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Evaluating the Impact of Corticosteroid Use in ICU Patients with Community-Acquired Pneumonia: A Comprehensive Drug Utilization Analysis.

Kendre Himesh

Ankit Bhuteker

Aakash Dhulshette

Yogita Dhaygude

Guide : Dinesh Gujrathi

University : Shivlingeshwar Collage of Pharmacy, Almala

Abstract:

Background: Corticosteroids are a significant category of medications in dermatology and are frequently prescribed. However, despite their effectiveness, they are associated with various adverse effects. Given that many skin conditions are chronic, it is crucial to ensure that the use of these drugs is rational. Consequently, this study was conducted with the objective of examining the utilization pattern of topical corticosteroids.

Methods: This was a hospital-based, prospective, and observational study conducted over a 12-month period. Data collection involved one-on-one consultations with patients, and the information collected was recorded in a specially designed form. Subsequently, the data were entered and analysed using Microsoft Excel.

Results: The study revealed that 48% of the patients were male, while 52% were female. The majority of patients fell within the 21-30 age group (30%). Scabies (30%) emerged as the most prevalent dermatological condition. Among the different topical corticosteroids prescribed, mometasone furoate (31.4%) was the most frequently chosen. In addition to topical corticosteroids, H1 antihistaminic drugs like levocetirizine (81.6%) were commonly prescribed, along with emollients (36.4%) and permethrin (29.2%). On average, each prescription included 3.6 drugs, all of which were prescribed using their generic names.

Conclusions: Regularly monitoring the drug utilization pattern through prescription auditing is an effective tool for establishing guidelines to improve the utilization of medications.

Introduction:

Community-acquired pneumonia (CAP) is a major contributor to global morbidity and mortality, with reported mortality rates reaching 20%~50% in cases of severe CAP. Despite advancements in antimicrobial treatments and life-support measures, there has been limited progress in reducing severe CAP-related mortality over the past few decades. Consequently, researchers have explored additional therapeutic approaches, alongside antibiotics, to enhance outcomes for severe CAP patients.

Corticosteroids, which have the ability to dampen the systemic inflammatory response in CAP, are commonly used as supplementary treatments. However, the use of corticosteroids in severe pneumonia patients remains a subject of debate within clinical practice. For instance, British guidelines advise against routine corticosteroid use in treating high-severity CAP, while South African guidelines recommend considering systemic corticosteroids for severe CAP patients requiring intensive care unit (ICU) admission. Several systematic reviews have investigated the effectiveness of corticosteroids in severe CAP treatment, but these overviews were either conducted a few years ago or lacked appropriate subgroup analysis. Consequently, there remain unanswered questions regarding which severe CAP patients are most likely to benefit from corticosteroids, the optimal type, dosage, and duration of corticosteroid therapy.
The primary objective of this systematic review and meta-analysis of previously published randomized controlled clinical trials was to assess the effectiveness and safety of systemic corticosteroid therapy in severe CAP patients(1).
The development of community-acquired pneumonia (CAP) starts when bacteria enter the lower respiratory tract through inhalation, aspiration of material from the oropharynx, or through the bloodstream from an infection at another site in the body. Once these microorganisms reach the lower airways, they infiltrate the tiny air sacs called alveoli and begin to multiply. At the same time, alveolar macrophages, which are part of the immune system, try to engulf and destroy these invading pathogens.

If the alveolar macrophages are unable to completely clear the microorganisms, the immune response becomes more intense, characterized by the release of inflammatory cytokines. This local inflammation can cause damage to the lung tissue, leading to the typical symptoms of CAP. Consequently, patients with CAP commonly experience symptoms such as difficulty breathing (dyspnoea), cough, production of sputum, sharp chest pain worsened by deep breathing (pleuritic chest pain), the presence of crackling sounds during lung expansion, and visible abnormalities like infiltrates or consolidations on chest X-rays(2).

In 1977, the World Health Organization (WHO) defined drug utilization research as the comprehensive examination of how drugs are marketed, distributed, prescribed, and used within a society, with a particular focus on the resulting medical, social, and economic consequences. The primary objective of drug utilization research is to promote the rational and effective use of medications within the population. Additionally, it offers insights into the efficiency of drug utilization.

One valuable tool for assessing the rationality of prescriptions and drug use in society is prescription auditing, typically conducted as part of a drug utilization study. Prescribing medications is a crucial skill that requires continuous evaluation and improvement. It reflects a physician's approach to selecting the most appropriate and rational treatment, aiming to enhance therapeutic effectiveness while minimizing the risk of adverse effects.

Unfortunately, there is a notable lack of data concerning the patterns of drug utilization, specifically in the case of topical corticosteroids for skin conditions. Recognizing this gap in knowledge, our study was undertaken with the goal of analysing the utilization patterns of topical corticosteroids through ongoing prescription monitoring(3).

Methods:

Patient Enrolment: This study prospectively enrolled patients between August 2005 and July 2008 at the Medical Centre Alkmaar, a 900-bed teaching hospital in the Netherlands. The study protocol received approval from the local medical ethics committee.
Eligibility Criteria: Patients were considered eligible if they met the following criteria: provided written informed consent, displayed clinical symptoms suggestive of community-acquired pneumonia (CAP) such as cough (with or without sputum), fever (≥38.5°C), pleuritic chest pain, or dyspnoea, and had new consolidations visible on chest radiographs. Additionally, patients needed to be 18 years or older.
Exclusion Criteria: Patients were excluded from the study if any of the following criteria applied to them: presence of severe immunosuppression (e.g., HIV infection or use of immunosuppressants), malignancy, pregnancy, or breastfeeding, use of macrolides for more than 24 hours, use of prednisone at a dose of 15 mg or more for more than 24 hours, any condition requiring corticosteroids, presence of any likely infection other than CAP, obstruction pneumonia (e.g., due to lung cancer), pneumonia that developed within 8 days after hospital discharge, and indications that patients were unable to comprehend and adhere to the protocols.
Subgroup Analysis: A planned subgroup analysis was conducted on patients with severe CAP, as determined by the CURB-65 (a severity index for community-acquired pneumonia evaluating Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older) score of 2 or higher or PSI class IV and V(4).

Study design:
Patients in the study were randomly assigned in a double-blind manner to receive either 40 mg of prednisolone once daily or a placebo for a total of 7 days. The administration of the study drug followed the same route as the antibiotics, whether intravenous or oral. Whenever patients transitioned from intravenous to oral antibiotics, a corresponding switch was made for the study drug. Randomization was achieved using prenumbered containers containing seven vials for intravenous administration and seven capsules. The allocation sequence was generated by a computer and securely stored in the hospital pharmacy throughout the study's duration.

All patients received antibiotic treatment in accordance with national guidelines. Urinary antigen testing for Legionella pneumophila was conducted for all patients. Typically, patients with mild to moderately severe CAP (CURB-65 < 3 or PSI I–III) were treated with amoxicillin. Those with moderate to severe CAP, suspected atypical pathogens, or an intolerance to amoxicillin were initiated on moxifloxacin. While changes in antibiotic treatment were permitted, the use of macrolides was discouraged due to their immunomodulatory effects. The duration of antibiotic therapy was at the discretion of the medical team in charge, as was the decision to switch from intravenous to oral treatment. No specific criteria for hospital discharge were established, and the investigators had no influence over discharge decisions(4).

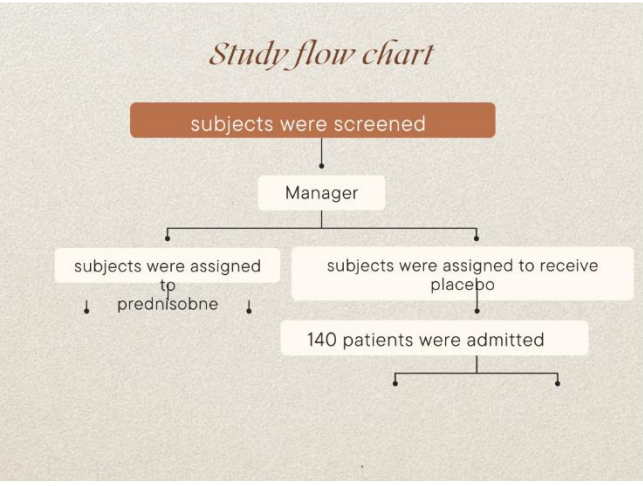

Figure 1 Study Flow Chart(5)

Laboratory:

Standard laboratory assessments were conducted upon patient presentation, encompassing evaluations of renal and liver functions, electrolyte levels, glucose levels, haematology, and CRP (C-reactive protein) levels using equipment from Beckman Coulter Inc., located in Fullerton, CA. Arterial blood gas analysis was performed as deemed necessary from a clinical perspective. Throughout the hospitalization period, serum samples were collected daily until Day 7 and on Day 14 to monitor CRP levels(4).

Outcomes:

Clinical outcomes at Day 7 and Day 30 were defined as follows:

1. Cure: This entailed the resolution or improvement of symptoms and clinical signs associated with pneumonia without the need for additional or alternative therapy.

2. Failure: Failure was characterized by the persistence or worsening of all signs and symptoms that initially developed during the acute disease episode after randomization. It also included the development of a new pulmonary or extrapulmonary infection, deterioration observed in chest radiography following randomization, death attributed to pneumonia, or the inability to complete the study due to adverse events.

3. Indeterminate: This category encompassed patients who received less than 80% of the study drug for reasons other than clinical failure. It also included those with a concomitant infection outside the respiratory tract requiring antibiotic treatment, individuals lost to follow-up, or those who experienced death unrelated to the primary diagnosis(6).

Additionally, there were distinctions between early and late failures. An early failure was defined as the absence of resolution of pneumonia signs and symptoms within 72 hours of treatment initiation, with persistence or progression thereafter. On the other hand, a late failure referred to a recurrence of pneumonia signs and symptoms after 72 hours of admission, following an initially positive response to treatment.

The assessment of time to clinical stability followed criteria established by Halm and colleagues. Essentially, patients were deemed clinically stable if they met all four of the following criteria: improvement in cough and shortness of breath, maintaining a temperature below 37.8°C for at least 8 hours, normalization of white blood cell count, and adequate oral intake with gastrointestinal absorption. Due to the potential impact of prednisolone use on white blood cell counts, the criterion for normalizing white blood cell count was replaced by a decline in serum CRP levels. Defervescence was defined as achieving a temperature below 37.5°C(7).

Statistical Analysis:

The data were presented in the form of frequencies or percentages for categorical variables and as means along with standard deviations for continuous variables. To assess differences between the treatment groups, we used the chi-square or Fisher exact test for categorical variables and employed the two-sample t-test or Mann–Whitney test for continuous variables(8).

TABLE 2. ANTIMICROBIAL TREATMENT IN THE TWO STUDY GROUPS

	Prednisolone Group	Placebo Group	*P* Value
Amoxicillin	58 (55.8)	64 (58.7)	0.66
Moxifloxacin	42 (40.4)	38 (34.9)	0.41
Amoxicillin/clavulanic acid	4 (3.8)	5 (4.6)	0.79
Amoxicillin and acyclovir	0	1 (0.9)	
Ciprofloxacin and cefuroxime	0	1 (0.9)	

Data are presented as n (%).

Figure 2Data are presented as n (%).1(9)

Results:

In the course of the study, we analysed a total of 140 prescriptions. Among these prescriptions, a total of 500 drugs were prescribed, with 141 of them being topical corticosteroids. On average, each prescription included 1 topical corticosteroid.

In this study, a total of 140 subjects were admitted with their first episode of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) alongside concomitant pneumonia. Lung function results were available for 64 patients, with 12 patients passing away before their scheduled spirometry appointment and two declining to return for lung function assessment. Among the 64 patients with lung function assessment, 5 had mild COPD, 13 had moderate COPD, 23 had severe COPD, and 23 had very severe COPD according to the GOLD classification. Before hospitalization, 42 patients (53.8%) were using Inhaled Corticosteroids (ICS) with an average daily dose of 1345 mcg beclomethasone-equivalent. There were no significant differences in demographic characteristics, including lung function values, between patients on ICS and those not on ICS. Furthermore, stratifying subjects on ICS into high (>1000 mcg beclomethasone-equivalent per day) and low-medium (≤1000 mcg beclomethasone-equivalent per day) dose groups revealed no differences in their demographic data. The mean doses for the high and low-medium dose ICS groups were 2050.0 and 836.4 mcg beclomethasone-equivalent per day, respectively.

Among the subjects, 28 (35.8%) had a history of hypertension, 11 (14.1%) had a history of cerebrovascular accidents, 7 (9.0%) had diabetes mellitus, 5 (6.4%) had ischaemic heart disease, 5 (6.4%) had congestive heart failure, and 7 (9.0%) had malignancies. All patients were managed on the general medical wards and none required invasive mechanical ventilation. There were no significant differences in mortality during the same admission, mortality at 12 months, and the use of Non-Invasive Positive Pressure Ventilation (NPPV) when comparing subjects on ICS with those who were not, or when comparing subjects on low-medium dose ICS with those on high-dose ICS.

The clinical presentations of the subjects are summarized. Prior to hospitalization, 10 episodes involved subjects who had taken antibiotics within 7 days. All subjects showed pneumonic changes on chest X-rays (CXRs). Among them, 7 episodes exhibited bilateral CXR changes, while 13 episodes had pneumonic changes affecting more than 1 lobe of the lungs. Three subjects developed pleural effusion. All patients received antibiotic therapy upon admission after sputum and blood cultures were collected.

Sputum culture results are shown. Overall, 40.8% of the episodes had positive sputum bacterial cultures, while 3.0% had positive mycobacterial cultures. Two out of the 8 patients (25.0%) with Streptococcus pneumoniae were resistant to penicillin, and none of the Haemophilus influenzae isolates exhibited beta-lactamase activity. No cases involved more than one bacterium isolated from the sputum. Episodes where antibiotics were administered in the previous week had a higher rate of positive sputum bacterial culture compared to those who did not ($p = 0.02$). However, there were no differences in the rates of identifying viral etiologies when comparing subjects on low-medium dose ICS with those on high dose ICS (5/22 [22.7%] vs 5/20 [25.0%], $p = 0.70$). There were also no differences in the rates of positive influenza A or B viruses between subjects who had received influenza vaccination within 12 months prior to admission and those who had not (3/33 [9.1%] vs 4/40 [10%], $p = 0.90$). All episodes had blood cultures performed, but none were positive. Among the 3 subjects with pleural effusion, 2 underwent pleural fluid aspiration. Overall, the rate of positive identification by sputum culture, Nasopharyngeal Aspirate (NPA) Polymerase Chain Reaction (PCR), NPA viral culture, and blood serology was 48.7% (38/78). Three subjects (3.8%) had both positive bacterial and viral etiologies identified (positive sputum cultures and positive viruses, either from NPA PCR, NPA viral culture, or blood serology).

Among subjects with bilateral pneumonia microorganisms identified. Of the 13 cases with pneumonic changes affecting more than 1 lobe (7 of them had bilateral pneumonia as well), 4 had bacteria. None of these subjects had both bacterial and viral etiologies identified concurrently.

The identification of organisms in relation to the lung function of the subjects. There was a trend toward a higher rate of positive sputum bacterial culture among subjects with FEV 1 < 50% predicted compared to those with FEV 1 ≥ 50% predicted (19/45 [42.2%] vs. 2/14 [14.3%], p = 0.04). However, the rate of positive sputum bacterial culture did not differ between patients with FEV 1 < 30% predicted and those with FEV 1 ≥ 30% predicted (8/20 [40.0%] vs. 13/39 [33.3%], p = 0.61). Similarly, the rate of positive viral etiology was not statistically different between COPD subjects with varying disease severity based on lung function.

Hospital length of stay, the need for NPPV support, death rates during the same admission and at 12 months, and re-admissions to the hospital within 12 months were assessed in relation to bacteriology and virology results. Patients with a positive viral etiology were more likely to require NPPV support than those without viral identification through either NPA or serology (41.7% vs. 11.5%, p = 0.01). Age, sex, the presence of co-morbid medical illnesses (such as diabetes mellitus, hypertension, cerebrovascular accidents, ischaemic heart disease, congestive heart failure.

Discussion:

This study represents the first randomized double-blinded placebo-controlled trial investigating the use of corticosteroids in hospitalized patients with Community-Acquired Pneumonia (CAP). Our findings revealed no discernible benefits associated with the adjunctive use of corticosteroids, whether administered intravenously or orally. It's important to note that the impact of prednisolone on the duration of intravenous antibiotic therapy is likely limited. CAP can be caused by various pathogens, and the effects of prednisolone may vary accordingly.

Notably, in our study, patients with pneumococcal pneumonia who received corticosteroids exhibited a higher clinical failure rate. While we did not observe any significant effects on outcomes for other pathogens, it's possible that the sample size for these groups was too small to detect any differences(10).

Several limitations should be acknowledged in our study. Firstly, we did not assess adrenal function in these patients, so we lack data regarding the presence of relative adrenal insufficiency. Secondly, our use of clinical cure as the primary outcome is a subjective parameter and susceptible to bias. However, we believe it closely mirrors routine clinical practice, and the randomized design minimizes the introduction of bias.

Moreover, the exclusion criteria necessitating corticosteroid therapy may have resulted in an underrepresentation of patients with Chronic Obstructive Pulmonary Disease (COPD). Patients with COPD who develop concurrent bronchial obstruction and CAP typically require systemic corticosteroids. Although the question of whether mortality from CAP is higher in COPD patients remains a topic of debate, the potential exclusion of these patients could introduce selection bias. In our study, the proportion of patients with COPD was 20.2%, whereas a previous study conducted in our hospital reported a figure of 36.6% for CAP patients with COPD. Therefore, it's important to refrain from extrapolating our findings to patients with CAP and COPD, as generalizability is limited.

Conclusion:

It's essential for all prescribers to adhere to the prescription format, maintain the average number of drugs per prescription as low as possible, and promote prescribing by generic name. This approach not only constitutes rational therapy but also leads to economic benefits and facilitates the identification of problems related to drug use, such as polypharmacy, drug interactions, and adverse reactions.

Conducting studies on this matter will assist health care providers in understanding the epidemiological behaviour of various dermatological conditions. This knowledge will enable them to ensure the uninterrupted availability of necessary medications. Ultimately, these measures will enhance the efficiency and effectiveness of our healthcare system.

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