Antibiotic treatment of moderate-severe community-acquired pneumonia: design and rationale of a multicentre cluster-randomised cross-over trial


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ABSTRACT

Background: For the empirical treatment of community-acquired pneumonia requiring admission to a non-ICU ward, the Dutch guidelines recommend either beta-lactam monotherapy, beta-lactam and macrolide combination therapy, or fluoroquinolone monotherapy. The lack of convincing evidence to preferentially recommend any of the three empiric regimens results from intrinsic limitations of current studies, such as bias by indication and residual confounding in observational studies, and the unknown effects of pre-randomisation antibiotic use in randomised controlled trials. In this paper we discuss the methodological drawbacks of observational cohorts and randomised controlled trials in antibiotic therapy. Next, we explain why we designed a multicentre cluster-randomised cross-over study to evaluate the effectiveness of three antibiotic treatment strategies, consisting of a preferred treatment regimen of beta-lactam monotherapy, beta-lactam and macrolide combination therapy or fluoroquinolone monotherapy, in adult patients admitted to a non-ICU ward with a clinical diagnosis of community-acquired pneumonia. Furthermore we outline different aspects of this design that deserve thorough consideration.

Conclusion: We discuss different aspects of a cluster-randomised cross-over trial that is designed to determine the effects of three recommended regimens of antibiotic treatment of CAP.

KEYWORDS

Antibiotic therapy, cluster randomisation, community-acquired pneumonia, study design, trial

INTRODUCTION

Community-acquired pneumonia (CAP) has an incidence ranging from 3.3-46 per 1000 per year in the elderly population. Reported case fatality rates are usually less than 5% in outpatients, but hospital mortality rates have ranged from 5-48%, depending on age, comorbidities, pneumonia severity and presence of bacteraemia. With the introduction of sulphonamides and penicillins in the 1930s, the estimated absolute risk of dying from CAP decreased by 10-25% for all CAP patients, and even by 48-65% in bacteraemic CAP patients. Yet exact estimates are difficult to derive since randomised placebo-controlled trials (RCTs) have not been performed. Advances in medical care, such as mechanical ventilation and vasopressor support, have most certainly improved survival in patients with high severity CAP, but for the majority of CAP patients, major improvements in the management of CAP are less obvious. Adjunctive treatment with immunomodulators, e.g. corticosteroids, have not demonstrated clear improvements in survival. Therefore, antimicrobial therapy remains the mainstay of CAP treatment.

Initial antibiotic therapy for CAP is usually empirical, covering the most frequent pathogens. Yet, patient and disease characteristics are not specific enough to guide antibiotic therapy in most patients. Therefore, CAP severity, as determined by prognostic scores or site of admission, is widely recommended for guiding empiric antibiotic therapy. In the Netherlands, it is recommended to treat patients with mild CAP empirically with doxycycline or amoxicillin, and those with severe CAP with combined treatment of a beta-lactam (such as second- and third-generation cephalosporins) and a macrolide,
or a beta-lactam (such as penicillin or amoxicillin) and ciprofloxacin, or monotherapy with one of the newer fluoroquinolones (moxifloxacin or levofloxacin). The mid-range severity group, labelled moderate-severe CAP, should be treated either as mild CAP or as severe CAP, based on the perceived risk of *Legionella* infection. Three different classification tools are recommended to categorise CAP severity, with the recommendation to consistently use one of them: CURB-65 (0-1 is mild, 2 is moderate-severe and >2 is severe), PSI (1-2 is mild, 3-4 is moderate severe and 5 is severe), or a pragmatic score based on the level of care needed (ambulant is mild, non-ICU ward is moderate-severe, ICU admission is severe). Because of the multiple options for severity classification and the subjectivity of clinical parameters, the use of these scoring systems promotes categorisation of patients as severe CAP, with corresponding treatment choices. This becomes apparent in different studies of moderate-severe CAP, in which 20-40% of patients were treated with quinolones or combination therapy with a macrolide.** Recently, our group has investigated guideline adherence in hospitalised CAP patients in the Netherlands, and reported very heterogeneous empirical treatments.** In the Netherlands the three recommended empirical regimens are considered equivalent for moderate-severe CAP. In the international literature, the discussion concerning the need for atypical coverage in non-ICU hospitalised CAP is still ongoing. Each strategy comes with different advantages and drawbacks. Beta-lactam antibiotics have less adverse events than macrolides, are less expensive than fluoroquinolones and the prevalence of antibiotic resistance in *Streptococcus pneumoniae* is not clinically relevant in the Netherlands.** Yet, atypical pathogens are not covered. Macrolides are active against most atypical pathogens and they might offer anti-inflammatory effects, possibly leading to faster clinical responses.** On the other hand, rapid development of resistance of *S. pneumoniae* against macrolides during treatment has been observed in vivo.** In the Netherlands, proportions of *S. pneumoniae* isolates from hospitalised patients that were resistant to macrolides were 2-3% in 1996, 7-10% in 2002 and 4.5% in 2011.** The newer fluoroquinolones, such as levofloxacin and moxifloxacin, are active against all common causes of CAP, can be used intravenously and orally, and might also have anti-inflammatory effects.** The major disadvantage, similar to macrolides, is a potentially higher risk of development of antibiotic resistance, as observed among *S. pneumoniae* after introduction of fluoroquinolones in Canada and Hong Kong.** In contrast, a study from Germany showed a low prevalence of quinolone resistance, while usage of moxifloxacin was high.**

The lack of well-designed randomised comparisons between beta-lactam monotherapy, beta-lactam and macrolide combination therapy and any of the newer fluoroquinolones is a serious limitation for interpreting the relative effectiveness of these strategies in patients hospitalised with CAP. Fluoroquinolones have been compared with beta-lactams and macrolides in randomised studies, but none yielded superiority of either treatment. Large meta-analyses failed to demonstrate an advantage of atypical coverage in the empirical antibiotic treatment of mild to moderately severe CAP patients not caused by *Legionella*. Some observational studies showed beneficial effects of atypical coverage on clinical outcome, but in a similar number of studies such effects could not be demonstrated. However, there are serious limitations in the design of observational studies and RCTs. To overcome some of the pitfalls of these classical study designs, we designed the ‘Community-Acquired Pneumonia – Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract infections’ (CAP-START, http://clinicaltrials.gov/show/NCT01660204), a cluster-randomised cross-over study to evaluate the (cost-)effectiveness of three empirical antibiotic strategies in patients hospitalised with CAP in non-ICU wards. The first aim of this paper is to discuss the pros and cons of observational studies and RCTs. Next, we discuss different aspects of designing a cluster-randomised cross-over study, which we consider beneficial for the development of future trials for the comparison of intervention strategies.

### Drawbacks of Observational Studies for Antibiotic Treatment of CAP

In observational studies, the decision for empirical antibiotic treatment was made by treating physicians. Consequently, these studies suffer from bias by indication, as the choice of therapy will be influenced by e.g. severity of disease or the patients’ overall prognosis. Thus, if patients receiving atypical coverage have a better outcome, this may in part result from the better prognosis at baseline, and not necessarily from better coverage of atypical pathogens. The magnitude of this form of bias was demonstrated by using a propensity score to predict treatment allocation based on clinical variables. The propensity was used in a multivariate analysis to adjust for confounding variables. The apparent beneficial effect of combination therapy (adjusted OR 0.39, 95% CI 0.19-0.79) was diminished after additional correction for the propensity score (OR 0.69, 95% CI 0.32-1.48). Although analytical control in multivariable analysis is usually attempted, many determinants may be unknown or measured with error, resulting in residual confounding. For example, (hidden) treatment restrictions may play a role in a substantial proportion of fatal CAP cases.
especially in elderly patients with severe comorbidities,\textsuperscript{7} which may also influence treatment decisions and, thus, confound observations. It is difficult, if at all possible, to predict the direction and quantity of residual confounding.

**DRAWBACKS OF RANDOMISED CLINICAL TRIALS FOR ANTIBIOTIC TREATMENT OF CAP**

Randomisation prevents bias by indication and residual confounding because treatment allocation is not influenced by patient or disease characteristics, but determined by chance. However, a consequence of an RCT is that the timeframe for initiation of the study medication is generally longer than in clinical practice, because the informed consent procedure and randomisation need to be realised. International guidelines for clinical trials demand that eligible subjects are given sufficient time to consider participation in the trial. At the other end, current CAP guidelines emphasise the importance of early antibiotic administration, and recommend initiation of treatment within four to eight hours of hospital admission.\textsuperscript{3,5,51} As a result, many patients have already received in-hospital antibiotic treatment before study enrolment. Since the adequacy of the first dose of antibiotics is considered crucial for patient outcome,\textsuperscript{51,55} this may severely compromise accurate evaluation of effectiveness of the randomised antibiotics. In fact, it might even be dangerous to accept non-inferiority if a large proportion of patients has received similar pre-randomisation antibiotics. Any difference in effectiveness will, to some extent, be diluted by the therapeutic effect of the antibiotics received prior to randomisation, leading to a reduced power to detect superiority of one of the antibiotics under study.

Another limitation of current RCTs is that their generalisability to daily clinical care is questionable. Prior antibiotic use, contraindications, and exclusion criteria can lead to a very restricted study population. A comparison of empirical antibiotic strategies, in which the aforementioned exclusion criteria are not applied, would lead to more generalisable results.

**CLUSTER-RANDOMISED CROSS-OVER DESIGN**

In an ideal comparison of empirical antibiotic therapies, the allocation of treatment would be unrelated to patient and disease characteristics, to ensure comparability of the treatment groups in terms of prognosis. Additionally, the timing of treatment and of concomitant therapy should be comparable with clinical practice. As pointed out, when studying empirical antibiotic treatment of CAP, the first requirement is not satisfied in observational studies, while RCTs do not comply with the second. Also, patients should be included on an intention-to-treat basis; treating physicians should be able to start another antibiotic because of prior use or contraindications. To overcome these limitations, we have designed a multi-centre cluster-randomised cross-over study, comparing empirical antibiotic strategies. Participating centres are randomised to three consecutive periods of four months, in which one of the three empirical antibiotic strategies applies. All CAP patients admitted to a non-ICU ward, irrespective of the PSI or CURB-65 classification, are eligible for the study. The empirical strategies consist of beta-lactam monotherapy, fluoroquinolone monotherapy and beta-lactam macrolide combination therapy.

In this way, allocation of empirical strategy is determined by the date of admission and cannot be biased by patient characteristics. In each hospital the local antibiotics committee has been asked to adopt this empirical strategy as the standard treatment for CAP during that period. Because of this, the medical ethics review board judged that this cluster-randomised study is not liable to the same regulations as an individually randomised trial. Consequently, written informed consent is not needed prior to the start of the preferred treatment of the study, but only for collection of individual patient data. Importantly, this is only legitimate for interventions that are registered for the disease under study and are considered equally effective.

Treating physicians will sometimes deviate from this strategy for medical reasons. These patients will also be included in the intention-to-treat analysis, which will be the primary analysis of our study. Thus, the strength of a cluster-randomised trial design is that it enables a comparison of treatment strategies, rather than the individual treatments. Since patients from one hospital may not be comparable with those from another hospital, the cross-over design is used, enabling adjustment for hospital-specific confounding factors.

The most important challenges with this design include adherence to the treatment strategy by the treating physicians, prevention of selection bias, and differences in number and severity of eligible CAP patients due to seasonality. These will be discussed in the next section.

**CHALLENGES IN CLUSTER-RANDOMISED CROSS-OVER TRIALS FOR ANTIBIOTIC TREATMENT OF CAP**

Protocol adherence and route of administration

Naturally, treating physicians sometimes deviate from study protocols. This may compromise the intention-to-treat analysis if the alternative antibiotic therapy is
different in effectiveness. If, however, the rationale for deviation from protocol is valid, i.e., in line with common practice, the intention-to-treat analysis will show the effect of implementation of either protocol in real life. Therefore, reasons for such deviations will be recorded to investigate their validity. Valid reasons include failure of prior antibiotic treatment with the same class of antibiotics, clinical suspicion of a pathogen that is not covered by the preferred regimen, targeted treatment because of previous microbiological results or a contraindication for the treatment of choice. Episodes of non-protocol adherent treatment without a valid medical reason are considered protocol violations. All CAP patients, including those with protocol deviations and protocol violations, will be included in the intention-to-treat analysis. Hence, in this analysis we compare hospital-wide strategies of empirical treatment rather than antibiotics in individual patients. For instance, patients receiving non-preferred antibiotics for medical reasons are still treated according to best medical practice during that study period. Rates of protocol deviations will provide insight into the implementation potential of each treatment strategy. In a classical RCT, such patients would be excluded because of a contraindication for one of the treatment options. On the other hand, the per-protocol analysis will only include patients treated according to the preferred antibiotic regimen. Reasons for non-adherence will probably differ between treatment arms, and protocol deviations may therefore confound the per-protocol analysis if the protocol adherent patients in one period have a different prognosis compared with those in another. This will be dealt with in the statistical analysis.

The specific choice of agents within the treatment category is left to the treating physician, e.g., amoxicillin, co-amoxiclav or ceftriaxone are all acceptable as beta-lactam monotherapy. All changes in therapy will provide insight into the implementation potential of each treatment. In a classical RCT, such patients would be excluded because of a contraindication for one of the treatment options. On the other hand, the per-protocol analysis will only include patients treated according to the preferred antibiotic regimen. Reasons for non-adherence will probably differ between treatment arms, and protocol deviations may therefore confound the per-protocol analysis if the protocol adherent patients in one period have a different prognosis compared with those in another. This will be dealt with in the statistical analysis.

Improving compliance to the protocol
Sub-optimal adherence to study protocol is a threat to any study. As most CAP patients receive their first antibiotic dose in the emergency room (ER), all pulmonary, internal and ER physicians, and especially the residents, need to be informed about the study. In some hospitals this comprises a group of over 50 people with multiple changes due to rotations, career choices, holidays and leaves. We designed a three-step approach to optimise study protocol adherence. First, all physicians were informed through presentations at the start of the study, and presentations are repeated regularly. Second, study progress was communicated through monthly (and later two-monthly) newsletters. Third, adherence to study protocol was continuously monitored and proportions of patients classified as ‘adherent’, ‘deviation with clinical reason’ and ‘protocol violation’ are regularly fed back to participating sites.

The intensity of information provided to physicians working ‘in the field’ is challenging, as in our experience there is a subtle balance between the level of knowledge required for such a trial and the risk of information fatigue. The return of investment of informative group sessions was considered limited as the awareness of the study seemed to decrease rapidly after such meetings. They are necessary at the start of the study, after which individual contacts, both through key persons in each hospital and directly with the care-providing physicians, are more essential for optimising protocol compliance.56-57

We, therefore, monitor compliance case by case directly after study inclusion, and ask the physician who initiated the treatment for the rationale of any deviation from study protocol that is not motivated in the patient records. Initially, we experienced some resistance to this approach, as it was perceived as criticism on treatment decisions by some. However, after explaining the reason, all understood and accepted this procedure. Along the way, an increasing number of physicians explicitly reported the rationale for deviations in the medical records.

Naturally, providing adequate information to caregivers is very important around the four-monthly switches of the preferred regimen to another antibiotic class. In our experience it takes one to two weeks to facilitate a change to the new standard treatment. As a consequence there are more protocol violations at the beginning of each cluster. In future studies using a similar design, investigators might consider the use of a run-in period, in which subjects are not included in the study while the interventional change is effectuated.

Figure 1 provides an example of how we reported the protocol compliance to the participating centres. Treatment according to protocol was highest during the fluoroquinolone period, and lowest during the periods of beta-lactam plus macrolide therapy.

Subject recruitment
A potential pitfall of a cluster-randomised study is patient inclusion with knowledge of treatment allocation. This
may induce bias if inclusion criteria are not applied uniformly across different treatment arms. Therefore, it is important to have clear inclusion criteria that are easily applicable. In CAP research the presence of an infiltrate on the chest X-ray is often used as one of the inclusion criteria. However, interpretation of the chest X-ray is not unambiguous and inter-observer agreement is therefore moderate. Also, appearance of an infiltrate is delayed in a proportion of CAP patients. Subsequent chest X-rays are mostly performed because of treatment failure, and will reveal an infiltrate in a proportion of the patients with initially negative chest radiographs. Therefore, if patients were to be included based on presence of an infiltrate, this could lead to selection bias.

In addition to that, the domain of interest of this study does not consist of patients with proven CAP, but of patients who are treated for CAP, regardless of the presence of an infiltrate. Hence, inclusion in our study is based on a working diagnosis of CAP. We intend to perform a sensitivity analysis of patients with proven CAP. Definitions of CAP are very diverse in the literature (for example, Oosterheert et al., Snijders et al., and Ewig et al.53–61). We used a combination of several clinical parameters and a working diagnosis of CAP documented by the treating physician, as detailed in box 1. Screening for eligible patients is performed daily by research nurses not involved in the treatment of patients and is based on the admission diagnosis in the medical charts. Written informed consent, for the purpose of individual patient data collection, is requested by the research nurse or the treating physician. Of all eligible patients who are not included, the admission date and reason for non-inclusion is recorded, so that inclusion practice can be compared between hospitals and between treatment arms. We expect that the most important reason for non-inclusion will be patient refusal. Logistical reasons, such as discharge before the patient has been approached for inclusion, and ethical reasons, such as a presumed undue burden to the patient, should be closely monitored to ensure that these are not different between treatment arms. Selective recruitment, if present, will become apparent in differences in the inclusion rate or in differences in CAP severity between treatment arms. The magnitude of this will be assessed analytically, which is discussed in the section on data analysis.

**Measurement of outcomes**

As optimal treatment may require protocol deviation, blinding for treatment is not feasible. Therefore, it is pivotal to have an unambiguous study endpoint, preventing any bias in this aspect. The primary endpoint is all-cause mortality up to 90 days after hospital admission with CAP, which can be obtained even if a patient’s status at day 90 is not available in the hospital records (i.e. no death recorded and patient is not seen alive after day 90) from the Municipal Personal Records Database. Secondary outcomes include the length of intravenous treatment, length of hospital stay, complications relating to pneumonia or treatment, time to return to work and usual activities and (non) healthcare costs. Length of stay and length of intravenous treatment can be measured accurately, but may be more prone to bias because of the open label design. Self-reported time to return to usual activities and non-healthcare costs will probably not be influenced by knowledge of the type of antibiotic received, as most patients will not be aware of the pharmacological properties of their antibiotics.

**Seasonality**

Because of the seasonality of CAP, numbers of eligible patients will change over the year, which may also be the case for the average severity of CAP and spectrum of pathogens. In RCTs, this does not have consequences, since patients are randomised individually, and treatment arms will consist of comparable patients. However, in cluster-randomised cross-over trials, seasonality poses a challenge, because, by design, patients in one cluster are in a different season compared with those in another cluster. This may lead to an unequal number of inclusions between arms, which is less efficient for the analysis. More important, if the severity of CAP differs between seasons, this would lead to a biased evaluation. Although no evidence exists that CAP severity differs between seasons, aetiology is known to show variation. Therefore, we aimed for a wedge start of periods to ensure continuous inclusion of patients across the year in all treatment arms.

Unfortunately, as the trial was initiated at different time points due to logistical reasons in some of the participating hospitals, we expected that the most important practice can be compared between hospitals and between seasons, aetiology is known to show variation. Therefore, we aimed for a wedge start of periods to ensure continuous inclusion of patients across the year in all treatment arms.
hospitals, the wedged start of periods was suboptimal. As a result, there are several months in the course of the study in which a substantial proportion of inclusions are made in one specific treatment arm. We are therefore planning to confirm analytically whether seasonality is of influence for the relative treatment effect. Furthermore we aim to compare proportions of pathogens between the treatment arms. For future studies with a cluster-randomised cross-over design, in which seasonality may play a role, we recommend to randomise based on calendar month. For example, assuming three periods of four months each, if the randomisation scheme of all centres is to start in January, and one centre, randomised to treatment order A-C-B, starts in July, it will start with two months of C, next have 4 months of B and 4 of A, and finish with two other months of C. Alternatively, if feasible, periods of one year could be chosen to avoid seasonality effects.

Sample size calculation

The study is designed to demonstrate non-inferiority of beta-lactam monotherapy on 90-day mortality. Based on an expected mortality rate of 5%, 650 patients per study arm are needed to demonstrate non-inferiority to either strategy with a non-inferiority margin of 3% (alpha of 0.05 and power of 0.80). Accounting for possible drop-outs, 700 patients need to be included in each study arm. Based on expected numbers of patients in each centre, a total study period of 24 months (6 periods of preferred antibiotic regimens) in seven participating centres was deemed necessary. In classical cluster-randomised studies, the statistical power is generally reduced because of the intra-cluster correlation and because cluster sizes are unequal. The cross-over design limits these cluster level effects.66 Furthermore, the effects of intra-cluster and inter-period correlation are considered limited, since treatment of one patient does not affect outcome of other patients, and clinical outcomes are associated with a low inter-cluster and intra-cluster correlation in general.67 We performed a power simulation, comparing a classical RCT design with the cluster-randomised cross-over design, and estimated that statistical power is reduced in the latter by only 0.5% (95% confidence interval: 0.2 to 0.8%; simulation script is available on request to the authors).

Data analysis

Analysis will be performed according to the CONSORT statement recommendations for cluster randomised trials.68 Since complexity and disease severity of patients might differ between hospitals, multilevel analysis will be used. The effect on the primary endpoint, 90-day all-cause mortality, will be determined by a random-effects logistic regression model. Both intention-to-treat and per-protocol analyses are planned, and stratified analyses are planned for severe CAP and non-severe CAP according to CURB-65 and PSI scores. The effect on length of hospitalisation and length of intravenous treatment will be determined by a random-effects cox regression model. Alternative approaches to the analysis of cluster-randomised trials have been proposed, including cluster-level analysis and hierarchical models, which are discussed elsewhere.69 Another consideration in cluster-randomised cross-over trials, similar to individual patient cross-over trials, is what is known as the carry-over effect: the effect of treatment in one period may continue to have an effect in the next period. If so, a wash-out period should be implemented, which should be sufficiently long to eliminate the carry-over effect. Further testing for and analytical control of carry-over effects is debatable, since the power to find a carry-over effect is often limited.70 Since in our trial the treatment of one patient does not affect the outcome of others, carry-over effects will not be present. Therefore, no wash-out period is used and the analysis will not take carry-over effects into account.

As mentioned before, different mechanisms may lead to incomparability of the treatment groups. Therefore, analytical control of potential confounders is deemed necessary in cluster-randomised trials. Unlike in observational studies, selection of potential confounders is not based on an expected association with treatment allocation, because this association, if present, will be the result of mere chance in a cluster-randomised trial. For this reason, all analyses will be adjusted for known prognostic factors of the outcome. For example for mortality, these include age, gender, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment, PSI score, prior admissions in the past year and receipt of immunosuppressive therapy.

Potential applications of this study design

A cluster-randomised cross-over trial could be suitable in other areas of acute care medicine. When study treatment has to be started within a short period of time, and cannot be delayed by study procedures, this design may be superior to an RCT. Examples would include any severe infection requiring antimicrobial therapy, comparisons of biomarker-guided treatment decisions on the ER, treatment of acute myocardial infarction or stroke, and others. Importantly, the study treatments should be considered equally effective, and they should therefore be registered treatment options.

Summary

This study aims to determine the (cost)-effectiveness of three recommended strategies for empirical treatment of patients with a working diagnosis of CAP admitted to a non-ICU ward. The three strategies are beta-lactam monotherapy, fluoroquinolone monotherapy and combination therapy of a beta-lactam and a macrolide.
The cluster-randomised design of the study overcomes potential effects of confounding by indication and of pre-randomisation antibiotic use. Moreover, since the present study will compare empirical antibiotic strategies and patient inclusion is based on a working diagnosis of CAP, the study results will be generalisable to the patients who are eligible for treatment in clinical practice.

Naturally, deviations from protocol are possible (and will be needed) for medical reasons. All patients will be included in the intention-to-treat analysis, allowing the comparison of the different treatment strategies as they would be implemented in clinical practice. However, true protocol violations (non-adherence without medical reason) are a threat to the study validity, and will, therefore, be monitored closely. Reasons for deviation will be recorded in the final study results and it is aimed to have less than 10% protocol deviations without medical reason.

Another important hazard for the validity of a cluster-randomised trial is differences in inclusion rates across study arms. We minimised this risk by using the clinical diagnosis as inclusion criterion, independent of compliance to the study protocol. Still, any differences in inclusion may lead to bias, which has to be dealt with analytically.

In conclusion, a properly executed cluster-randomised cross-over trial will provide a valid evaluation of empirical antibiotic strategies for patients hospitalised with CAP.

Disclosures

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