

# Inhalational antibacterial regimens in non-cystic fibrosis patients

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## Inhalational antibacterials: two approaches

1. For acute treatment of pneumonia (usually for HABP/VABP) aerosol therapy is administered as adjunctive antibacterial therapy to improve the cure rate.
2. For long term suppressive therapy of chronic airway infection in non-CF lung conditions [bronchiectasis, COPD] aerosol therapy is usually administered as antibacterial monotherapy to improve (slow) the rate of deterioration.

Both of these approaches are (a) relatively new and (b) require superiority trials. Several different appropriate primary end points could be supported.

## 1: Adjunctive inhalation therapy for HABP/VABP

- The unmet need remains unquestionably high. Morbidity and mortality is significant in HABP/VABP, even when antibacterial therapy is active.
  - Both drug-susceptible and -resistant, Gram-positive and -negative bacteria contribute to the high mortality and failure rate.
- Adjunctive inhalation therapy could improve outcomes
  - Concentration at the site of infection many fold (>100x) beyond the levels achieved through systemic dosing. There is minimal systemic exposure
  - Improving technology more effectively delivers drug to infection site.
- Aerosol delivery is adjunctive to systemic SOC.<sup>1</sup>
  - Bacteremia and ex-pulmonary spread is addressed by the SOC treatments.

## A mortality end point is not feasible in superiority trials of adjunct inhalation agents.

### Trial assumptions:

- 20% all cause mortality, some of which is attributable to the infection
- non-bacterial mortality independent from treatment effect
- study statistics alpha = 0.05; power = 80%, 2 sided

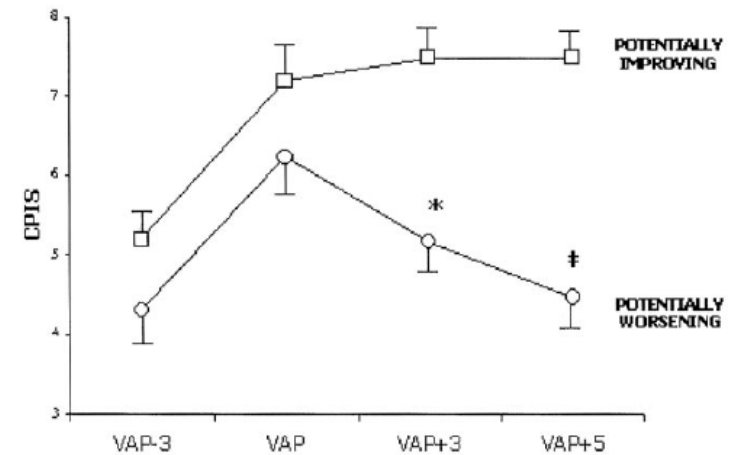
| Scenario                 | Case 1                                | Case 2                                | Case 3                                | Case 4                               |
|--------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|
| Scenario                 | High attributable<br>High drug effect | High attributable<br>Good drug effect | Med. attributable<br>Good drug effect | Low attributable<br>Good drug effect |
| Attributable mortality   | 50% of total                          | 50% of total                          | 33% of total                          | 15% of total                         |
| Treatment effect         | 50% reduction<br>(0.5)                | 25% reduction<br>(0.25)               | 25% reduction<br>(0.25)               | 25% reduction                        |
| Overall mortality        | 20% and 15%<br>(0.75)                 | 20% and 17.5%                         | 20% and 18.3%                         | 20% and 19.3%                        |
| <b>Patients required</b> | <b>1,800</b>                          | <b>7,250</b>                          | <b>16,800</b>                         | <b>100,000</b>                       |

## Rationale for alternative end points for HABP/VABP

- These adjunctive inhalation trials are for superiority. It is reasonable to consider several end points since the most appropriate have not been validated. Superiority trials are self-validating, since they show that (a) drug x is superior, and that (b) the trial design allowed for measuring the difference.
- The early clinical response and/or the overall cure rate could improve in inhalational trials for HABP/VABP.
- The best evaluation may be a composite that utilizes both early evaluations and later clinical cure outcome.
- Early evaluations are relevant and can be studied:
  - There are many early measurable factors (cough, chest pain, temperature, white cell count, tracheal secretions, oxygenation, bacterial culture) that change early in response to the infection<sup>1</sup>. The CPIS index [next slide] uses some of these data.

## Example of early clinical measures: Clinical pulmonary infection score (CPIS)

| Parameter                          | Value                          | Points |
|------------------------------------|--------------------------------|--------|
| Temperature                        | $\geq 36.5$ and $\leq 38.4$    | 0      |
|                                    | $\geq 38.5$ and $\leq 38.9$    | 1      |
|                                    | $\geq 39.0$ or $\leq 36.5$     | 2      |
| Leukocytes                         | $\geq 4,000$ and $\leq 11,000$ | 0      |
|                                    | $< 4,000$ or $> 11,000$        | 1      |
| Tracheal secretions                | Few                            | 0      |
|                                    | Moderate                       | 1      |
|                                    | Large                          | 2      |
|                                    | Purulent                       | +1     |
| PaO <sub>2</sub> /FiO <sub>2</sub> | $> 240$ , ARDS                 | 0      |
|                                    | $\leq 240$ and no ARDS         | 2      |
| Chest radiograph                   | None                           | 0      |
|                                    | Diffuse or patchy infiltrate   | 1      |
|                                    | Localized infiltrate           | 2      |

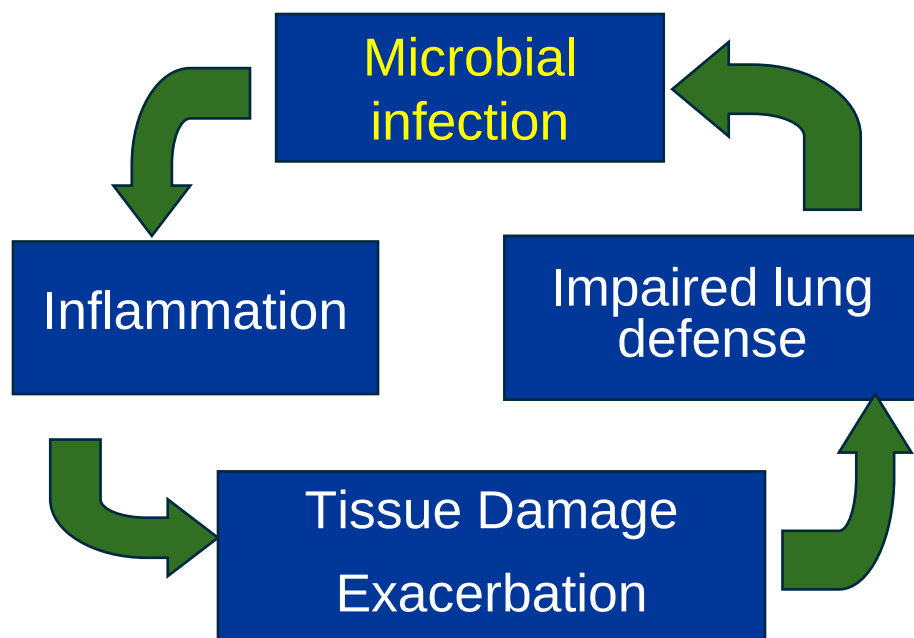


CPIS index in 32 improving and 31 worsening patients. This result was correlated to adequate antimicrobial therapy<sup>1</sup>. P/F ratio was most differential. But CPIS shows great variability between observers.

The CPIS is an example of an index criteria that could improve in response to the efficacy of treatment. Some CPIS factors are not specific to the pulmonary disease. The FNIIH has recommended four factors as an early evaluation of CABP: cough, chest pain, sputum, and dyspnea. Superiority inhalation trials offer the potential to correlate early criteria to later clinical outcome.

. 1. Luna et al. Crit Care Med. 2003, 31:676-82.

## 2: Chronic Inhalation treatment of chronic non-CF lung conditions: A cyclic pathobiology driven by bacterial infection.



- Superiority trials in Bronchiectasis and COPD
- Three types of patients:
  - Those with daily signs & symptoms
  - Those who suffer frequent exacerbations
  - Those who have both daily signs & symptoms and suffer frequent exacerbations.
- Trials have to carefully define patient type and appropriate end points.

## There is significant unmet need in chronic non-CF lung conditions

- Example: Bronchiectasis (BE) is an orphan drug disease in the USA, with an estimated 110,000 patients receiving treatment\*.
- Clinically, patients present with many negative signs
  - Productive cough, large volume of mucopurulent sputum, hemoptysis, pleuritic chest pain, dyspnea, wheezing and fatigue).
  - Frequent acute exacerbations of airway symptomatology are common, requiring hospitalization, increases in antibacterial and other therapies.
- Patient burden is extensive, with multiple rounds of daily medications and procedures similar to that of a CF patient.
- No approved chronic inhalation antibacterial drugs for BE. This necessitates placebo-controlled superiority trials.

## Rationale for improvement of outcomes in non-CF patients using long term inhalation therapy

- Inhalation therapy has shown in short term studies to produce high lung concentrations and to disrupt bacterial colonization. This has not yet been correlated to clinical benefit.
- The hypothesis for clinical benefit is based on long term reduction of bacterial burden.
  - Lowering bacterial burden should reduce chronic inflammation and resulting tissue damage.
  - Reduction in exacerbations, and improvement in signs & symptoms should result.
  - Drug holidays (on/off cycle) from inhalation therapy should reduce selection of resistance
- Inhalation therapy can best accomplish the disruption of bacterial colonization while minimizing systemic toxicity.

## Long term antibacterial inhalation treatment of chronic non-CF lung conditions: End Points

- Multiple primary end points are possible. The most relevant are based on the patient population (and COPD  $\neq$  BE):
  - Exacerbations: Frequency of exacerbations, and time to 1<sup>st</sup> event have both been proposed. Clear definitions and harmonization needed.
  - Signs & symptoms: Patient reported outcomes have gained acceptance (EXACT-PRO, etc). Validation needed for each indication.
- Both exacerbations and PROs are currently proposed as primary end points by different Sponsors for BE. Improvement in either of these would benefit the patient.
- The most appropriate end point in these settings depends on the patient population and drug therapy. PRO for daily signs and symptoms, and exacerbations for clinical end point.

*Measure what is measurable, and make measurable what is not so.* Galileo Galilei (1564–1642)

## Long term treatment of chronic non-CF lung conditions: one final issue - selection of resistance

- An “on-off” cycle (example 28/28 days on/off therapy) of chronic aerosol therapy is typically used.
  - This is directly traced to the original trials of Tobramycin in CF.
  - Rationale for on/off is based on reducing probability of selection of resistant clones (or suppression of resistant clones) during the off cycle.
  - But “resistance” as defined by EUCAST is likely different in aerosol-treated patient and systemically-treated patient.
- Clinical trials of chronic aerosol therapy show little/no selection of resistance. Tobramycin, aztreonam, amikacin, ciprofloxacin, and levofloxacin aerosol trials all show little/no increase in MIC.
- Resistance will remain part of the risk-benefit, but the rationale of the on/off cycle has not been tested.

## Inhalational antibacterial regimens in non-cystic fibrosis patients

- As adjunctive therapy for HABP/VABP: Early pulmonary evaluations along with later clinical evaluations offer the best potential to capture the positive effect of inhalation-based therapies in superiority trials. There is an opportunity to correlate early measures to later clinical outcomes in these superiority trials. Improvement in early and later measures are important.
- As chronic suppressive therapy for bronchiectasis, COPD: Both exacerbations (clinical type evaluations) and PROs have been proposed as primary end points. Both of these end points are of value to the patient; the most appropriate evaluation depends on the patient population and expected benefit. Bronchiectasis and COPD patients are different; each patient population will require end point validation.