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# Exploring the role of ceftaroline in the treatment of community-acquired pneumonia

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**ABSTRACT** A critical appraisal and clinical application of File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, Llorens L, Critchley IA, Thye DA, FOCUS 1 investigators. FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother*. 2011 Apr;66 Suppl 3:iii19-32. doi: 10.1093/jac/dkr096.

***Keywords***: *Ceftaroline, Ceftriaxone, pneumonia, community-acquired pneumonia*

## Clinical Context

The patient is a 68 year old African American woman with a past medical history of heart failure with preserved ejection fraction and chronic kidney disease stage II. She was hospitalized with community-acquired pneumonia (CAP) of Pneumonia Severity Index (PSI) risk class III after her symptoms began 2 days prior to admission. Her chest radiograph showed new pulmonary infiltrates and physical exam showed an increased cough, wheezing, positive whispered pectoriloquy, and dyspnea. The treatment team explored the current best treatment for CAP and the role of ceftaroline was considered. The patient was treated with intravenous ceftriaxone and azithromycin and was well enough for discharge after 3 nights.

## Clinical Question

Would ceftaroline with a macrolide provide better clinical cure rates than ceftriaxone with a macrolide?

## Research Article

File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, Llorens L, Critchley IA, Thye DA, FOCUS 1 investigators. FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother*. 2011 Apr;66 Suppl 3:iii19-32. doi: 10.1093/jac/dkr096

## Related Literature

A search on UpToDate for ceftaroline in the treatment of community-acquired pneumonia yielded a page with references that included the one chosen for this critical appraisal. PubMed was then searched using the key words “ceftaroline ceftriaxone,” “ceftaroline ceftriaxone pneumonia,” and “ceftaroline pneumonia.” This yielded several hundred abstracts, which were then reviewed to determine that the best article had been chosen for appraisal. The FOCUS 1 and 2 trials were phase III, double-blinded,

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randomized, multi-national, multicentre trials with nearly identical methods and results.[1,2] These trials were chosen because of their quality and size, but the FOCUS 1 article was ultimately selected for two reasons: its larger number of patients in the same age range as this article's patient, and the lack of Black or African American patients in the FOCUS 2 article. The patients were a mean age of 61.1, approximately 90% white, 5% Asian, and 5% black, with pneumonia of PSI risk class III or IV, and very similar illness histories to this article's patient. 298 patients received ceftaroline fosamil as the experiment group and 308 received ceftriaxone as the comparator group. Ultimately, 600 mg of ceftaroline iv every 12 h was demonstrated to be non-inferior to 1 g of ceftriaxone iv every 24 h, achieving higher cure rates in hospitalized patients with CAP of PSI risk class III or IV across all predefined populations.[1]

The only other high quality clinical trial was an international, randomized, controlled, double-blind, phase 3, non-inferiority with nested superiority trial, with only adult Asian patients suffering from PSI risk class III or IV community-acquired pneumonia. Subjects included 217 (84%) of 258 patients receiving ceftaroline fosamil and 178 (74%) of 240 patients receiving ceftriaxone were clinically cured. Ceftaroline fosamil was found to be superior to ceftriaxone in all patient groups except those under the age of 65. This study was not chosen because the patient population was the most different from my patient, it had fewer patients in the study, and there was high industry involvement resulting in an increased risk of selective outcome reporting.[3]

There were a number of articles that delved into the efficacy of ceftaroline in patients with pneumonia, and most showed it to be either non-inferior or superior to ceftriaxone. However, these studies were inferior to the article chosen for critical review for reasons that included non-human patients, smaller study size, no comparison to ceftriaxone, pneumonia complications like bacteremia, and pediatric patients. None of these studies refuted the findings of the FOCUS 1 study and most were congruent with its conclusion of non-inferiority with ceftriaxone.[4-13]

## Critical Appraisal

The study chosen for this appraisal was a phase III, double-blinded, randomized, multinational, multicentre trial, which is an excellent design to minimize bias on the part of the patients or the providers. The patients were randomized in a 1:1 ratio to each treatment group stratified by PSI risk class so that there was an even number of each risk class in both groups. The patients were also placed into the clinically evaluable (CE) population and/or the modified intent-to-treat efficacy (MITTE) population. The MITTE population included patients with community-acquired pneumonia of PSI risk class III or IV at the time of randomization. The authors report data on a "clinically evaluable" subgroup, but this group was so highly selective that these results are not useful for making clinical decisions. Only patients who had been diagnosed with CAP of PSI risk class III or IV that began within the last 7 days could enter this study; these criteria ensured patients were of a similar disease burden compared to this article's patient. The intervention group received identical treatment compared with the control group except that the intervention group received ceftaroline as part of their treatment instead of ceftriaxone. A shortcoming of this study was the lack of details concerning outcome assessments. Everything was measured in microbiological outcomes and clinical cure rates; the criteria for these were somewhat unclear, but it was concluded to not impede the application of this research to other patient populations. It is also worth noting that pharmaceutical company Forest Laboratories provided the funding for this research, and Cerexa, Inc, a subsidiary of Forest Laboratories, performed the statistical analysis.[1]

This study had the most similar patient population to our patient in regards to age and race. The only factor that would make using ceftaroline less feasible is the extremely high price of treatment that currently exists. Patients receiving ceftaroline or ceftriaxone, respectively, had drop out rates of 3.7% and 3.9% because of treatment-related adverse events. Diarrhea was the most common adverse event experienced in both treatment groups. It appears that blinding was successful in preventing both patients and providers from being biased, and both groups were able to be treated in nearly identical manners.[1]

This double blinded, randomized, study comparing two treatments regarding their success rate and adverse effects has a level of evidence that could be labeled as 1b. Clinical cure rates were as follows: MITTE population, 83.4% (244/291) for ceftaroline and 77.7% (233/300) for ceftriaxone. This means the number needed to treat was 16. The adverse events that resulted in discontinuation of treatment were as follows: 3.7% for ceftaroline and 3.9%.

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## Clinical Application

The patient is a 68 year old African American woman with community acquired pneumonia of PSI risk class III. This study's conclusion shows that ceftaroline is a non-inferior treatment for community acquired pneumonia when compared to ceftriaxone.[1] The patient met the study's inclusion criteria, however, despite the demonstrated noninferiority and the potential higher cure rates, using ceftaroline might not be the best initial choice for a community acquired pneumonia patients.[1] It is typically the goal to use the least powerful antibiotic possible to cure a disease, therefore it is of questionable prudency to use a powerful antibiotic like ceftaroline as an initial treatment for community acquired pneumonia.

Secondly, ceftaroline is a relatively new antibiotic, which means its use also comes with a heavy financial burden. With these two thoughts in mind, it seems that ceftriaxone is still the best choice in treating community-acquired pneumonia. The earlier clinical question arose from a desire to confirm this patient was receiving the best evidence based treatment, which requires an assessment of both risk of benefit and risk of harm. The patient could have arguably benefited from the potentially higher cure rates of ceftaroline. However, when cost and antimicrobial stewardship were considered, it was concluded that ceftriaxone was still the best treatment option. The patient completely recovered in a timely manner without complication.

Learning points:

1. Cases of community-acquired pneumonia with MRSA and drug resistant Streptococcus pneumoniae are on the rise. With the rising rates of drug resistant pneumonia and the impact such diseases have, it may become increasingly important to consider more effective antibiotics like ceftaroline.[1]

2. Risk of harm and risk of benefit for newer antimicrobial agents need to be balanced with consideration for antimicrobial stewardship, cost, and adverse events. As diseases and guidelines evolve over time, it will be the duty of physicians to balance these concerns.

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