



Evaluation of Albumin Utilization in a Major Teaching Hospital in Iran before and after Guideline Implementation

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ABSTRACT

Background: Inappropriate use of drugs is one of the major issues in health care system. Rational drug utilization based on the appropriate guidelines has an important role in management of use of expensive medications. We aimed to evaluate albumin usage's appropriateness based on evidence-based indications before and after implementing albumin prescription guideline in a teaching hospital.

Methods: This study was performed in two phases. During two-month periods, all the patients who were ordered to receive albumin were evaluated. The first phase was done in November and December of 2017, during which, based on physicians' comments, the guideline was finalized and then implemented. Phase two was performed in May and June 2018.

Results: Albumin was prescribed appropriately in 33 patients (55%) in the first phase and 43 (70%) patients in the second phase. 299 vials in the first phase and 456 vials in the second phase were prescribed which 198 vials (66%) and 394 (86%) vials were used with appropriate indications, respectively. The number of vials consumed with inappropriate indication decreased significantly from 101 vials (34%) in the first phase to 62 vials (14%) in the second phase (P-value=0.01). The average cost of the inappropriate indication per patient decreased from \$197.3 ± 131.6 in the first phase to \$183.5 ± 126.8 in the second phase (P-value=0.52).

Conclusion: This study showed implementing a DUE program and designing a guideline for rational prescribing of albumin and interventional methods can optimize treatment duration, significantly decrease inappropriate usage, and avoid unnecessary hospital costs.

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Introduction

Lately, the increased drug costs due to inappropriate use of

medications have become a major issue in every health care system (1). Rational drug utilization is based on the appropriate

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guidelines and clinical needs of patients and has an important role in health care management (2). Drug use evaluation (DUE) is explained as a program for evaluating the process of prescribing, dispensing, or administering a drug (dose, indications, drug interactions, and length of administration) and ensuring the rational consumption of that drug (3). DUE is of great importance for expensive and great volume drugs, drugs with a narrow therapeutic index and broad-spectrum antibiotics due to their clinical and economic impacts (4). DUE is a valuable method for evaluating the quality and financial aspect of prescriptions. Conducting DUEs and reporting their results will help physicians to change their prescribing patterns, especially for expensive or commonly used drugs, and reduce treatment costs.

Albumin is one of the most significant blood proteins, which has various physiological functions and plays an important role in maintaining oncotic pressure, metabolite transportation, immune-modulation and endothelial stabilization (5). Albumin is the first-line therapy in plasmapheresis, paracentesis, extensive burn, and spontaneous bacterial peritonitis. Several studies have been implemented on albumin usage, indicating it is used in unjustified and unapproved indications that are not supported by high-grade clinical evidence (6-10). Compared with crystalloids, albumin has not revealed any advantage concerning hospital stay or mortality when used for volume resuscitation (11). Therefore, to improve albumin's rational consumption, educational programs and institutional and local guidelines are required. Due to albumin's high cost, controversies regarding its indications and potential adverse reactions (12), hard production process, the likelihood of disease transmission, and accessibility of other reasonably priced alternatives with the same efficacy, it is essential to launch a feasible guideline for albumin usage and restrict its inappropriate consumption (13).

In a report of Iran Food and Drug Administration in 2008, albumin had the highest cost paid for a single drug in hospitals (10). In the first six months of 2017 in Razi hospital, a teaching hospital of Guilan University of medical sciences, 3082 vials of albumin 20% were used at the cost of \$98,218 and albumin was one of the most expensive drugs in this hospital. We aimed to evaluate albumin usage's appropriateness based on evidence-based indications before and after implementing albumin prescription guideline in this hospital.

Methods

This study was a prospective cross-sectional before and after interventional study, which was conducted in 2-months phases, and all patients with albumin prescriptions in each phase were recruited into the study. Before starting the first phase, a standard guideline on albumin indications based on albumin studies (5-9, 13), international guidelines such as the American Society of Health-System Pharmacists (ASHP) (14), and the approved protocol of the ministry of health of Iran was designed and approved by two physicians and a clinical pharmacist. Also, a data collection form was developed by the clinical pharmacist.

During the first and second phases, medical records of all patients who received albumin were examined. Relevant data, including age, gender, and laboratory data including serum levels of albumin and total protein, and dose (vial number), duration, and an indication of albumin were collected. Additional information, including data related to costs and hospital stay, was obtained from the hospital information system. During the study, we did not count repeated physicians' orders as a separate order unless indications were different.

The first phase was done in November and December of 2017. All patients who were prescribed albumin were included in the study. Each patient was evaluated based on the designed guideline. Patients who received albumin based on standard indications were considered to have an appropriate indication, and patients who received albumin without indication were defined as having inappropriate indication. If the indication for prescribing albumin was inappropriate, the clinical pharmacist would consult the physician to stop or not prescribe albumin to the patient.

After the first phase, Educational sessions were held to present the designed guideline to physicians, including medical students (residents and interns). Obtained data from the first phase were reported to the physicians involved in the prescription of albumin. After the physicians' final review and corrective comments, the guideline was approved by the drug and therapeutic committee (Table 1). The approved guideline was then sent to all hospital wards before starting phase 2 of the study, after that the request for albumin must have been accompanied by filling out the application form.

Table 1. Approved indications for the albumin use.

Therapeutic plasmapheresis	Plasma exchange more than 20 mL/kg in one session, or more than 20 mL/kg/week in frequent sessions. Dose: 15%-25% of 1-1.5 total plasma volume with albumin 20% and the remaining with normal saline 0.9%.
Paracentesis	If >4-5 L of ascitic fluid removed. Dose: 6-8 g of albumin for each L removed
Spontaneous bacterial peritonitis (SBP)	If one of the below conditions present <ul style="list-style-type: none"> • serum creatinine >1 mg/dL • blood urea nitrogen >30 mg/dL, or • total bilirubin >4 mg/dL Dose: 1.5 g albumin/kg (up to 150 g) within 6 h of finding and 1.0 g/kg on third day (up to 100 g)
Hepatorenal syndrome (HRS)	Diagnosis of HRS: serum creatinine not falling below 1.5 mg/dL after cessation of diuretics for at least two days and start of volume expansion with an albumin infusion Dose: 1 g/kg (up to 100 g) daily for two consecutive days Treatment of Type I HRS in critically ill: Dose: Albumin for at least two days as an intravenous bolus (1 g/kg per day [100 g maximum]) in combination with Norepinephrine (0.5 to 3 mg/hr).
Liver transplantation	Patients with ascites and peripheral edema who have not responded to first-line diuretic therapy, hemoglobin of more than 8 g/dL and serum albumin less than 2.5 g/dl; Dose: $(2.5 - \text{Alb}) \times \text{Kg} \times 0.8$
Nephrotic syndrome	If serum albumin <2.5 g/dl: provided that diuresis is not established by 1) increasing the diuretic dose 2) reached the ceiling dose of furosemide (maximum 80 mg three times a day 3) not responding to furosemide infusion Dose: 40 to 80 mg of furosemide mixed with 6.25 to 12.5 g of albumin.
Major gastrointestinal Surgery >40% of liver resection or extensive intestinal resection	if one of the below conditions exists: <ul style="list-style-type: none"> • Crystalloid refractory hemodynamic compromise (mean arterial pressure <60, central venous pressure <8 in spite of maximum 40 mL/kg crystalloid as 500 mL doses every 30 min in the setting of hypoalbuminemia (serum albumin \leq2.5 g/dL) Dose: single-dose intravenous infusion of 100 mL (20 g) of albumin 20%, in addition to 300 mL appropriate crystalloid solution • Clinical instability: Mesenteric ischemia, allograft function in the setting of hypoalbuminemia Dose: Intravenous infusion of 100 mL albumin 20% every 8 h up to three doses
Hypovolemic shock	If no response to crystalloids or colloids; Contraindication to non-protein colloids.

We performed the second phase in May and June 2018; the clinical pharmacist assessed all albumin requests in the format of above-mentioned application form received from wards. After the clinical evaluation of patients, if there was no indication according to the guideline, the patient's medical team was informed to stop or not prescribe albumin. If the patient's physician accepted the consultation for not requiring albumin, the patient would not be prescribed albumin. If not, albumin was administered to the patient.

Specific outcome criteria including indications, duration of albumin therapy, distribution of albumin consumption in different wards, and cost reduction were evaluated and compared between the first and second phases.

It should be noted that the available albumin dosage form during the study was 50-mL vials containing 20% albumin solution. The cost of each albumin vial was estimated based on the average price announced by the Ministry of Health of Iran. All costs are stated in US dollars (1 US\$ = 38,000 Rials).

Data analysis was done using SPSS software (Statistical Package for the Social Sciences, version 25.0; SPSS Inc.,

Chicago, Illinois, USA). Quantitative results were reported as mean ± SD and qualitative results as a number and percentages. The Chi-square test was used for nominal variables. The independent t-test was also used to compare the differences before and after implementing the guideline (the first and second phases) for quantitative variables. The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1397.010), and the privacy of the patients was assured.

Results

In the first phase, 60 requests, and in the second phase, 61 requests were registered. Demographic data and laboratory tests, including serum albumin and total protein levels, in both groups are given in Table 2. There was no significant difference between patients' demographic and laboratory data in the first and second phases. An overview of the appropriateness of prescriptions regarding the indication, albumin usage details, and the cost of albumin used for each phase are presented in Table 2.

Table 2. Patients' demographic and laboratory data.

	First phase (60)		Second phase (61)		P-Value
Age (mean ± SD)	16.764 ± 53.63		13.694 ± 58.662		0.107
(%) (Gender (male))	(60) 36		(59) 36		0.91
Weight (Kg) (mean ± SD)	13.05 ± 67.45		69.54 10.5 ±		0.33
Serum albumin (g/dl) (mean ± SD)	0.44 ± 2.69		0.53 ± 2.79		0.28
Total protein (g/dl) (mean ± SD)	0.58 ± 5.34		0.55 ± 5.07		0.56
Albumin use duration	2.962.74±		3.342.89±		-
Total cost of used albumin	\$10,512		\$16,032		-
Clinical outcome of patients N (%)					0.47
Total Recovery	29 (48.3)		26 (42.6)		
Partial Recovery	13 (21.7)		11 (18)		
Demise	17 (28.3)		24 (39.4)		
Discharge Against Medical Advice	1(1.7)		0 (0)		
Hospital Stay (days) (mean ± SD)	Patients with an inappropriate indication	Patients with an appropriate indication	Patients with an inappropriate indication	Patients with an appropriate indication	0.136
	16.96 11.58 ±	17.30 13.14 ±	21.27 16.09 ±	17.20 15.47±	

The total number of vials of albumin consumed in the first phase of the study was 299 and in the second phase was 456. In the first phase, the highest demand was for the nephrology department with 17 requests (28.3%), and the poisoning department and emergency department had the lowest number with one request (1.6%). In the second phase, the highest number of requests came from the ICU with 18 requests (29%), and the Endocrinology and Rheumatology wards with one request (1.6%) had the lowest number. In the first phase of the study, 27 cases (45%) were identified as inappropriate indications, and this decreased to 18 cases (30%) in the second phase, which was not statistically significant (P-value = 0.39). Also, the number of vials consumed with inappropriate indication decreased significantly from 101 vials (34%) in the first

phase to 62 vials (14%) in the second phase (P-value = 0.01). The highest number of inappropriate indications in both phases were in the nephrology and ICU wards.

The two most common inappropriate albumin indications in the first phase of the study were hypoalbuminemia (56%) and nephrotic syndrome (17%) and in the second one were hypoalbuminemia (46%) and paracentesis (13%).

In the first phase, the total cost of consumed albumin was \$10,512, and in the second phase was \$16,032 if the price of each vial (\$35) remained constant. The average cost of the inappropriate indication per patient decreased from \$197.3 ± 131.6 in the first phase to \$183.5 ± 126.8 in the second phase (P-value = 0.52). Also, if we approved inappropriate requests that were not answered in the study, it could have cost \$2,863.

Table 3. Comparison of inappropriate indication of albumin in before and after intervention in different wards.

Ward	Total orders		Inappropriate indication		P-Value
	First phase	Second phase	First phase	Second phase	
Intensive care unit	N=6	N=18	N= 2 Hypoalbuminemia: 1 Paracentesis: 1	N= 4 Hypoalbuminemia: 3 Paracentesis: 1	0.68
Operating room	N= 7	N= 7	N= 0	N= 0	-
Emergency department	N= 6	N= 3	N= 4 Hypoalbuminemia: 3 Paracentesis: 1	N= 0	0.18
Acute care unit	N= 1	N= 3	N= 1 Hypoalbuminemia: 1	N= 3 Hypoalbuminemia: 3	1
Urology department	N= 2	N= 0	N= 0	N= 0	-
Triage	N= 1	N= 0	N= 1 Hypoalbuminemia: 1	N=0	
Surgery department	N= 3	N= 5	N= 2 Hypoalbuminemia: 1 Paracentesis: 1	N= 3 Hypoalbuminemia: 1 Paracentesis: 1 Nephrotic syndrome: 1	0.92
Internal department	N= 6	N= 4	N= 4 Hypoalbuminemia: 4	N= 3 Hypoalbuminemia: 3	0.9
Pulmonary department	N= 3	N= 0	N= 1 Hypoalbuminemia: 1	N= 0	-
Endocrinology & Rheumatology department	N= 2	N= 1	N= 1 Hypoalbuminemia: 1	N= 0	0.5
Gastroenterology department	N= 4	N= 9	N= 1 Hypoalbuminemia: 1	N= 1 Hypoalbuminemia: 1	0.32
Poisoning department	N= 1	N= 2	N= 1 Paracentesis: 1	N= 2 Hypoalbuminemia: 2	1
Nephrology department	N= 17	N= 9	N= 9 Hypoalbuminemia: 6 Nephrotic syndrome: 3	N= 2 Hypoalbuminemia: 1 Nephrotic syndrome: 1	0.31

Discussion

Today, the cost of drugs is one of the main parts of the entire hospital's budget, so controlling the use of drugs and their rational prescribing will save many hospital expenses. This study showed that at an academic medical center, albumin's prescribing practices are inconsistent among physicians. Our study presented that more than 45% of the indications were inappropriate during the whole study period. Studies in other medical centers have shown that 36 to 95% of albumin indications were inappropriate (7, 8, 15), disagreement on albumin prescription indications in different studies and implemented guidelines are the cause of differences in these studies' results.

During this study, interventions were performed in both phases to rationalize albumin consumption. The total number of vials consumed with inappropriate indication was significantly reduced from 34% in the first phase to 14% in the second phase (P -value = 0.01). Due to the high costs of albumin, inappropriate usage of albumin leads to great wastage of treatment funds. Although this study only evaluated patients for two months, if we extrapolate data before and after the intervention to evaluate one-year cost, our hospital would have spent \$21,210 before the intervention and \$13,020 after the intervention per year on albumin for indications which are not standard or unsupported by literature, emphasizing a major opportunity for cost avoidance. In other studies, 67.9% (10) and 77% (9) of the albumin vials were used irrationally, so the role of continuing education in patients' beds is important in reducing irrational prescription. A reduction in the cost of albumin consumption per patient and a reduction in the number of inappropriate albumin vials per patient was observed in the second phase of the study, consistent with similar studies (6, 7).

In this study, despite the decrease in albumin requests for hypoalbuminemia from the first to the second phase, this indication remained the most inappropriate indication for both the first and second phases of the study, which is consistent with Laki et al., (6). In the first phase, 34 out of 60 requests were related to hypoalbuminemia, of which 18 requests were inappropriate, and in the second phase, 28 out of 61 requests were related to hypoalbuminemia, of which 13 requests were inappropriate. The purpose of using albumin in this indication is to correct hypoalbuminemia, which can improve edema due to hypoalbuminemia by increasing osmotic pressure and causing diuresis. However, the use of albumin is not recommended just to increase the concentration of plasma albumin, and in these cases, the underlying cause of this complication should be identified and treated (16). Before this study, the appropriate time to discontinue albumin in patients with hypoalbuminemia was unknown in this center. There were several cases that after a daily order of albumin due to hypoalbuminemia, albumin

vials were continued for several days without supervision. Currently, in this center, physicians follow the guideline and follow the prescribed dose of 60 grams of albumin (7). In addition, after starting albumin, periodic albumin levels are checked for patients during treatment, and if the albumin level is reached above 2.5 g/dl, it will be temporarily stopped. Therefore, it seems that the implementation of the guideline has played an important role in creating this change. It should be noted that in different guidelines, there is a disagreement on the management of patients with severe hypoalbuminemia and the target level for treatment. Different guidelines have defined different threshold levels in the range of 1.5-2.5 g/dl for albumin prescription (6), which in our study was considered 2.5 g/dl.

In this study, the number of appropriate requests in the second phase increased compared to the first phase. However, one of the important cases observed during this study was the lack of knowledge about the correct dose of albumin for each of its indications. In other words, although albumin was started with the appropriate indication, the appropriate prescribed dose was not prescribed for that indication, or after the start of albumin, the albumin was not discontinued at the appropriate time. It was observed that following the rationalization of albumin consumption in the second phase, the number of prescribed albumin decreased for some indications, but for some other indications that, according to the guideline, required high amounts of albumin, such as paracentesis, plasmapheresis, and hepatorenal syndrome; with the knowledge of the correct dose, the number of albumin consumption increased. Therefore, informing and educating about the appropriate indications for albumin consumption in order to rationalize the use of this drug does not necessarily mean a reduction in the number of vials consumed. Also, due to the addition of a liver transplant patient with the indication of receiving albumin in the second phase of the study and the absence of a liver transplant patient in the first one, the amount of rational albumin consumption increased. A lack of effective communication with the treatment staff, in other words, non-compliance of some physicians with the hospital guideline, caused some inappropriate requests.

Conducting DUE studies without repeated follow-ups has a limited role in improving rationalization of drug consumption. Therefore, periodic re-evaluations are recommended to continue the implementation of the rational albumin prescribing guideline. It is also necessary to hold regular sessions with physicians in order to provide reports on the implementation of hospital guidelines for correction and subsequent changes. Establishing a stable and regular interaction with physicians to receive feedback and opinions about the designed guidelines will improve this process.

Limitations: This study had some limitations due to

resource shortage. Firstly, a limited number of patients could be evaluated in the first and second phases. The use of albumin guideline for the second phase was not obligatory for physicians, so some continued their prescription practice. At present, there is no complete guideline or protocol in our country that is based on evidence and accurately states the rational indications for albumin consumption.

This study showed that implementing a DUE program and designing a guideline for rational prescribing of albumin and interventional methods such as continuing education and feedback for albumin prescribing can optimize treatment duration, significantly decrease inappropriate vials' usage, and avoid unnecessary hospital costs.

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