Intravenous versus oral antibiotics for eradication of *Pseudomonas aeruginosa* in cystic fibrosis (TORPEDO-CF): a randomized controlled trial[1]

Background[1]:

Cystic Fibrosis is a multisystem autosomal recessive disorder that affects over 30,000 Americans[2]. Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein leads to poor mucous clearance and retention of secretions in the lung. This dysregulation can lead to infections and exacerbations. Among the potential bacterial causes of infection, *Pseudomonas aeruginosa* has proven to lead to lung function decline and increased mortality amongst patients with cystic fibrosis[3]. To improve patient outcomes, it is recommended to start treatment directed at *Pseudomonas aeruginosa* eradication when infection is diagnosed.

Currently, guidelines suggest the use of inhaled tobramycin first-line for the eradication of *Pseudomonas aeruginosa* in this population[4]. Additionally, practitioners may use intravenous medications active against *Pseudomonas aeruginosa* in an attempted to achieve a higher rate of eradication. The data supporting this practice does not have substantial evidence from randomized controlled trials. The use of intravenous medications comes with potential disadvantages of increased expense, increased length of hospitalization, and potential for adverse effects associated with the medication. Due to this, providers should only use intravenous medications when clinically necessary. This trial sought to evaluate the extent of eradication of *Pseudomonas aeruginosa* using intravenous versus oral antibiotics in patients with cystic fibrosis.

Trial Design:

This trial was a multicenter, parallel group, open-label, randomized controlled trial utilizing 72 cystic fibrosis centers in Europe (70 in the UK and two in Italy). Researchers used a web-based randomization technique to assign patients to either 14 days of intravenous ceftazidime and tobramycin or 12 weeks of oral ciprofloxacin. Both treatment arms received 12 weeks of inhaled colistimethate sodium, a standard of therapy in the United Kingdom. The trial started October 5, 2010 when researchers recruited the first patient and ended April 10, 2018 after the last follow-up visit. The protocol defined the follow-up period as 15 months following treatment allocation. Patients were able to receive their intravenous medications at home, if applicable.

Inclusion Criteria:

- Older than 28 days old
- Confirmed diagnosis of cystic fibrosis
- Must have isolate of *Pseudomonas aeruginosa*
- *Pseudomonas* naïve or must have been *Pseudomonas* free (infection free for at least 1 year)

Exclusion Criteria:

- *Pseudomonas aeruginosa* resistant to one of the treatment antibiotics
- Contraindication to one of the treatment antibiotics
- Already receiving *Pseudomonas aeruginosa* suppressive therapy
- Received *Pseudomonas aeruginosa* eradication therapy in last 9 months
- Pregnant or breast feeding

Primary Outcome:

The primary outcome was the eradication of *Pseudomonas aeruginosa* from respiratory samples at 3 months from the beginning of treatment and remaining free of infection to 15 months.

Secondary Outcomes:

Secondary outcomes include forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), forced expiratory flow in mid expiration (FEF_{25-75}), oxygen saturation, height, weight, body-mass index (BMI), number of pulmonary exacerbations, number of hospital admissions, number of days spent as an inpatient, caregiver or patient burden. Caregivers and participants described their quality of life using health-related quality of life instruments (CFQ-R and EQ-5D-3L).

Safety Outcomes:

Adverse events assessed at each visit and until 28 days after the completion of treatment. Throughout the trial, the principal investigator assessed the relationship between the adverse events and the trial treatment.

Economic Impact:

The net monetary benefit of changing to oral therapy rather than intravenous therapy was investigated by subtracting the change in cost from the change in quality-adjusted life year.

Results:

Total patients assessed for eligibility = 1308 (1022 excluded, 286 randomized)

- 137 patients allocated to intravenous antibiotic therapy
- 149 allocated to oral antibiotic therapy

Baseline Characteristics:

- No significant different in patient baseline characteristics
- There was a higher, but not significant, number of infant and toddlers (28 days to 23 months) in the intravenous group
- Only 5% (15 patients) of the population were adults (18 years or older)

Primary Outcome:

- Eradication achieved and sustained by 55 (44%) of 125 patients in intravenous group and 68 (52%) of patients in the oral group
- This was not a statistically significant difference in successful eradication
- Fives sensitivity analyses were conducted post-hoc and confirmed the conclusion of the primary analysis

Secondary Outcomes:

- The percentage of predicted FVC was significantly higher in the intravenous antibiotic therapy group (p=0.04)
- The BMI was significantly higher in the oral antibiotic therapy group (p=0.029)
- No significant difference in other secondary endpoints including quality of life

Safety Outcomes:

- No significant difference in non-serious or serious adverse events in the trial groups
- Most common adverse event from therapy was cough, upper respiratory tract infection and productive cough

Economic Impact:

- The cost of oral therapy was consistently less than that of intravenous therapy during this trial
- Oral therapy was consistently more cost effective than intravenous therapy during this trial

Strengths

- Large sample size
- Use of standard of therapy
- Length of follow up
- Multicenter, randomized

Limitations:

- Small population of adults
- Preference for oral therapy by participants
- Low rate of consent from eligible patients

Authors' Discussion/Conclusion:

When comparing intravenous therapy versus oral therapy for eradication of *Pseudomonas aeruginosa*, the intravenous antibiotics did not achieve a greater proportion of sustained eradication for patients with cystic fibrosis. Furthermore, the cost of intravenous antibiotics is higher than that of oral therapy. This study does not confirm an advantage of intravenous therapy over oral therapy in the eradication of *Pseudomonas aeruginosa* in patients with cystic fibrosis.

Clinical Takeaways:

- In patients who are capable of being treated at home rather than requiring hospitalization, oral therapy is likely a better option rather than trying to send the patient home with a home infusion.
- This study lacks involvement from a substantial number of adults and many patients refused intravenous therapy. It is possible that if there were more adults in the study, they may have been more accepting of intravenous therapy and the quality of life questionnaire results may have been different.
- Because this trial was in Europe, the healthcare model will be different from that of the United States. Many patients who experience an exacerbation require hospitalization even if they can tolerate oral medications. Intravenous therapy may be required for their insurance to cover the hospital stay and would drastically change the cost of therapy.
- The trial did not discuss therapeutic drug monitoring, so it may be possible that some of the intravenous therapy group received suboptimal treatment.

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