.

[0030] "Dosage form" is the type of formulation in which the compositions
30 of this invention are administered, such as but not limited to amoxicillin-

clavulanate potassium. A dosage form may be a discrete unit such as a tablet or may be a liquid form or a suspension, from which unit dosages are measured.

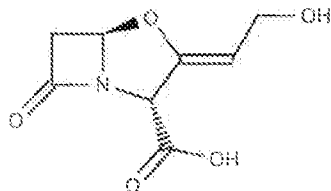
[0031] "Patient" may be any living thing treated with a composition of this invention. The patient is preferably a human child or adult, but could also be a non-human such as an animal.

[0032] "About" when used in connection with an amount shall mean a scientifically reasonable variance above and below that amount keeping in mind artifacts of measurement and other variables. For example, a ratio of about 1:15 may encompass $\pm 5\%$ of the unit of measure used. A concentration of 1 mg/mL may encompass a range of about ± 0.05 mg, while a concentration of 1000 mg/mL may encompass a range of ± 50 mg.

[0033] "Amoxicillin" and "clavulanate potassium" or "clavulanic acid" refer to any existing acid and salt forms, whether alkali, alkaline, or acid salts, polymorphs, hydrates, solvates, racemates and mixtures. Examples are amoxicillin trihydrate or sodium, and potassium clavulanate. The weights of amoxicillin and clavulanate potassium refer to weight in equivalents of corresponding free acids unless otherwise indicated. The weights used in a formulation may also be adjusted by known methods depending on potency.

[0034] Standard abbreviations may be used. All publications cited herein, including but not limited to patents and patent applications, are incorporated by reference in their entirety as if individually specified as incorporated by reference, unless otherwise indicated.

[0035] The inventive composition includes amoxicillin and clavulanate potassium. Clavulanate potassium includes clavulanic acid, which is the generic name for (2R,5R,Z)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, which is a known compound of the following formula:



[0036] The inventive composition also includes amoxicillin, which is an analog of ampicillin, derived from the basic penicillin nucleus 6-aminopenicillanic acid. Chemically, a=Amoxicillin is (2S,5R,6R)-6-[1-(-)-2-amino-2-(p-
 5 hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

[0037] The composition of the invention contains no more than about 21.5 mg/5 mL of clavulanate potassium, with amoxicillin within the inventive composition. Preferably the clavulanate potassium is present in an amount of
 10 between about 5mg/5 mL to about 21.5 mg/5 mL.

[0038] A particularly preferred mode of administration of the inventive composition is orally via an aqueous suspension. For preparing such suspensions amoxicillin and clavulanate potassium can be combined with buffers, emulsifying and suspending agents. If desired, certain sweetening and/or
 15 flavoring agents can be added. These active compounds can be directly mixed with liquid ingredients to provide a suspension, or can be formed into granules or powders which are then made into a suspension, by known methods and using known ingredients examples of which are provided below. The resulting suspension can be stored in the presence of water, especially if refrigerated, for
 20 an appropriate period. However, a preferred method is to store the mixture as a dry powder until its use is required, at which time it is mixed with an appropriate diluent, e.g., water.

[0039] The prescribing physician will ultimately determine the appropriate dose for a given human subject, and this can be expected to vary according to
 25 the age, weight, and response of the individual patient as well as the nature and severity of the patient's symptoms. The patient may be pediatric, an adult or a

geriatric human.

[0040] Dosage forms contemplated for the compositions of this invention containing amoxicillin and clavulanate potassium, include any known liquids for pharmaceutical use, preferably oral suspensions as the typical patient will be a human child or adult. The most common formulation is a powder for suspension to be mixed with water at the time of use.

[0041] The inventive composition may also contain excipients, vehicles, and solvents include sterile water, saline, Ringer's solution, polyalkylene glycols, natural and synthetic fatty acids, mono, di, and triglycerides and oils, and hydrogenated naphthalenes. Carriers may be included such as but not limited to lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, and gelatin.

[0042] Disintegrants may be included such as but not limited to starch such as pregelatinized and sodium starch glycolate, cellulose such as microcrystalline, sodium carboxymethyl, hydroxypropyl, croscarmellose sodium, crosspovidone, and crosslinked polyvinyl pyrrolidone. Fillers may be included such as but not limited to cellulose, dibasic calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and fats and oils for capsules.

[0043] Antifriction agents may be included such as but not limited to magnesium and calcium stearates, and polyethylene glycol waxes. Glidants may be included such as but not limited to colloidal silicon dioxide and talc.

Lubricants may be included such as but not limited to talc, silica, colloidal silicon dioxide, and fats such as zinc or magnesium stearate or stearic acid.

Preservatives may be included such as but not limited to m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (hexahydrate), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate, thimerosal, antioxidants (vitamins A, C, E, retinyl palmitate), selenium, cysteine, methionine, citric acid, sodium citrate, and lower alkylparabens. Mucoadhesives may be included such as but not limited to methyl, hydroxypropyl, and sodium carboxymethyl cellulose, chitosan, polyvinyl pyrrolidone, and hydrogels.

[0044] Binders may be included such as but not limited to polyvinylpyrrolidone, pregelatinized starch, methacrylic acid polymers, gelatin, and hydroxypropylcellulose. pH modifiers may be included such as but not limited to various organic and inorganic acids, bases, and their salts such as

5 orthophosphoric acid, hydrochloric acid, nitric acid, sulphuric acid, sulfamic acid, hydrofluoric acid, oxoacids, sodium and potassium dihydrogen phosphates, citric acid, ascorbic acid, tartaric acid, malic acid, malonic acid, succinic acid, fumaric acid, maleic acid, adipic acid, lactic acid, levulinic acid, sorbic acid, polyacrylic acid, sodium carbonate, sodium bicarbonate, magnesium carbonate, magnesium

10 oxide, calcium carbonate, calcium oxide, aluminium hydroxide, magnesium hydroxide, and sodium hydroxide.

[0045] Buffers may be included such as but not limited to acetic acid, citric acid, boric acid, and phosphoric acid. Isotonicity agents may be included such as but not limited to glycerin, mannitol, sorbitol, sodium chloride, and other

15 electrolytes. Emulsifiers may be included such as but not limited to soy lecithin, calcium stearoyl dilactate, various esters of polyglycerol and sorbitan, and monoglycerides. Suspending agents may be included such as but not limited to natural and synthetic polysaccharides such as gums (acacia, tragacanth, guar, and xanthan), celluloses (sodium carboxymethyl, methyl, hydroxyethyl,

20 hydroxypropyl, and microcrystalline), cargeenan, sodium alginate, carbomer, colloidal silicon dioxide, and clays (aluminum magnesium silicate, bentonite, hectorite).

[0046] Further components such as solubilizers may be added including but not limited to Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween

25 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) and non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, polyols, other block co-

polymers, and chelators such as EDTA and EGTA.

30 [0047] Flavorants may be included such as but not limited to sodium saccharin, sugar, and other natural and artificial compounds which mask or

enhance flavor. Colorants may be included such as but not limited to natural dyes such as caramel coloring, annatto, cochineal, betanin, turmeric, saffron, paprika, elderberry, pandan, and butterfly pea, and artificial dyes such as FD&C Blue Nos. 1 and 2, Green No. 3, Yellow Nos. 5 and 6, and Red Nos. 3 and 40.

- 5 Thickening agents may be included such as but not limited to alginic acid and salts (such as sodium, potassium, ammonium, calcium), agar, carrageenan, locust bean gum, gelatin, and pectin. Stabilizing agents may be included such as but not limited to fatty acid salts, sulfates, sulfate esters and phosphate esters (for example polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters such as polyoxyethylene sorbitan monooleate, polysorbate 80 and polysorbate 20). Surfactants may be included such as but not limited to sorbitan trioleate, soya lecithin, and oleic acid.

- [0048] The sweetener of the composition may be any natural or synthetic compound, or combination of compounds, which provides adequate sweetening to overcome the bitterness of the inventive composition. Natural sweeteners include carbohydrates such as sucrose, dextrose, fructose, invert sugar, mannitol, sorbitol, and the like. Synthetic sweeteners include saccharin, aspartame, cyclamates, and other so-called artificial sweeteners familiar to those of skill in the art. The flavoring of the composition may be any natural or synthetic compound, or combination of compounds, which provides acceptable taste to overcome the blandness of the base composition. Such flavorings include bubble gum, grape, cherry, berry, citrus, other fruits, peppermint, spearmint, other mints, vanilla, chocolate, and the like, familiar to those of skill in the art.

- 25 [0049] In more detail, the compositions of this invention may be liquid formulations for oral use. Such formulations may include a suitable selection of appropriate known ingredients such as those provided above alone or in combination. The liquid formulations may be formulated as syrups, solutions or emulsion, elixir, suspensions or other known types of liquid suitable for oral administration. The liquid formulations may be aqueous or nonaqueous and include for example buffers with any pharmaceutically acceptable salts,

preservatives, emulsifiers, humidifiers, isotonicity agents, solubilizers, buffers, thickening and suspending agents, dyes, and flavorants.

[0050] Specific ingredients may include water, saline, polyalkylene glycols, oils, hydrogenated naphthalenes, sugar, ethanol, glycerol, propylene glycol, dyes, flavorants, and thickening agents. The liquid formulations may be prepared by known methods using the compositions of this invention. The active compounds of the amoxicillin and clavulanate potassium may be obtained from existing powders, granules, or tablets for liquid formulations.

[0051] The liquid formulations of this invention may be provided for oral administration. For example the formulations may be taken in measured doses using a cup, straw, spoon, syringe, or other device. The formulations may be provided in liquid form, or may be provided in dry form (for example granule or powder) to which an appropriately formulated water or liquid solvent is added to provide a liquid formulation of a composition of this invention. Ingredients suitable for liquid formulations are known and such a formulation may be made by methods known in the art.

[0052] A liquid formulation (for example solution, suspension, emulsion) can be made by combining the amoxicillin and clavulanate potassium with suitable aqueous and or nonaqueous diluents, water, buffers, and preservatives as discussed above and mixing with known methods under suitable known conditions. The specific ingredients and concentrations will depend on the type of formulation desired, for example oral suspension as known in the art. However, as an example, a oral suspension may also include a vehicle such as water, saline, Ringer's solution, dextrose, serum albumin, sodium chloride, mannitol, buffers, and preservatives. The formulation may be sterilized by known techniques.

[0053] Dosage forms contemplated for the compositions of this invention include any known liquid, aerosolized, or solid formulations whether formulated for enteral (for example oral, nasal, buccal, sublingual, or rectal), parenteral or injectable (for example intravenous, intradermal, intraosseous, intramuscular, intraperitoneal, and subcutaneous), topical, inhaled, rectal or vaginal, via mucous

surfaces (such as corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal) or any other route of administration. Examples are capsules, powders, sachets, pills, tablets, hard or soft gelatin capsules, colloids, granules, lozenges, crystals, douches, pessaries, 5 suppositories, injectable solutions, syrups, suspensions, pastes, elixirs, films, emulsions, ointments, lotions, gels, liniments, balms, creams, eye or ear drops, skin patches, and aerosols, inhalants, nebulized forms, vaporized forms, liposomes, microspheres, and any other known formulations.

[0054] The dosage forms of the inventive composition may be formulated 10 for any convenient release profile such as immediate, sustained, or delayed by well known methods.

[0055] The composition may be in the form of a tablet, capsule, powder or any other known dosage delivery. The composition may include carriers such as but not limited to lactose, saccharose, sorbitol, mannitol, starch, amylopectin, 15 cellulose derivatives, and gelatin. A tablet or capsule form may include coatings and enteric coatings such as but not limited to talc, cellulose, shellac, corn protein, zein, sugar, gum arabic, titanium dioxide, gelatin, or other polymers such as polysaccharides.

[0056] Disintegrants may be included such as but not limited to starch 20 such as pregelatinized and sodium starch glycolate, cellulose such as microcrystalline, sodium carboxymethyl, hydroxypropyl, croscarmellose sodium, crosspovidone, and crosslinked polyvinyl pyrrolidone. Fillers may be included such as but not limited to cellulose, dibasic calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and fats and oils for capsules.

[0057] Antifriction agents may be included such as but not limited to 25 magnesium and calcium stearates, and polyethylene glycol waxes. Glidants may be included such as but not limited to colloidal silicon dioxide and talc. Lubricants may be included such as but not limited to talc, silica, colloidal silicon dioxide, and fats such as zinc or magnesium stearate or stearic acid.

30 Preservatives may be included such as but not limited to m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol,

formaldehyde, chlorobutanol, magnesium chloride (hexahydrate), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate, thimerosal, antioxidants (vitamins A, C, E, retinyl palmitate), selenium, cysteine, methionine, citric acid, sodium citrate, and lower alkylparabens. Mucoadhesives may be included such as but not limited to methyl, hydroxypropyl, and sodium carboxymethyl cellulose, chitosan, polyvinyl pyrrolidone, and hydrogels. The tablets and capsules may also include binders, buffers, flavorants, colorants, thickening agents, stabilizing agents, surfactants, and other additives.

[0058] In more detail, the compositions of this invention, which contain a first and second pharmaceutically active compound, preferably amoxicillin/clavulanate, may be liquid formulations for oral use. Such formulations may include a suitable selection of appropriate known ingredients such as those provided above alone or in combination. The liquid formulations may be formulated as syrups, solutions or emulsion, elixir, suspensions or other known types of liquid suitable for oral administration. The liquid formulations may be aqueous or nonaqueous and include for example buffers with any pharmaceutically acceptable salts, preservatives, emulsifiers, humidifiers, isotonicity agents, solubilizers, buffers, thickening and suspending agents, dyes, and flavorants.

[0059] Specific ingredients may include water, saline, polyalkylene glycols, oils, hydrogenated naphthalenes, sugar, ethanol, glycerol, propylene glycol, dyes, flavorants, and thickening agents. The liquid formulations may be prepared by known methods using the compositions of this invention. The active compounds such as amoxicillin and clavulanate may be obtained from existing powders, granules, or tablets for liquid formulations.

[0060] The liquid formulations of this invention may be provided for oral administration. For example the formulations may be taken in measured doses using a cup, straw, spoon, syringe, or other device. The formulations may be provided in liquid form, or may be provided in dry form (for example granule or powder) to which an appropriately formulated liquid solvent is added to provide a liquid formulation of a composition of this invention. Ingredients suitable for liquid

formulations are known and such a formulation may be made by methods known in the art.

[0061] The liquid formulations of this invention can also be provided for inhalation in the form of an aerosol by known methods as described further below. A liquid formulation as described above is useful also as an aerosol. Ingredients suitable for aerosol liquid formulations are known and such a formulation may be made by methods known in the art. Various types of spraying devices are known in the art. A suitable formulation may include known excipients, buffers, isotonicity agents, preservatives, surfactants, and zinc. Stabilizing agents may be included.

[0062] A liquid formulation (for example solution, suspension, emulsion) can be made by combining a first and second pharmaceutically active compound of this invention, preferably amoxicillin and clavulanate with suitable aqueous and or nonaqueous diluents, water, buffers, and preservatives as discussed above and mixing with known methods under suitable known conditions. The specific ingredients and concentrations will depend on the type of formulation desired, for example oral or parenteral as known in the art. For example, a parenteral formulation may include a vehicle such as water, saline, Ringer's solution, dextrose, serum albumin, sodium chloride, mannitol, buffers, and preservatives. The formulation may be sterilized by known techniques.

[0063] Formulations for use as liquid aerosols may be aqueous and include suitable excipients, buffers, isotonicity agents, preservatives, surfactants, and possibly zinc. Bulk proteins may be used for stabilizing, such as albumin or protamine. Carbohydrates such as sucrose, mannitol, lactose, trehalose, and glucose may be used. A surfactant may also be included, such as polyoxyethylene fatty acid esters and alcohols or polyoxyethylene sorbital fatty acid ester.

[0064] Formulations of this invention for use with metered dose inhalers may take the form of finely divided powders. Compositions of this invention can be made by combining the amoxicillin and clavulanate in a nonaqueous suspension such as in a propellant. The propellant can be a conventional

propellant such as a fluorocarbon (chloro, hydrochloro, hydro, dichloro, trichloro) or other halogenated hydrocarbons such as dichlorotetrafluoroethanol, 1,1,1,2-tetrafluoroethane, hydrofluoroalkane-134a, and hydrofluoroalkane 227. A surfactant such as sorbitan trioleate, soya lecithin, and oleic acid may be used.

5 [0065] Compositions of this invention can be provided in the form of powders or granules or lyophilized preparations using suitable ingredients provided above by methods known in the art. Such granules and powders may be used to make liquid formulations by addition of a suitable solvent by known methods, or may be provided for inhalation as an aerosol by known methods, or
10 be used in capsules. An example of a powder formulation is provided by the packet insert for Augmentin. The powder contains colloidal silicon dioxide, xanthan gum, and flavorings, aspartame and/or hypromellose and/or mannitol and/or silica gel and/or silicon dioxide and/or sodium saccharin.

 [0066] The compositions of this invention may be provided in tablet form.
15 The amoxicillin and clavulanate may be mixed with a suitable solid carrier as described above (for example lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, and an antifriction agent such as magnesium stearate, calcium stearate, or polyethylene glycol waxes. Once pressed, the resulting tablets can be coated with coating solution of ingredients
20 provided above such as sugar, gum arabic, gelatin, talc, or titanium dioxide. Various dyes may be added if desired, for example to indicate different amounts of clavulanate.

 [0067] Tablets may be designed for delayed release of the inventive composition. Ingredients suitable for delayed or immediate release are
25 combined with the granules, to provide immediate or delayed release amoxicillin and clavulanate forms. Bilayer tablets may also be used, made by known methods. Such tablets may contain a layer of amoxicillin on a layer of clavulanate, two such layers separated by a barrier layer, and may or may not have a coating layer over all or some of the tablet. Either or both of the layers
30 may be formulated for immediate or sustained release by known methods. More than two layers are possible. In the alternative, a tablet with a core and

surrounding component separated by barriers may also be made by known methods, having delayed or immediate release properties if desired. An example of chewable tablets is provided by the packet insert for Augmentin (Augmentin prescribing information, September 2009 GlaxoSmithKline). The tablets contain
5 colloidal silicon dioxide, flavorings, magnesium stearate, mannitol, and 1 or more of aspartame, D&C Yellow No. 10, FD&C Red No. 40, glycine, sodium saccharin and succinic acid.

[0068] The compositions of this invention may be provided in the form of soft or hard gelatin capsules. Soft gelatin capsules may include vegetable oil or
10 polyethylene glycol. Hard gelatin capsules may contain powder or granules of compositions of this invention made with carriers, for example, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin. Suppositories may be prepared from the compositions of this invention as gelatin capsules or a formulation in a base of
15 polyalkyleneglycols and/or neutral fats such as Vaseline, or cocoa butter.

[0069] Compositions of this invention may be formulated for absorption through mucosal surfaces, for example in the form of an emulsion made up of active particles and mucoadhesive in an aqueous phase. Mucoadhesion of the emulsion permits absorption of the active ingredients through mucosal surfaces.
20 Intranasal formulations can be aqueous or nonaqueous, or can be solid with excipients such as lactose. Buccal formulations may include excipients such as sugars, calcium or magnesium stearate, and pregelatinized starch.

[0070] Compositions of this invention may be formulated for transdermal administration. Delivery devices known in the art, such as liposomes,
25 nanoparticles, microparticles, microcapsules, or microspheres may be used. These may be produced from various synthetic polymers such as polyhydroxy acids, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other proteins, alginate and other polysaccharides.

30 [0071] Liquid formulations of compositions of this invention can be prepared by mixing the pharmaceutically active compounds preferably amoxicillin

and clavulanate with a preservative and any desired buffers in an aqueous diluent using conventional procedures for mixing and dissolution. Liquid formulations can be made by reconstituting powders or granules or lyophilized preparations.

5 [0072] Suspensions of this invention may be provided at any concentration providing acceptable stability for the pharmaceutically active compounds (for example the length of the desired treatment period, optionally with refrigeration) and within the range that would provide a composition having suitable flow parameters for dispensing the inventive composition. Reconstituting oral
10 suspensions from an amoxicillin/clavulanate powder composition may be done as follows from a powder prepared for oral suspension (provided above). The suspension may be prepared from freely flowing powder in a suitable container. A little over half of the solvent such as water needed should be added and the container shaken vigorously to suspend. Then the rest of the solvent should be
15 added and the container shaken vigorously.

 [0073] Granules prepared from the compositions of this invention can be provided by known methods, either wet or dry. For example, a binding agent is suspended in a solvent while solid ingredients may be ground to a desired particle size. The first and second pharmaceutically active compounds,
20 preferably amoxicillin and clavulanate, are mixed with the binding agent in solution to form a suspension. The mixture is sieved and dried for a predetermined length of time. The granules may be sieved again and other ingredients added. Other ingredients such as disintegrating agents, antiadhesive agents, and antifriction agents may be added. Amoxicillin, clavulanate, and the
25 various carrier ingredients discussed above are all available from known suppliers, or may be made by known methods.

 [0074] Tablets may be prepared from the granules by use of punches and dies in the appropriate pressing machine. Modified release tablets may be prepared by known methods using immediate release granules, inert barrier
30 granules, and slow release granules formed into layers.

[0075] Certain known dosing combinations of amoxicillin and clavulanate potassium are listed in Table 2 below. In these conventional dosing combinations the amount of clavulanate potassium is between about 28.5 mg/5 mL to about 62.5 mg/5 mL. The previous known and used ratios of amoxicillin to clavulanate potassium are between 4:1 to 14:1.

TABLE 2

	Amoxicillin	Clavulanate potassium	Ratio
1	125 mg/5 mL	31.25	4:1
2	200 mg/5 mL	28.5	7:1
3	250 mg/5 mL	62.5	4:1
4	400 mg/5 mL	57	7:1
5	600 mg/5 mL	42.9	14:1

[0076] The inventive composition instead contains amoxicillin and clavulanate potassium wherein the amount of clavulanate potassium does not exceed about 21.5 mg/5 mL. Further, another embodiment of the inventive composition contains amoxicillin and clavulanate potassium in a ratio of at least about 28:1 and preferably between about 28:1 and about 56:1. Both embodiments of the invention result in a reduced amount of clavulanate potassium compared to current known compositions. While not being bound by theory, the reduced amount of clavulanate potassium may be especially good for geriatric and pediatric patients as it may lead to reduced chance of diarrhea, nausea, and vomiting, as well as for pediatric patients experiencing diaper rash. The reduced amount of clavulanate potassium does not affect the treatment efficacy of the amoxicillin to treat acute otitis media or other illnesses such as respiratory illnesses.

[0077] The method of the invention is to patients with a dosing regimen of about one to about fourteen days, using a composition of amoxicillin and clavulanate potassium wherein the clavulanate potassium is present in an amount not to exceed about 21.5 mg/5 mL. In one embodiment of the method of

the present invention the amount of clavulanate potassium remains constant, with the amount being less than about 21.5 mg/5 mL.

[0078] In another embodiment of the method of the present invention it is preferred that the first dose contains more of clavulanate potassium, than the second, or any subsequent dosage. For example, in a multiple day method spanning ten (10) days, the dosage of clavulanate potassium on days 1 and 2 may be in an amount of about 21.5 mg/5 mL, then an amount of about 15 mg/5 mL on days 3-10.

[0079] A further embodiment of the method of the present invention includes a dosage for the first two days of the treatment containing no more than about 21.5 mg/5 mL of clavulanate potassium and then the subsequent dosages contain a less amount of clavulanate potassium. In yet another embodiment of the method of the present invention the first dose contains more of the clavulanate potassium than the second dose, and the subsequent dosages contain decreasing amounts of clavulanate potassium. The less amount of clavulanate potassium may be constant or can continue to decrease over the treatment days. For example, in a multiple day method spanning ten (10) days, the dosage of clavulanate potassium on days 1 and 2 may be in an amount of about 21.5 mg/5 mL, then an amount of about 15-20 mg/5 mL on days 3-6, and an amount of about 5-10 mg/5 mL on days 7-10. In all the embodiments of the inventive method the amounts used should be effective for the treatment contemplated, as can be determined by a person skilled in the art.

[0080] In another embodiment of the inventive method, the method of the invention is to treat patients with a dosing regimen of one to about fourteen (14) days, using a composition of amoxicillin and clavulanate potassium in a ratio of at least about 28:1. In another embodiment of the invention is to treat patients with a dosing regimen of about five (5) or about seven (7) days, using a composition of amoxicillin and clavulanate potassium in a ratio of at least about 28:1, whether in constant or tapered doses over the treatment days. In another embodiment of the method of the present invention it is preferred that the first dose contains more of clavulanate potassium, than the second, and any subsequent dosages

contain decreasing amounts of clavulanate potassium, so that the ratio increases over the dosage treatment regimen. The amounts used should be effective for the treatment contemplated, as can be determined by a person skilled in the art.

[0081] The amounts of the amoxicillin in either embodiment of the inventive method, will preferably remain the same during the treatment regimen, but may also decrease, or may even increase for any treatment that would require increasing amounts. The amounts of the clavulanate potassium may decrease with each dosage or may remain constant over several doses, or even increase if the treatment requires. But it is most preferable that the amount of the clavulanate potassium, decreases with successive dosages. The dosages may be formulated to contain more than one unit dose and thus be administered more than once. Thus it is possible that two or more successive dosages as administered may contain the same amount of the clavulanate potassium, while the next subsequent dosage contains less. The dosages may also be provided as a unit dose, in which case each is only provided once. Any combination of dosages and unit doses may be used. One embodiment of the method is for a multiple day dosage wherein the clavulanate potassium is a constant amount over the treatment days, with the days being anywhere from about two days to about fourteen days or more. Another embodiment of the method is for a multiple day dosage wherein the clavulanate potassium is reduced over the dosage period. The dosage period may also be about two days or increased up to about fourteen days or more, with either constant or reduced clavulanate potassium over the dosing period.

[0082] For instance, the amount or concentration of the clavulanate potassium can remain constant in the ratio of at least about 28:1 to the amoxicillin, or could taper down in succeeding dosages of the method. In the reducing embodiment, thus each composition will contain less of the clavulanate potassium and the ratio will increase. The final dosing composition may optionally contain none of the clavulanate potassium.

[0083] In general the compositions of this invention contain effective amounts for the treatment contemplated of the amoxicillin and clavulanate

potassium. These amounts may be determined by a skilled person with routine experimentation.

[0084] However preferred amounts of amoxicillin and clavulanate potassium are provided as follows. In any liquid formulations of the compositions of this invention described above, preferably suspensions, each composition may contain from about 100 to about 1200 mg/5 mL (or about 20 to about 140 mg/mL) of amoxicillin and about 0.1 to about 21.5 mg/5 mL of clavulanate potassium. The compositions preferably contain from about 125 mg/6 mL to about 600 mg/5 mL of amoxicillin. Preferably the amount of clavulanate potassium is from about 0 mg/5 mL to about 21.5 mg/5 mL of liquid formulation. For purposes of dosing 5 mL is equal to one teaspoon.

[0085] For any given dispensing system of this invention, the amount of clavulanate potassium in the first composition should preferably determine the amount in the second (and succeeding) compositions in an embodiment wherein there will be the same or less clavulanate potassium in succeeding doses. For example, if the first composition contains about 600 mg/5 mL of amoxicillin and about 21.5 mg/5 mL of clavulanate potassium, then the second dosing composition contains equal to or less than about 21.5 mg/5 mL clavulanate potassium.

[0086] This invention is also directed to a liquid composition of amoxicillin and clavulanate potassium which contains less than about 21.5 mg/5 mL and more than about 0.1 mg/5 mL of clavulanate potassium. A preferred composition has from about 15 mg/5 mL to about 21.5 mg/5 mL. Another preferred composition has from about 10 mg/5 mL to less than 21.5 mg/5 mL. Another preferred range is from about 2.5 mg to about 10 mg of clavulanate potassium.

[0087] The concentrations of the invention are preferably expressed in mg as above. This invention also contemplates ratios to express the concentrations. For example the amoxicillin may be present in a ratio of about 28:1 to about 56:1 where 1 represents the amount of the clavulanate potassium. Preferably the amount of the amoxicillin is from about 30:1 to about 35:1. These ratios are

preferably weight ratios. As discussed above, compositions of this invention may start with any amount or concentration of the clavulanate potassium as long as the succeeding compositions contain the same or lower amounts or concentrations.

5 [0088] The amounts and concentrations of the pharmaceutically active compounds, preferably amoxicillin and clavulanate potassium, may also determined by known methods using desired serum concentrations at various points in the treatment regimen.

10 [0089] The compositions of the present invention can be prepared by known processes. Amoxicillin and clavulanate potassium, the preferred pharmaceutically active compounds can be obtained from suppliers or made by known methods. See for example U.S. Pat. Nos. 6,218,380 and 7,534,781.

15 [0090] The formulations discussed above can be made by methods known in the art using the various "inactive" formulation ingredients discussed with amoxicillin and clavulanate potassium. These known ingredients can be made by methods known in the art or obtained from chemical supply houses. The amounts and concentrations preferred for the amoxicillin and clavulanate potassium compositions of this invention are discussed above. The amounts of
20 the other ingredients should be sufficient to provide the properties for which each of the ingredients are being used, for example, flavorant or other additives.

25 [0091] Liquid formulations of compositions of this invention can be prepared by mixing the pharmaceutically active compounds preferably amoxicillin and clavulanate potassium with a preservative and any desired buffers in an aqueous diluent using conventional procedures for mixing, suspension or dissolution. Liquid formulations can be made by reconstituting powders or granules or lyophilized preparations.

30 [0092] Suspensions of this invention may be provided at any concentration providing acceptable stability for the pharmaceutically active compounds (for example the length of the desired treatment period, optionally with refrigeration) and within the range that would provide a composition having suitable flow

parameters for dispensing systems of this invention. Reconstituting oral suspensions from an amoxicillin and clavulanate potassium powder composition may be done as follows from a powder prepared for oral suspension.

The suspension may be prepared from freely flowing powder in a suitable container. A little over half of the solvent such as water needed should be added and the container shaken vigorously to suspend. Then the rest of the solvent should be added and the container shaken vigorously.

[0093] The preferred active ingredients are amoxicillin and clavulanate potassium used together in the treatment regimen described, however other active ingredients may be used in the same type of composition of this invention. Further, the amoxicillin and clavulanate potassium may be present throughout the multiple day dosing method in a constant amount of about 21.5 mg/5 mL or less of clavulanate potassium to at least 600 mg/5 mL, or more of amoxicillin, in a ratio of at least about 28:1.

[0094] Any pharmaceutically acceptable formulation of the compositions of this invention including the amoxicillin and clavulanate potassium at a ratio of at least about 28:1 may be used in the dispensing systems of this invention. Such compositions may contain pharmaceutically acceptable ingredients whose nature and amounts will be known to a skilled practitioner depending on the dosage form and route of administration selected. Amoxicillin and clavulanate in any pharmaceutically acceptable form may be used in any combinations, including salts, complexes, prodrugs, hydrates, solvates, or polymorphs. Clavulanate potassium is preferred. Other pharmaceutically active ingredients may also be included in the compositions of this invention.

[0095] This invention is directed to a method of treatment by providing two or more doses of a composition containing amoxicillin and clavulanate potassium. A preferable condition to be treated is a bacterial infection, most preferably acute otitis media. Other conditions for treatment include respiratory bacteria illness such as sinusitis.

[0096] The patient or treatment subject may be a human such as a child, adult or elderly individual. Other patients may include non-humans such as

animals. Therefore the method would include a veterinary method to treat infections and bacteria in mammals, fish, birds and animals.

[0097] The amount of the compounds used in the inventive composition and method of treatment are amounts effective to treat the condition. More specific amounts have been discussed in detail above. The dosage will depend on the age, weight, condition, and disease of the patient. In general the compositions of this invention contain effective amounts for the treatment contemplated of the amoxicillin and clavulanate potassium. These amounts may be determined by a skilled person with routine experimentation.

[0098] The method of the claimed invention may include two or more doses of amoxicillin combined with clavulanate potassium where the dosing remains constant or the initial doses contain more or less clavulanate potassium than any subsequent doses. The clavulanate potassium amount may be constant throughout the dosage, with the amount being less than conventional dosages, such as less than about 21.5 mg/5 mL. In another embodiment, the initial dose may be a unit dose which contains more clavulanate potassium than the second dose which is a unit dose and any subsequent unit doses. The initial dosage may be more than one unit dose containing more clavulanate potassium than the second and subsequent unit dosages which also may include more than one unit dose. Similarly the first dose may be a unit dose and subsequent dosages include more than one unit dose. The first dosage may be more than one dose and second and/or subsequent doses may be unit doses. The distinction between the first and subsequent doses is an embodiment of this invention.

[0099] In a further embodiment of the inventive method, the treatment regimen may be over multiple days where the initial dosage amount of clavulanate potassium is about or less than about 21.5 mg/5 mL, the middle doses are a higher amount than the first while still being less than about 21.5 mg/5 mL, and the next subsequent doses are in an amount lower than the middle doses. For example, in a multiple day method spanning ten (10) days, the dosage of clavulanate potassium on days 1 and 2 may be in an amount of about

10-19 mg/5 mL, then an amount of about 20-21.5 mg/5 mL on days 3-6, and an amount of about 5-10 mg/5 mL on days 7-10.

[0100] The compositions of this invention and the methods of this invention may be used to provide various treatment regimens to patients as
5 methods of treatment of this invention. A method of treatment regimen of the present invention may be one day or multiple days, between about two days to about fourteen days, though it is preferred the dosing be for about three through about ten days. The dosage schedule below are given solely as examples, many others may readily be developed by a skilled practitioner based on known
10 methods and information provided herein. In these examples "day" is a twelve hour period.

[0101] For example a treatment period of about ten days providing amoxicillin and clavulanate potassium wherein the dosing remains constant of amoxicillin and clavulanate potassium where the clavulanate is in an amount
15 of about 21.5 mg/5 mL or less.

[0102] Another example of a treatment period of ten days may include the following dosing as follows:

Days 1-4: 600 mg/kg amoxicillin and 21.5 mg/kg clavulanate potassium;
20 and

Days 5-10: 600 mg/kg amoxicillin and 10.75mg/kg clavulanate potassium, should provide suitable dosages for a patient.

[0103] In another embodiment a treatment period of ten days providing
25 amoxicillin and clavulanate potassium wherein the dosing remains constant of amoxicillin and clavulanate potassium where the clavulanate potassium is present in an amount of about 21.5 mg/5 mL or less.

[0104] Another example of a treatment period of ten days may include the
30 following dosing as follows:

Days 1-2: 600 mg/kg amoxicillin and 21.5 mg/kg clavulanate potassium;
Days 3-5: 600 mg/kg amoxicillin and 10.75mg/kg clavulanate potassium;
and

Days 6-10: 600 mg/kg amoxicillin and 5.5 mg/kg clavulanate potassium,
5 should provide suitable dosages for a patient.

[0105] As can be seen this exemplary regimen can be modified for
different formulations, reduced or extended in length, and designed to provide
further clavulanate potassium gradients if desired, by varying the amounts and
10 concentrations of the compositions of this invention and selecting the appropriate
dispensing system of this invention. Other examples will be apparent to a skilled
practitioner and are part of this invention.

[0106] Preferably the amount of clavulanate potassium in subsequent
dosages is from about 0.1 mg/5 mL of suspension to about 21.5 mg/5 mL of
15 suspension. More preferably the amount of clavulanate potassium is from about
10 mg/5 mL of suspension to about 21.5 mg/5 mL of suspension.

[0107] In general, this invention provides methods of treatment as
discussed above for infections in a patient, of any part of the body including
specific cells, tissues, or organs. The infections may be acute or chronic and are
20 primarily bacterial such as *meningitis*, *peritonitis*, *Chlamydia pneumoniae*, *S.*
pneumoniae, *listeriosis*, *salmonellosis*, toxic shock syndrome, *tuberculosis*, and
other bacterial infections. Syndromes and conditions caused by bacterial
infections may also be treated, such as hemolytic uremic syndrome and Lyme
disease.

25 [0108] Bacterial infections for treatment with the compositions of this
infection include but are not limited to acute otitis media and other infections such
as those of the lower respiratory tract, sinusitis, skin and skin structure infections
and urinary tract infections. These can be caused by caused by various bacteria
both gram positive and gram negative. Among them are *staphylococcus aureus*,
30 *Enterobacter species* in urinary tract infections, *escherichia coli*, *H. influenzae*,
Moraxella catarrhalis, *S. pneumoniae*, *Neisseria gonorrhoeae*, *Eikenella*

corrodens, *Proteus mirabilis*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Streptococcus pyogenes*, *viridans group streptococcus*, *Klebsiella species* *Bacteroides species*, *Fusobacterium species*, and *Peptostreptococcus species*.

5 [0109] As discussed above there are various formulations and dispensing methods for compositions of this invention. The appropriate dosages may be determined as discussed above within the bounds of this invention regarding initial and subsequent doses with regard to the relative amounts of the amoxicillin and clavulanate potassium. Delivery methods include but are not limited to liquid
10 and oral suspensions. Dispensing systems include containers, syringes, spoons, straws and the like.

[0110] The inventive oral suspension composition containing the reduced amount of clavulanate potassium compared to conventional compositions should correspondingly reduce possible less common but severe side affects of jaundice
15 and hepatitis, hemorrhagic/pseudomembranous colitis, angioedema, Stevens-Johnson syndrome, hypersensitivity vasculitis, tooth discoloration, and seizure , as well as the more common and disruptive side effects of diarrhea, vomiting or diaper rash, headache, mycosis, vaginitis and agitation, all while still maintaining the efficacy and benefits of the antibiotic treatment for acute otitis media and
20 other illnesses. This should be seen whether the clavulanate potassium remains in a constant dosage throughout the about one to about fourteen day treatment regimen method, of less than about 21.5 mg/5 mL, or if the clavulanate potassium dosage is reduced through the respective about one day to about fourteen day dosage, being reduced either once, more than once or with each
25 subsequent unit dose.

[0111] The present invention thus is a composition having amoxicillin-clavulanate potassium of minimally sufficient quantity so as to maintain the efficacy of the composition in view of beta-lactamase mediated resistance *H. influenzae* and *M. catarrhalis*, without elevating the possibility of the severe
30 side effects of jaundice and hepatitis and the more common and disruptive side effects of diarrhea, diaper rash and vomiting. The composition allows the

amoxicillin to be used as intended while reducing the side effects of the clavulanate potassium while further still maintaining the efficacy of the overall composition when dealing with various beta-lactamase mediated resistance issues.

5 [0112] Further, the reduced dosage composition and treatment of the present invention may either be maintained throughout the treatment or further reduced throughout the treatments over subsequent days. Again, this reduced amount of clavulanate potassium in the total composition may be constant throughout the treatment regimen or preferably reduced throughout the treatment
10 regimen, with the amount being of minimal sufficient quantity so as to maintain the efficacy of the total composition in view of beta-lactamase mediated resistance *H. influenzae* and *M. catarrhalis*.

 [0113] Having generally described the invention, the same will be more
15 readily understood by reference to the following example, which is provided by way of illustration and are not intended as limiting.

Example

Formulations:

20 [0112] These formulations are provided as examples of possible oral suspension formulations of this invention. It will be apparent that these formulations and many variations of these formulations are available as compositions of this invention. Other types of formulations as discussed above such as aerosols, injectable solutions, capsules, topical formulations, and others
25 may be included among these examples.

Oral suspension (amounts in 5 mL)

200 mg Amoxicillin trihydrate and 3.36 mg (0.15mEq) sodium
250 mg Amoxicillin trihydrate and 3.39 mg (0.15 mEq) sodium
30 400 mg Amoxicillin trihydrate and 4.33 mg (0.19 mEq) sodium
20 mg clavulanate potassium
10 mg clavulanate potassium
5 mg clavulanate potassium

Oral suspension:

200, 250, 400 mg Amoxicillin trihydrate

20, 10, 5 mg clavulanate potassium

FD&C Red No 3

- 5 flavorings
silica gel
sodium benzoate
sodium citrate
sucrose
10 xanthan gum

These ingredients are sieved and milled separately and together, then blended and remilled, compacted by roller compaction, and screened with vibration to provide granules.

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[0112] The invention has been described in terms of embodiments thereof, but is more broadly applicable as will be understood by those skilled in the art. The scope of the invention is only limited by the following claims.

Claims

1. A composition comprising amoxicillin and clavulanate potassium wherein the clavulanate potassium is present in an amount equal to or less than about 21.5 mg/5 mL.
2. The composition of claim 1 wherein the amount of clavulanate potassium is present in an amount of about 5 mg/5 mL to about 21.5 mg/5 mL.
3. The composition of claim 2 wherein the amount of clavulanate potassium is present in an amount of about 10 mg/5 mL to about 21.5 mg/5 mL.
4. The composition of claim 1 wherein the composition is in the form of a liquid.
5. The composition of claim 4 wherein the liquid is chosen from the class of liquids including but not limited to suspensions, emulsions, solutions and colloids.
6. The composition of claim 5 wherein the composition is a pediatric oral liquid suspension.
7. The composition of claim 1 wherein the composition is a solid chosen from the class of solids including but not limited to tablets, capsules, and powders.
8. A composition comprising amoxicillin and clavulanate potassium in a ratio of at least about 28:1.
9. The composition of claim 8 wherein the ratio of amoxicillin and clavulanate potassium is between about 28:1 to about 56:1.
10. The composition of claim 9 wherein the ratio is about 35:1.
11. The composition of claim 8 wherein the amoxicillin is present in an amount of about 200 mg/5 mL to about 600mg/5 mL and the clavulanate potassium is present in an amount of about 0.1 mg/5 mL to about 21.5 mg/5 mL.
12. The composition of claim 8 wherein the composition is in the form of a liquid.
13. The composition of claim 12 wherein the liquid is chosen from the class of liquids including but not limited to suspensions, emulsions, solutions and colloids.

14. The composition of claim 8 wherein the composition is a solid chosen from the class of solids including but not limited to tablets, capsules, and powders.

5 15. A pediatric oral suspension comprising amoxicillin and clavulanate potassium wherein the amoxicillin is present in an amount of about 600 mg/5 mL and the clavulanate potassium is present in an amount of about 21.5 mg/5 mL, wherein the ratio of amoxicillin to clavulanate potassium is about 28:1.

10 16. The composition of claim 15 wherein the amoxicillin is present in an amount of about 90 mg/kg per pediatric patient and the clavulanate potassium is present in an amount of about 3.2 mg/kg.

17. A pharmaceutical product consisting of at least two different compositions of claim 1.

18. The pharmaceutical product of claim 16 containing at least two dosages.

15 19. The pharmaceutical product of claim 17 containing at least two different dosages.

20. The pharmaceutical product of claim 17 containing at least two different dosages of amoxicillin.

20 21. The pharmaceutical product of claim 17 containing at least two different dosages of clavulanate.

22. The pharmaceutical product of claim 17 containing at least two different dosages of amoxicillin and clavulanate.

23. The pharmaceutical product of claim 17 capable of dispensing dosages of these at least two different compositions.

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