Claims

1. A monoclonal antibody with high affinity for the target antigen suitable for reducing the duration and/or severity of diarrhoea, morbidity and/or mortality in a patient with *Clostridium difficile* infection or at risk of said infection wherein the antibody is specific to: antigen TcdA and binds 3 or more times thereto with an EC50 in the range 1 to 10 ng/ml when toxin is used at an LD60 or higher or a monoclonal antibody specific to antigen TcdB with affinity of 600pM~~, wherein the antibody has high affinity for the target antigen and is suitable for reducing the duration and/or severity of diarrhoea , morbidity and/or mortality in a patient with *Clostridium difficile* infection or at risk of said infection~~.
2. A monoclonal antibody according to claim 1, wherein the ~~antibody has high potency, for example an EC_{50} of 200ng/ml or less such as 150ng/ml or less, in particular 100ng/ml or less when toxin is used at an LD_{80} or higher~~anti-TcdA antibody binds 12 times.
3. A monoclonal antibody according to claim 2, wherein the antibody EC_{50} is between 0.1 and 10ng/ml when toxin is at an LD_{80} or higher.
4. A monoclonal antibody according to claim 2 or claim 3 wherein the maximal inhibition of toxin is between 50 and 100% when toxin is used at an LD_{80} or higher.
5. A monoclonal antibody according to any one of claims 1 to 4, wherein the antibody to TcdB binds the target antigen ~~multiple~~ 2 times.
6. A monoclonal antibody according to claim 5, wherein the antibody binds the target antigen 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 times or more.
7. A monoclonal antibody according to any one of claims 1 to 6, wherein the antibody is specific to TcdA.
8. A monoclonal antibody according to any one of claims 1 to 6, wherein the antibody is specific to TcdB.
9. A monoclonal antibody according to any one of claims 1 to 8, wherein the antibody has an affinity ~~of 1nM or less, for example 600pM, such as~~in the range 50 to 600pM.
10. A monoclonal antibody according to any one of claims 1 to 9, wherein the antibody is a neutralizing antibody including at high concentrations of toxin, in particular effective against ribotypes 003, 012, 027 and 078.
11. ~~A monoclonal antibody according to any one of claims 1 to 10, wherein the antibody has an EC_{50} in a TEER assay in the range of 60 to 80ng/ml when measured at 4h after initiation of the assay.~~

~~12.~~11. A monoclonal antibody according to claim 1 which specifically binds TcdA comprising a heavy chain wherein the variable domain of the heavy chain comprises at least one of a CDR having the sequence given in SEQ ID NO:44 for CDR-H1, a CDR having the sequence given in SEQ ID NO:45 for CDR-H2 and a CDR having the sequence given in SEQ ID NO:46 for CDR-H3.

~~13.~~12. A monoclonal antibody according to claim 1~~12~~ further comprising a light chain wherein the variable domain of the light chain comprises at least one of a CDR having the sequence given in SEQ ID NO:41 for CDR-L1, a CDR having the sequence given in in SEQ ID NO:42 for CDR-L2 and a CDR having the sequence given in SEQ ID NO:43 for CDR-L3.

~~14.~~13. A monoclonal antibody according to claim ~~13~~ 12 having a heavy chain comprising the sequence given in SEQ ID NO:49 and a light chain comprising the sequence given in SEQ ID NO:47.

~~15.~~14. A monoclonal antibody according to claim 1 which specifically binds TcdA comprising a heavy chain wherein the variable domain of the heavy chain comprises at least one of a CDR having the sequence given in SEQ ID NO:54 for CDR-H1, a CDR having the sequence given in SEQ ID NO:55 for CDR-H2 and a CDR having the sequence given in SEQ ID NO:56 for CDR-H3.

~~16.~~15. A monoclonal antibody according to claim 1~~45~~ further comprising a light chain wherein the variable domain of the light chain comprises at least one of a CDR having the sequence given in SEQ ID NO:51 for CDR-L1, a CDR having the sequence given in in SEQ ID NO:52 for CDR-L2 and a CDR having the sequence given in SEQ ID NO:53 for CDR-L3.

~~17.~~16. A monoclonal antibody according to claim 1~~56~~ having a heavy chain comprising the sequence given in SEQ ID NO:59 and a light chain comprising the sequence given in SEQ ID NO:57.

~~18.~~17. A monoclonal antibody according to claim 1 which specifically binds TcdB comprising a heavy chain wherein the variable domain of the heavy chain comprises at least one of a CDR having the sequence given in SEQ ID NO:124 for CDR-H1, a CDR having the sequence given in in SEQ ID NO:125 for CDR-H2 and a CDR having the sequence given in SEQ ID NO:126 for CDR-H3.

~~19.~~18. A monoclonal antibody according to claim 1~~78~~ further comprising a light chain wherein the variable domain of the light chain comprises at least one of a CDR having the sequence given in SEQ ID NO:121 for CDR-L1, a CDR having the sequence given in in SEQ ID NO:122 for CDR-L2 and a CDR having the sequence given in SEQ ID NO:123 for CDR-L3.

~~20.~~19. A monoclonal antibody according to claim 1~~89~~ having a heavy chain comprising the sequence given in SEQ ID NO:129 and a light chain comprising the sequence given in SEQ ID NO:127.

~~21.~~20. A monoclonal antibody according to claim 1 which specifically binds TcdB comprising a heavy chain wherein the variable domain of the heavy chain comprises at least one of a CDR having the sequence given in SEQ ID NO:154 for CDR-H1, a CDR having the sequence

given in in SEQ ID NO:155 for CDR-H2 and a CDR having the sequence given in SEQ ID NO:156 for CDR-H3.

~~22.~~21. A monoclonal antibody according to claim 20~~1~~ further comprising a light chain wherein the variable domain of the light chain comprises at least one of a CDR having the sequence given in SEQ ID NO:151 for CDR-L1, a CDR having the sequence given in in SEQ ID NO:152 for CDR-L2 and a CDR having the sequence given in SEQ ID NO:153 for CDR-L3.

~~23.~~22. A monoclonal antibody according to claim 22 having a heavy chain comprising the sequence given in SEQ ID NO:159 and a light chain comprising the sequence given in SEQ ID NO:157.

~~24.~~23. A monoclonal antibody according to claim 1 which specifically binds TcdA having a heavy chain and a light chain wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:19, SEQ ID NO:29 and SEQ ID NO:39 and the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:17, SEQ ID NO:27 and SEQ ID NO:37.

~~25.~~24. A monoclonal antibody according to claim 1 which specifically binds TcdB having a heavy chain and a light chain wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:79, SEQ ID NO:89, SEQ ID NO:99, SEQ ID NO:109, SEQ ID NO:119, SEQ ID NO:139, SEQ ID NO:149 and SEQ ID NO:159 and the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO:67, SEQ ID NO:77, SEQ ID NO:87, SEQ ID NO:97, SEQ ID NO:107, SEQ ID NO:117, SEQ ID NO:137, SEQ ID NO:147 and SEQ ID NO:157.

~~26.~~25. A pharmaceutical composition comprising one or more antibodies as defined in any one of claims 1 to 2~~45~~.

~~27.~~26. A pharmaceutical composition according to claim 25~~6~~, comprising two or more antibodies specific to TcdB.

~~28.~~27. A pharmaceutical composition according to claim 25~~6~~, comprising two or more antibodies specific to TcdA.

~~29.~~28. A pharmaceutical composition according to claim 25~~6~~, wherein at least one antibody in the composition is specific to TcdA and at least one antibody in the composition is specific to TcdB.

~~30.~~29. A pharmaceutical composition according to claim 28~~9~~, wherein the composition further comprises at least a second antibody specific to TcdB.

~~31.~~30. A pharmaceutical composition according to claims 2~~5~~6 to ~~30~~29, wherein the composition comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 distinct antibodies to the target antigen or antigens, such as 2, 3, 4, or 5 antibodies.

~~32.~~31. A pharmaceutical composition or mixture comprising the antibodies of claims 1~~3~~4, ~~20~~19 and 2~~2~~3.

32. A pharmaceutical composition according to any one of claims 2~~5~~6 to 3~~1~~2, which further comprises a pharmaceutically acceptable excipient.

33. Use of a monoclonal antibody with high affinity for the target antigen suitable for reducing the duration and/or severity of diarrhoea, morbidity and/or mortality in a patient with *Clostridium difficile* infection or at risk of said infection wherein the antibody is specific to: antigen TcdA and binds 3 or more times thereto with an EC50 in the range 1 to 10 ng/ml when toxin is used at an LD60 or higher, and/or

a monoclonal antibody specific to antigen TcdB with affinity of 600pM,

in the manufacture of a medicament for the treatment or prophylaxis of *C. difficile* infection or complications associated therewith.

34. Use according to claim 33, wherein the complication is diarrhea, colitis, bloating, abdominal pain and toxic mega colon.

35. Use according to claim 33 or 34, wherein the *C. difficile* infection is a secondary infections or re-infection.

~~33.~~36. Use according to any one of claims 33 to 35, wherein an antibody combination or a composition comprising at least one TcdA antibody, and two TcdB antibodies is employed.

~~34. A monoclonal antibody according to any one of claims 1 to 25 or pharmaceutical composition according to claims 26 to 33, for use in treatment, for example the treatment or prophylaxis of *Clostridium difficile* infection or complications therefrom.~~

~~35. A method of treating a patient with a *Clostridium difficile* infection or at risk therefrom comprising administering a therapeutically effective amount of a monoclonal antibody according to any one of claims 1 to 25 or a pharmaceutical composition according to any one of claims 26 to 33.~~

~~36. A method of treatment according to claim 35, wherein the treatment is employed in combination with a further treatment for *Clostridium difficile* treatment, for example selected from the group comprising metronidazole, vancomycin, clindamycin, fidaxomicin and combinations thereof.~~

~~37. Use of an antibody as defined in any one of claims 1 to 25 or a composition as defined in any one of claims 26 to 33, for the manufacture of a medicament for the treatment or prophylaxis of *Clostridium difficile* infect or complications therefrom.~~

38. A method of selecting an antibody as defined in any one of claims 1 to 11 using assays to measure protection against loss of TEER (trans-epithelial electrical resistance).

39. A method of selecting an antibody as defined in any one of claims 1 to 11 using assays to measure thermal stability (Tm) and resistance to shaking aggregation.

40. A method of selecting an antibody mixture for the treatment of *Clostridium difficile* infections by combining measurements of toxin neutralization, TEER measurements, thermostability measurements (Tm), shaking aggregation measurements and isoelectric point (pI) suitable for coformulation.

41. A monoclonal antibody according to any one of claims 1 to 26 combined with toxoid or pharmaceutical composition comprising same, for example for use in vaccination, such as the treatment or prophylaxis of *Clostridium difficile* infection or complications therefrom.