AABIP JOURNAL CLUB

SLIM it down: Short vs Long Course of Antibiotics for Pleural Infections

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The clinical question

Does a short course (14-21 days) of antibiotics lead to a higher rate of treatment failure compared to a longer course (28-42 days) for the treatment of empyema in low to intermediate risk patients treated medically?

Take Home Message

This pilot study (N=50) demonstrated the feasibility of utilizing a shorter course of antibiotics for carefully selected low to intermediate risk patients with pleural infections, but was not powered to show a difference in treatment failure between groups.

Background

Antibiotic duration should be decreased to the minimum effective duration to reduce the risk of antimicrobial resistance and drug toxicity. There is limited evidence to guide the optimal duration of antibiotic therapy in adults with pleural infections. Only one other randomized clinical trial exists for the evaluation of antibiotic duration in the treatment of pleural infection. The ODAPE trial studied 2 vs 3-week courses of amoxicillin-clavulanate in the treatment of complicated parapneumonic effusions and suggests noninferiority, though the trial was terminated early for lack of enrollment and only 23% of the initially screened patients were enrolled which limits generalizability. Despite the lack of evidence from clinical controlled trials, expert consensus-driven guidelines recommend an antibiotic course typically including intravenous administration until clinical improvement followed by oral antibiotics to complete at least a 3-week course.

Study Design

- **Single center** (Alexandria University, Alexandria, Egypt) pilot open-label pragmatic randomized controlled clinical trial.

Primary outcome: Treatment failure at 6 weeks post-admission as defined by:

- **Clinical deterioration (i.e. worsening or recurrence of symptoms)**
- **Plus one of:**
  - Biochemical parameters (worsening of white cell count (by 2000 mm−3) or CRP (by >20%) from discharge values)
  - Radiological parameters (chest radiography and/or TUS evidence of increasing or new pleural collection).

Secondary Outcome(s)

- Total length of antibiotic treatment
- Proportion of patients who resumed normal activity levels within 6 weeks post-admission
- Time from discharge to resuming normal activity levels
- Incidence of antibiotic-related adverse reactions.

Intervention(s)

- Both groups were treated with empiric intravenous antibiotics which were tailored to cultures and sensitivities when available while inpatient for ≤ 14 days and then discharged on similarly chosen oral antibiotics.
- In the short course (intervention) group, the total antibiotic regimen was planned to remain within 14-21 days with at least 7 days of outpatient oral antibiotics provided.
- The long course group was treated for a total planned antibiotic course of 28-42 days.

Population

Inclusion criteria

- Adults (≥18 years old) admitted to hospital for treatment of non-tuberculous pleural infection (parapneumonic effusion or primary pleural infection).
- Inclusion required acute respiratory infection with at least one of the following:
  - Presence of pus in the pleural space
  - Positive pleural fluid Gram stain or culture
  - Pleural fluid pH <7.2
  - Pleural fluid glucose <40 mg.dL−1.
- Participants had to have a low-to-intermediate RAPID score (0–4) at admission.
- Required patients to be fit for discharge within 14 days of admission.

Exclusion criteria

- Referral for surgery during admission
- Infection was a recurrent ipsilateral pleural infection within the last 3 months
- The infected pleural collection was not amenable to drainage at time of diagnosis
- If a large residual collection persisted despite inpatient drainage and therefore a prolonged antibiotic course was deemed necessary by the treating clinician.

Baseline characteristics

- **N** = 50 (25 in each group)
- **Enrollment:** Consecutive patients admitted with pleural infection. Patients enrolled at the point of discharge if this occurred in less than 14 days.
- **Treatment period:** Enrollment between 9/28/2020 and 10/30/21. Final follow up visit 12/9/2021.
- **Follow up:**
- One visit at 2 weeks post-discharge and a second visit 6 weeks post admission.
- **Patients (intention to treat, patients excluded from % when data not available):**
  - Age:
    - Short group: 43 (34-49)
    - Long group: 52 (39-59)
  - Male
    - Short group: 18 (72%)
    - Long group: 17 (68%)
  - Symptom duration before admission (days)
    - Short group: 17 (9.25-39)
    - Long group: 16.5 (10-27.5)

Population continued...

- Septations on ultrasound
  - Short group: 4 (28.6%)
  - Long group:14 (77.7%)
- Split pleura sign on CT
  - Short group: 18 (81.1%)
  - Long group: 17 (70.8%)
- Multiloculated on CT
  - Short group: 10 (40%)
  - Long group: 10 (41.7%)
- Infection source: community-acquired pneumonia
  - Short group: 20 (80%)
  - Long group: 22 (88%)
- Infection source: hospital-acquired pneumonia
  - Short group: 5(20%)
  - Long group: 3 (12%)
- Infection type: primary pleural infection
  - Short group: 19 (82.6%)
  - Long group: 18 (72%)
- Infection type: parapneumonic effusion
  - Short group: 4 (17.4%)
  - Long group: 7 (28%)
- Purulent fluid:
  - Short group: 20 (80%)
  - Long group: 16 (64%)
- Low RAPID score:
  - Short group: 17 (68%)
  - Long group: 10 (40%)
- Intermediate RAPID score:
  - Short group: 8 (32%)
  - Long group: 15 (60%)
- Chest tube <18 Fr:
  - Short group: 9 (45%)
  - Long group: 12 (57%)
- Chest tube ≥18 Fr:
  - Short group: 11 (55%)
  - Long group: 9 (43%)
- Length of IV antibiotics (days):
  - Short group: 9.12 ± 3.56
  - Long group: 11.2 ± 2.51

Outcomes

Primary outcomes:

- Treatment failure occurred in 4/24 patients (16.7%) in the short course group compared to 3/24 patients (12.5%) in the long course group in the intention to treat analysis.
- Treatment failure occurred in 4/20 (20%) and 3/24 (12.5%) of patients in the short and long course groups, respectively, in the per-protocol analysis.
- Neither analysis was found to show a statistically significant difference
- An analysis of the primary outcome adjusted for the RAPID score, infection source (community or hospital-acquired), sonographic septations, and split pleura sign using binary logistic regression also demonstrated no difference.

Secondary outcomes:

- Total antibiotic days were found to be significantly different between the short and long course groups at 20.5 (IQR 18-22.5) days and 34.5 (IQR 32-38) days, respectively (P<0.001).
- No significant difference was found in the number of patients who could return to their activities of daily living 11 (55%) vs 9 (42.9%) in the short vs long course groups.
- There was also no difference in time to return to activities of daily living at 10 days (IQR 4.5-18) vs 13 days (IQR 6-18)
- Residual pleural collection was found in 4 patients in the short course group (20%) compared with 2 patients (9.5%) in the long course group, though this was not significant P=0.409
- 9 patients (45%) in the short course group compared with 11 patients (52.4%) had at least one persistent symptom at 6 weeks post-admission (P=0.537).

Adverse events:

- There were no antibiotic-related adverse events in the short course group vs 2 (8.3%) in the long course group (P=0.488).

Commentary

This was an innovative study that challenged a guideline-endorsed standard of care that is based predominantly on expert opinion. However, the study has numerous limitations that mostly stem from its nature as a single center study with a small sample size. This was a pilot study which was not powered to find a difference in outcomes between the two groups. In fact, the only statistically significant difference was the median number of antibiotic days at 20.5 days (IQR 18-22.5) in the short course group and 34.5 days (IQR 32-38) in the long course group. Despite randomization there were discrepancies between the groups. Some of these imbalances include age, presence of septations on ultrasound and the RAPID score category. Despite its limitations, this study does demonstrate feasibility of a shorter course of antibiotic therapy for carefully selected low-intermediate risk patients with pleural infections.

Funding

None.

Suggested Reading

1. Roberts ME, Rahman NM, Maskell NA, Bibby AC, Blyth KG, Corcoran JP, et al. British Thoracic Society Guideline for pleural disease. Thorax. 2023 Jul 1;78(Suppl 3):s1–42.
2. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clinical Infectious Diseases. 2019 Mar 1;44(Supplement_2):S27–72.
3. Bedawi EO, Ricciardi S, Hassan M, Gooseman MR, Asciak R, Castro-Anon O, et al. ERS/ESTS statement on the management of pleural infection in adults. European Respiratory Journal. 2022 Oct 13;2201062.

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