Study Protocol

2017 Global survey on nebulization of antimicrobial agents in mechanically ventilated patients—SANEME 2 study protocol

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Abstract: Antimicrobial agents are increasingly administered by aerosol for therapy of respiratory infections in mechanically ventilated (MV) patients. A prior survey was undertaken to reveal how they are used worldwide, in December 2014. Respondents from 192 intensive care units (ICUs) completed a structured online questionnaire, consisting of questions regarding aerosol antimicrobials patterns (in the prior week) and indications, as well as antimicrobial dosage for MV adults. We plan a follow up a new survey in 2017, with more significant representation of ICUs in key regional areas. It is expected to have information: (I) on the most common indications for nebulization; (II) the most commonly aerosolized antibiotics and daily doses prescribed for VAP and VAT; (III) changes in prescription patterns. This global survey will provide regional information on current practices, particularly indications, dosing and antibiotic combinations to improve clinical outcomes. The 2017 study protocol is reported herein.

Keywords: Dosage; pulmonary infections; aerosolized antibiotics; ventilator-associated pneumonia (VAP); hospital-associated pneumonia; colistin; amikacin

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Background

Infections are inextricably linked with critical illness, with pulmonary infections the most common form of infection. Whilst parenteral administration of antimicrobials remains the standard treatment for pulmonary infections in mechanically ventilated (MV) patients, nebulization of antimicrobials has become an increasingly reported therapy (1).

The clinical outcome data confirming the advantages of nebulization of antimicrobial therapy in MV patients over systemic therapy, or as adjunctive therapy, remains sparse (2,3). However, the pharmacokinetic and mechanistic data supportive of the concept is logical even though there are few antimicrobial formulations that have been optimized for nebulization (4,5). Boisson *et al.* (5) reported that both CMS and colistin ELF concentrations were much higher (100 to 1,000-fold in average) after CMS aerosol delivery using a vibrate mesh nebulizer than after i.v. administration. Moreover, limited systemic absorption in patients suggests limited systemic toxicity after aerosol delivery. Antimicrobials including colistin, tobramycin, gentamicin, amikacin have numerous clinical reports published for various indications (6-9), including ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP).

For these reasons, it is thought that nebulization of antimicrobials may be relatively commonly used clinically. Approval has been obtained from regulatory agencies for aerosol administration of colistin, aztreonam and aminoglycosides in patients with cystic fibrosis or bronchiectasis. The lack of patient outcome data is also associated with a lack of guidelines for best practice for antimicrobial nebulization (10-12) raising questions of which drugs critical care clinicians are nebulizing and which

doses are used? Indeed there is little large-scale international data to address this question and whether critical care clinicians use different doses for clinical scenarios. Indeed, evidence of efficacy and safety is MV patients is weak or even absent for some scenarios (13). With this background and due to imbalances in representation of some key countries in a prior survey, we developed the international Survey of Antimicrobial NEbulization in MEchanically ventilated patients (SANEME) 2. Results of antimicrobial prescription and use of aerosol devices has been reported elsewhere (14,15).

The main objectives of SANEME 2 are to assess the indications, antimicrobial agents and dosages of nebulized agents used in current practice. A secondary objective was to identify whether geographical location significantly influence practice. Our hypothesis was that use in VAP is different than in VAT.

Study population

The survey will be performed from the 1st of February 2017 to the 31st of May 2017, using an electronic platform (SurveyMonkey®). The survey will be distributed by invitation by members of the Steering Committee. The survey will be an online and anonymous questionnaire requiring no specific data of patients and no informed consent is required.

In order to develop a more realistic understanding of clinical practice, we encouraged all clinicians that care for critically ill patients to participate, regardless of their training. Children and neonatal intensive care units (ICUs) are excluded. It is requested that only one professional per unit complete the questionnaire, to have consistency and to avoid data multiplication.

Questionnaire

The survey will compile data on key aspects of the prescription of nebulized drugs, particularly the indications for which they are used, the antimicrobial agents administered and their dosage. Regarding dosing regimens, the questionnaire will propose doses of colistin, tobramycin and amikacin for the treatment of VAP and VAT. A quality assessment will be done by the project manager.

Statistical analysis

Responses will be analyzed by using descriptive statistics, reporting proportions (percentages). Chi-Square test will be performed to evaluate a potential association between the geographical location of the participants and the particularities of the prescription of nebulized agents, such as their indications or the criteria for initiation of the therapy (16). A P value less than 0.05 was considered statistically significant.

Outcomes

Details of the survey are summarized in Appendix. Access to the survey can be done using the link: https://es.surveymonkey.com/r/NF5JVRL.

In order to evaluate the presence of different practices according to geographical location and health care system, we will do different analyses for specific regions. Specific data collected regarding the experience on practical aspects of the delivery and the occurrence of adverse events are out of the scope of this manuscript.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Appendix

Questionnaire

Contact details

1. Name of the person answering the questionnaire:
2. E-mail:
3. Name of the unit:
4. Name of the hospital:
5. City/town:
6. State/province:
7. Country:

1. Do you belong to any of these organizations?
   A. CIBERES;
   B. ESCMID;
   C. ESCIM;
   D. ERS;
   E. ATS/IDSA;
   F. Other (please specify):
2. What is your ICU's specialty?
   A. Trauma;
   B. Cardiac surgery;
   C. Pulmonary;
   D. Medical-surgical;
   E. Neurological & neurosurgical.
3. Does it include transplant patients?
   A. Yes;
   B. No.
4. How many beds are there in your unit?
5. How many years have you been in clinical practice?
6. What is your primary specialty?
   A. ID/microbiology;
   B. Critical care anesthesiology;
   C. Medical/pulmonary;
   D. Respiratory physiotherapist;
   E. Surgical;
   F. Nurse/HCW pharmacy;
   G. Other (please specify):
7. During the last month, how many days was ventilation provided at your unit? (total amount of ventilation days amongst all patients)
8. And how many patients were mechanically ventilated patients?
9. How long has the nebulization of antibiotics been a current practice at your unit? (in years)
10. How long (in days) do you treat with aerosolized antibiotics?
11. How many patients received nebulization of the following antibiotics during the last month?
    A. Colistin base:
    B. Colistimethate sodium:
    C. Amikacin:
    D. Gentamicin:
    E. Carbapenems:
    F. Macrolides:
    G. Polymyxin B:
    H. Netilmycin:
    I. Aztreonam:
    J. Amphotericin B (treatment):
    K. Amphotericin B (prophylaxis):
    L. Tobramycin:
    M. B-lactams:
    N. Ribavirin:
    O. Pentamidine:
       a) 0;
       b) 1;
       c) 2–5;
       d) >5.
12. During the last month, have you observed any of the following adverse events related to antibiotic nebulization?
    A. Moderate decrease in O_2 saturation;
    B. Severe decrease in O_2 saturation (SpO_2 <90%);
    C. Hypoxemia (<10% reduction from baseline);
    D. Moderate increase in peak inspiratory pressure;
    E. Severe increase in peak inspiratory pressure;
    F. Expiratory filter occlusion;
    G. Cough;
    H. Bronchospasm;
    I. Supraventricular arrhythmia;
    J. Ventricular arrhythmia;
    K. Cardiac arrest;
    L. Nephrotoxicity;
    M. Neurotoxicity;
    N. Anaphylaxis;
    O. Other systemic toxicity (please specify):
13. As a consequence:
    A. Sedation was increased;
    B. Cardiac arrest;
    C. Nebulization was stopped;
    D. Added bronchodilators;
    E. Other (please specify):
14. If you observe one of the following respiratory complications cited above, how do you usually solve it?

A. Stop the nebulization;
B. Dilute the next administration;
C. Reduce the dose in the next administration;
D. Administer bronchodilators prior to the next administration;
E. Change the expiratory filter.

15. If you do NOT use nebulized antibiotics, this is due to:
A. Lack of appropriate material/resources;
B. Lack of personal experience in their administration;
C. Weak recommendations;
D. Poor evidence;
E. Lack of clinical guidelines;
F. Risk of adverse events;
G. Fear they will increase resistance;
H. Other (please specify):

16. What type of nebulizer do you use?
A. Ultrasonic nebulizer;
B. Jet nebulizer;
C. Vibrating-mesh nebulizer;
D. Other (please specify):

17. If you use the jet nebulizer, do you use it with
A. An external gas source;
B. Is ventilator-integrated.

18. If you place a filter on the expiratory limb, how frequently do you change it?
A. After every nebulization;
B. Every day;
C. Twice a week;
D. Once a week.

19. When prescribing nebulized antibiotics, do you:
A. Change characteristics of the ventilator breath;
B. Increase PEEP;
C. Decrease inspiratory flow;
D. Use a constant inspiratory flow;
E. Increase inspiratory time;
F. Insert an end-inspiratory pause;
G. Increase tidal volume;
H. Stop the active humidifier;
I. Place a filter on the expiratory limb;
J. Use sedation to avoid discoordination with the ventilator;
K. Use continuous flow or breath actuation.

20. In your daily practice, do you prescribe nebulized antibiotics for the following indications?
A. Treatment for ventilator-associated pneumonia (VAP);
B. Treatment for ventilator-associated tracheobronchitis (VAT);
C. Prevention for ventilator-associated respiratory infection;
D. Only for ventilator-associated infections due to multidrug-resistant pathogens (MDR);
E. Respiratory tract colonization by multidrug-resistant pathogens (MDR);
F. Treatment of viral infections (nebulized antivirals);
G. Prevention of invasive aspergillosis (nebulized antifungals);
H. Treatment of invasive aspergillosis (nebulized antifungals).

21. What criteria do you use to start the nebulization?
A. Prophylaxis in non-immunocompromised patients;
B. Prophylaxis in immunosuppressed patients;
C. Empirically: increase in secretions;
D. Empirically: fever or leukocytosis;
E. Empirically: decrease in PaO_2/FiO_2 ratio;
F. Empirically: CXR infiltrates;
G. Positive microbiological cultures of respiratory samples;
H. Positive microbiological cultures of respiratory samples that evidence multidrug-resistant organisms.

22. In particular, for patients with ventilator-associated tracheobronchitis (VAT), do you use nebulized antibiotics?
A. I treat VAT only with nebulized antibiotics;
B. I use them as adjunctive therapy to intravenous antibiotics;
C. I use them as adjunctive therapy to intravenous antibiotics only if a MDR is involved I do not use nebulized antibiotics for VAT;
D. I do not believe VAT should be treated.

23. In case of a patient with severe ARDS under NO treatment, would you administer nebulized antibiotics?
A. Yes;
B. No.

24. In case of a patient with severe ARDS with need of veno-venous ECMO support, would you administer nebulized antibiotics?
A. Yes;
B. No.

25. In your current practice, do you have experience nebulizing
A. Colistin base;
B. Colistimethate sodium Polymyxin B;
C. Tobramycin;
D. Amikacin;
E. Gentamicin;
F. Netilmicin;
G. Vancomycin;

H. B-lactams;
I. Carbapenems;
J. Macrolides;
K. Aztreonam;
L. Ribavirin;
M. Pentamidine;
N. Amphotericin B (prophylaxis);
O. Amphotericin B (treatment);
P. Other (please specify):

26. When prescribing nebulized COLISTIMETHATE SODIUM for VAP, what dose do you prefer? (MIU = Million International Units). Please note that 1 MIU of colistimethate sodium is equivalent to approx. 30 mg of colistin base.
A. 1 MIU/8 h;
B. 2 MIU/8 h;
C. 2 MIU/12 h;
D. 3 MIU/8 h;
E. 5 MIU/12 h;
F. 5 MIU/8 h;
G. Other (please specify):

27. When prescribing nebulized COLISTIMETHATE SODIUM for VAT, what dose do you prefer? (MIU = Million International Units). Please note that 1 MIU of colistimethate sodium is equivalent to approx. 30 mg of colistin base.
A. 1 MIU/8 h;
B. 2 MIU/8 h;
C. 2 MIU/12 h;
D. 3 MIU/8 h;
E. 5 MIU/12 h;
F. 5 MIU/8 h;
G. Other (please specify):

28. When prescribing nebulized TOBRAMYCIN for VAP, what dose do you prefer?
A. 150 mg/12 h;
B. 300 mg/24 h;
C. 300 mg/12 h;
D. Other (please specify):

29. When prescribing nebulized TOBRAMYCIN for VAT, what dose do you prefer?
A. 150 mg/12 h;
B. 300 mg/24 h;
C. 300 mg/12 h;
D. Other (please specify):

30. When prescribing nebulized AMIKACIN for VAP, what dose do you prefer?
A. 15 mg/kg/24 h;
B. 15 mg/kg/12 h;
C. 20 mg/kg/24 h;
D. 20 mg/kg/12 h;
E. Other (please specify):

31. When prescribing nebulized AMIKACIN for VAT, what dose do you prefer?
A. 15 mg/kg/24 h;
B. 15 mg/kg/12 h;
C. 20 mg/kg/24 h;
D. 20 mg/kg/12 h;
E. Other (please specify):

32. Do you have a specific protocol directing the use of aerosolized antibiotics in your ICU?
A. Yes;
B. No.

33. Do you use bronchodilators before nebulizing antibiotics?
A. Always;
B. Sometimes;
C. Never.

34. Please indicate which formulations are available at your unit:
A. Aztreonam;
B. Aminoglycosides;
C. Colistin;
D. Amphotericin;
E. Other (please specify):

35. Do you use intravenous formulations to administer aerosolized antibiotics?
A. Yes;
B. No.

36. What do you use for dilution?
A. Saline;
B. Sterile water;
C. Specific formulation;
D. I'm not sure.

37. What level of PEEP do you use?
A. Zero PEEP;
B. PEEP 1–5;
C. PEEP 6–10;
D. PEEP >10.

38. Do you exclude patients with
A. PaFi >300;
B. FaFi <200;
C. PaFi <100;
D. No exclusion.

39. Do you use any of the following:
A. Pressure control;
B. Pressure support;

C. Volume control;
D. SIMV;
E. High frequency;
F. Other (please specify):

40. Are you familiar with the SANEME reports?
A. Yes, in CMI;
B. Yes, in Resp Care;
C. Yes, in both CMI and Resp Care;
D. No.

41. Do you agree with the 2015 ATS/IDSA guideline recommendations for aerosolized antibiotics?
A. Yes;
B. Partially;
C. No.

42. Do you believe that the evidence to support their use in VAP-HAP is:
A. Very weak;
B. Weak;
C. Strong;
D. Very strong.

43. In VAT:
A. Very weak;
B. Weak;
C. Strong;
D. Very strong.

44. Have you participated in RCTs investigating this issue?
A. Yes;
B. No.

45. Do you think that more RCTs are required before implementing their use?
A. Yes;
B. No.

46. Do you ask for informed consent?
A. Yes;
B. No.

47. Which is your primary objective when administering nebulized antibiotics?
A. Survival;
B. MV days;
C. Adverse event;
D. CPIS score;
E. Emergence of resistance;
F. Hypoxemia resolution;
G. Other (please specify):