et al, 2003). The combinations of two antibiotics have shown different effects on each other and in many cases the effect is synergistic or strengthening but, in some cases, antagonism is observed (Montero et al, 2004; Tripodi et al, 2007). Rifampicin (an antibiotic belonging to the rifamycin class antibiotic like rifabutin) targets the bacterial DNA-dependent RNA polymerase B subunit (rpoB) and is an antibiotic which is frequently used with other antibiotics. Rifampicin (also known as rifampin) has shown synergy with colistin towards *A. baumannii*, however, the result of this combination is dependent on the rifampin's MICs (Giannouli *et al*, 2012). In particular no synergistic effect of rifampicin and colistin was observed in *A. baumannii* isolates in which elevated rifampicin MICs were due to mutations in the rpoB target gene.

Summary

The ~~invention~~disclosure provides combination therapies that include rifabutin and a second antibiotic, such as a polymyxins (e.g. colistin, polymyxin B, polymyxin B nonapeptide; polymyxin analogues as exemplified by MRX-8,) other cationic antimicrobial peptides (e.g. SPR741; chimeric peptidomimetic antibiotics exemplified by POL7306; octapeptin cyclic peptides) or cefiderocol, for treating *A. baumannii* infections. The ~~invention~~disclosure is based on the finding that rifabutin acts synergistically with certain other antibiotics to inhibit growth of *A. baumannii* cells. The combinations of antibiotics display synergy to a wide range of *A. baumannii* strains. The synergy greatly increases the susceptibility of *A. baumannii* cells to rifabutin and colistin, with some strains displaying over a 500-fold increase in sensitivity to one of those antibiotics used in combination with the other compared to when that antibiotic is used by itself. Moreover, and unexpectedly, combinations of rifabutin and colistin act synergistically to inhibit growth of strains that are resistant to both of those antibiotics when they are provided individually and therefore making those strains susceptible to the combination treatment even when the elevated MICs to rifabutin and rifampicin are due to mutations in the rpoB gene. This observation is in stark contrast to that observed with the combination of rifampicin and colistin where the strains with mutations remain resistant to the combination. Thus, the ~~invention~~disclosure unlocks the therapeutic potential of antibiotics in settings in which they are otherwise impotent and provides effective therapies for treatment of serious *A. baumannii* infections.

In one aspect, the present disclosure provides a use of rifabutin and a second antibiotic selected from the group consisting of a polymyxin and cefiderocol in the manufacture of a medicament for combination therapy to treat an *A. baumannii* infection in a subject. In another aspect, the present disclosure provides a use of rifabutin in the manufacture of a first medicament and use of a second antibiotic selected from the group consisting of a polymyxin and cefiderocol in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an *A. baumannii* infection in a subject. In yet another aspect, the present disclosure provides a use of rifabutin in the manufacture of a medicament for use in combinatorial therapy for treating an *A. baumannii* infection in a subject, wherein said medicament is to be administered in combination with a second antibiotic selected from the group consisting of a polymyxin and cefiderocol.

In a further aspect, the present disclosure provides a combination therapy comprising rifabutin and a second antibiotic selected from the group consisting of a polymyxin and cefiderocol, wherein the combination therapy comprises rifabutin and the second antibiotic in a therapeutically effective amount to treat an *A. baumannii* infection in a subject.

In an ~~aspect~~example, the ~~invention~~disclosure provides methods of treating an *A. baumannii* infection in a subject by providing to a subject infected with *A. baumannii* rifabutin and a second antibiotic.

ciprofloxacin, colistin, doripenem, gentamicin, imipenem, levofloxacin, meropenem, penicillin, piperacillin, polymyxin B, rifabutin, rifampicin, tazobactam, and tigecycline.

In another ~~aspect~~example, the ~~invention~~disclosure provides combination therapies that include rifabutin and a second antibiotic in a therapeutically effective amount to treat an *A. baumannii* infection in a subject. The second antibiotic may be a polymyxin (e. g. colistin, polymyxin B, polymyxin B nonapeptide) or cefiderocol.

The subject may be infected with strain of *A. baumannii* that is resistant to one or more antibiotics, such as any of those described above.

Each antibiotic may be administered by a separate route of administration. Two or more of the antibiotics may be administered by the same route of administration. Each antibiotic may independently be administered intravenously, orally, parenterally, subcutaneously, by inhalation, by injection, and/or by infusion.

Each antibiotic may be administered in a separate formulation. Two or more of the antibiotics may be administered in a single formulation. The antibiotics may be administered according to the same dosing regimen, or two or more antibiotics may be administered according to different dosing regimens. The dosing regimen may include one or more of a dosage, dosage frequency, or interval between dosages.

The subject may be human or a class of humans, such as any of those described above.

The combination therapy may include providing, in a therapeutically effective amount, one or more additional antibiotics, such as any of those described above.

In another ~~aspect~~example, the ~~invention~~disclosure provides uses of combinations the include rifabutin and a second antibiotic for making one or more medicaments for treating an *A. baumannii* infection in a subject. The second antibiotic may be colistin or cefiderocol.

In ~~embodiment~~examples of the use, the subject may be infected with strain of *A. baumannii* that is resistant to one or more antibiotics, such as any of those described above.

In ~~embodiment~~examples of the use, each antibiotic is administered by a separate route of administration. In ~~embodiment~~examples of the use, two or more of the antibiotics are administered by the same route of administration. In ~~embodiment~~examples of the use, each antibiotic is independently be administered intravenously, orally, parenterally, subcutaneously, by inhalation, by injection, and/or by infusion.

In ~~embodiment~~examples of the use, each antibiotic is administered in a separate formulation. In ~~embodiment~~examples of the use, two or more of the antibiotics are administered in a single formulation. In ~~embodiment~~examples of the use, the antibiotics are administered according to the same dosing schedule. In ~~embodiment~~examples of the use, two or more of the antibiotics are administered according to different dosing schedules. The dosing schedule may include one or more of a dosage, dosage frequency, or interval between dosages.

In ~~embodiment~~examples of the use, the subject is a human or a member of a class of humans, such as any of those described above.

In ~~embodiment~~examples of the use, the combination includes one or more additional antibiotics, such as any of those described above.

Brief Description of the Drawings

FIG. 1 is an image of a 96-well plate checkerboard of *A. baumannii* cells cultured in various concentrations of rifabutin and colistin.

FIG. 2 is an image of a 96-well plate checkerboard of *A. baumannii* cells cultured in various concentrations of rifabutin and cefiderocol.

Detailed Description

The invention provides combination therapies for treating an *A. baumannii* infection in a subject. The combination therapies are based on the finding that rifabutin acts synergistically with antibiotics such as colistin and cefiderocol to inhibit growth of *A. baumannii* cells. Therefore, the use of rifabutin in combination with either colistin or cefiderocol is more effective than use of any of those antibiotics alone in treating *A. baumannii* infections. Moreover, and unexpectedly, the combination of rifabutin and colistin are even effective against *A. baumannii* strains that are resistant to both of the antibiotics when given individually but become susceptible to treatment when given in combination.

Combination therapies

The combination therapies of the invention include two antibiotics that act synergistically to inhibit growth of *A. baumannii* cells. Synergy between antibiotics, such as a rifabutin and colistin, may be determined by any suitable method. One method includes determining the

Claims

What is claimed is:

~~1. A method of treating an *A. baumannii* infection in a subject, the method comprising providing to a subject infected with *A. baumannii* rifabutin and a second antibiotic selected from the group consisting of colistin and cefiderocol.~~

~~2. The method of claim 1, wherein the subject is infected with a strain of *A. baumannii* that is resistant to rifabutin.~~

~~3. The method of claim 1, wherein the subject is infected with a strain of *A. baumannii* that is resistant to the second antibiotic.~~

~~4. The method of claim 1, wherein the second antibiotic is colistin.~~

~~5. The method of claim 1, wherein the second antibiotic is cefiderocol.~~

~~6. The method of claim 1, wherein the rifabutin is administered intravenously.~~

~~7. The method of claim 1, wherein the rifabutin is administered by inhalation.~~

~~8. The method of claim 1, wherein the rifabutin and the second antibiotic are provided in a single formulation.~~

~~9. The method of claim 1, wherein the rifabutin and the second antibiotic are provided separately.~~

~~10. The method of claim 1, wherein the *A. baumannii* comprises a rpoB mutation.~~

~~11. A combination therapy comprising rifabutin and a second antibiotic selected from the group consisting of colistin and cefiderocol, wherein the combination therapy comprises~~

~~rifabutin and the second antibiotic in a therapeutically effective amount to treat an *A. baumannii* infection in a subject.~~

~~12. The combination therapy of claim 11, wherein the subject is infected with a strain of *A. baumannii* that is resistant to rifabutin.~~

~~13. The combination therapy of claim 11, wherein the subject is infected with a strain of *A. baumannii* that is resistant to the second antibiotic.~~

~~14. The combination therapy of claim 11, wherein the second antibiotic is colistin.~~

~~15. The combination therapy of claim 11, wherein the second antibiotic is cefiderocol.~~

~~16. The combination therapy of claim 11, wherein the rifabutin is administered intravenously.~~

~~17. The combination therapy of claim 11, wherein the rifabutin is administered by inhalation.~~

~~18. The combination therapy of claim 11, wherein the rifabutin and the second antibiotic are provided in a single formulation.~~

~~19. The combination therapy of claim 11, wherein the rifabutin and the second antibiotic are provided separately.~~

~~20. The combination therapy of claim 11, wherein the *A. baumannii* comprises a rpoB mutation.~~

1. Use of rifabutin and a second antibiotic selected from the group consisting of a polymyxin and cefiderocol in the manufacture of a medicament for combination therapy to treat an *A. baumannii* infection in a subject.

2. Use of rifabutin in the manufacture of a first medicament and use of a second antibiotic selected from the group consisting of a polymyxin and cefiderocol in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an *A. baumannii* infection in a subject.

3. Use of rifabutin in the manufacture of a medicament for use in combinatorial therapy for treating an *A. baumannii* infection in a subject, wherein said medicament is to be administered in combination with a second antibiotic selected from the group consisting of a polymyxin and cefiderocol.

4. The use of any one of claims 1-3, wherein the polymyxin is a polymyxin derivative or analog.

5. The use of any one of claims 1-3, wherein the polymyxin is polymyxin B.

6. The use of any one of claims 1-3, wherein the polymyxin is colistin.

7. The use of any one of claims 1-3, wherein the second antibiotic is cefiderocol.

8. The use of any one of claims 1-3, wherein the rifabutin is to be administered intravenously.

9. The use of any one of claims 1-3, wherein the rifabutin is to be administered by inhalation.

10. The use of any one of claims 1-3, wherein the rifabutin is to be administered orally.

11. The use of any one of claims 1-3, wherein the rifabutin and the second antibiotic are to be provided in a single formulation.

12. The use of any one of claims 1-3, wherein the rifabutin and the second antibiotic are to be provided separately.

13. The use of any one of claims 1-3, wherein the *A. baumannii* comprises a rpoB mutation.

14. A combination therapy comprising rifabutin and a second antibiotic selected from the group consisting of a polymyxin and cefiderocol, wherein the combination therapy comprises rifabutin and the second antibiotic in a therapeutically effective amount to treat an *A. baumannii* infection in a subject.

15. The combination therapy of claim 14, wherein the subject is infected with a strain of *A. baumannii* that is resistant to rifabutin.

16. The combination therapy of claim 14, wherein the subject is infected with a strain of *A. baumannii* that is resistant to the second antibiotic.

17. The combination therapy of claim 14, wherein the polymyxin is a polymyxin derivative or analog.

18. The combination therapy of claim 14, wherein the second antibiotic is cefiderocol.

19. The combination therapy of claim 14, formulated for intravenous administration.

20. The combination therapy of claim 14, formulated for administration by inhalation.

21. The combination therapy of claim 14, formulated for oral administration.

22. The combination therapy of claim 14, wherein the rifabutin and the second antibiotic are to be provided in a single formulation.

23. The combination therapy of claim 14, wherein the rifabutin and the second antibiotic are to be provided separately.