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Tigecycline Use in Surgical Intensive Care Unit for the Treatment of Complicated Intra-Abdominal Infections: A Real-World Study

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Abstract

OBJECTIVES: To describe real-world use of tigecycline in cIAIs patients. **METHODS:** A retrospective, observational study enrolled cIAIs patients hospitalized in The First Affiliated Hospital, Sun Yat-sen University from January 1, 2013 to June 30, 2017 was conducted. Patients' data were collected and matched based on age, gender, and Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score according to receiving first-line, later-line, or no tigecycline during hospitalization. **RESULTS:** Data were collected for 52 patients. 82.6% were male. Mean age was 57.8 years and APACHE II score was 14.8. The incidence of both extended-spectrum beta-lactamase producing and carbapenem-resistant pathogens was high on initial culture; however, few patients received first-line tigecycline. No significant difference in mortality rate was identified among first-line, later-line and no tigecycline users. Of surviving patients, shorter hospital length of stay was observed for patients receiving first- vs later-line or no tigecycline, respectively. ICU length-of-stay was shorter in patients receiving first- vs later-line or no tigecycline. **CONCLUSIONS:** First-line tigecycline use was rare in our surgical intensive care unit. Resistant organisms were commonly cultured from initial specimens. Although these results are limited by small patient numbers and single center, our results suggest that early tigecycline use may have significant benefits with similar mortality. Further research is warranted to demonstrate the values of early tigecycline use in cIAIs patients.

Keywords

Tigecycline, Complicated Intra-Abdominal Infection, Multidrug-Resistant

1. Introduction

Intra-abdominal infections have a high incidence and are often associated with poor prognosis [1]. Complex intra-abdominal infections (cIAIs) refer to bacteria passing through defects in the digestive tract and invading the peritoneal cavity, leading to abscess formation or peritonitis. The clinical treatment of complex intra-abdominal infections is complicated, and patients admitted to the ICU are generally difficult to solve by a single treatment. The treatment includes drainage of effusion or control of infection under surgical and interventional guidance, supplemented by broad-spectrum antibiotics. Appropriate empirical antimicrobial therapy can increase the success rate of clinical treatment, reduce the length of hospital stay and hospitalization costs, and minimize antimicrobial resistance caused by selective pressure. Inappropriate treatment can lead to treatment failure, prolong hospital stay, and increase mortality.

The conditions of critically ill patients are complex, and most of them have used a variety of anti-infective drugs in the early stage. As a result, it is very difficult to choose antibiotics after being transferred to ICU [2] [3]. Tigecycline, as a new type of glycyl-type broad-spectrum antibacterial drug, is the first antibiotic approved by the U.S. FDA for the treatment of complex intra-abdominal infections [4]. It is particularly effective to multiple pathogens isolated from patients with complex intra-abdominal infections and has good antibacterial activity *in vitro*. This article retrospectively analyzes the real-world data of tigecycline use in a surgical ICU for the treatment of complex intra-abdominal infections, and provides a basis for the selection of antibiotics for clinical complex intra-abdominal infections.

2. Methods

2.1. Data Source

We performed a retrospective analysis of hospitalization data obtained from the surgical intensive care unit of The First Affiliated Hospital, Sun Yat-sen University.

Patients

All patients hospitalized in our surgical ICU from January 1, 2013 to June 30, 2017 were screened. The inclusion criteria are: 1) diagnosed with cIAIs; 2) ≥ 18 years old. The exclusion criteria include: 1) tigecycline administration is not for abdominal infections; 2) severe infection in other parts of the body; 3) existence of immunodeficiency (e.g. HIV); 4) history of alcohol abuse; 5) no drug susceptibility results, or no culture specimens obtained within one week after using antibiotics. Patients were categorized into the case group if they received tigecycline within 24 hours of confirmed pathogen test results. Those who did not receive tigecycline during this time period were categorized into the control group. Matched controls were selected based on age, gender, the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, lab results, and previously used antibiotics. First-line TGC users were those who received TGC

as the first antibiotic during hospitalization. Later-line TGC users were those who received TGC after prior antibiotic administration. All patients were followed up to discharge or death, which came first.

2.2. Analyses

Descriptive analyses were conducted on patient baseline characteristics. Clinical and economic outcomes were compared between the treatment groups. Antibiotic use prior to TGC administration was assessed among patients treated with later-line TGC therapy and confirmed carbapenem-resistant or extended spectrum beta-lactamase (ESBL)-producing organisms.

3. Results

3.1. Patient Characteristics

Data from 52 patients were collected. 82.6% of the patients were male, with the mean age of 57.8 years and the mean APACHE II 14.8. Despite matching patients receiving TGC to those not receiving TGC therapy on APACHE II score, the score was lower in patients not receiving TGC vs those receiving TGC. Patients not receiving TGC may not be comparable to patients receiving TGC due to their underlying conditions. Therefore, comparisons between the TGC and no TGC treatment groups were not performed. APACHE II scores were similar in patients receiving first- vs later-line TGC. The incidence of both carbapenem-resistant pathogens and ESBL-producing organisms was high on the initial abdominal culture; however, few patients received first-line TGC (**Table 1**).

3.2. First-Line vs Later-Line TGC

Among TGC users, no statistically significant differences were found in mortality. Of surviving patients, shorter hospital length of stay was observed for patients who received first- vs later-line TGC therapy. Of survivors admitted to the ICU, length of ICU stay was shorter in patients receiving first- vs later-line TGC, but with no statistical significance. No statistically significant difference was found in antibiotic costs between patients receiving first- and later-line TGC therapy.

Table 1. Baseline Characteristics by TGC Use.

		No TGC	First-line TGC	Second-line TGC	P value
Age		61.7 ± 9.68	55.4 ± 16.4	51.2 ± 17.0	0.066
Gender	Male	25	10	8	0.222
	Female	3	2	4	
APACHE-II		13.7 ± 5.7	15.8 ± 8.6	17.4 ± 4.9	0.348
Bacteria	Gram-Negative	19	10	6	0.219
	Gram-Positive	9	2	6	
ESBL (N)		15	6	1	0.069
Carbapenem-resistant (N)		4	2	2	0.821

3.3. Antibiotics Used Prior to TGC Therapy

Among patients with carbapenem-resistant infections, imipenem, teicoplanin, and meropenem were the most frequently used antibiotics before initiation of TGC therapy. Among patients with ESBL infections, imipenem was the most frequently used antibiotics before initiation of TGC therapy.

4. Discussion

Since the pathogenic bacteria of early complicated intra-abdominal cavity infections are mostly Enterobacteriaceae, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, etc., the sensitivity rate of carbapenems to Enterobacteriaceae was almost 100% in early years; therefore, carbapenem antibiotics have always been the most effective antibiotics for the treatment of severe cIAIs. However, in recent years, bacteria resistant to carbapenem antibiotics in local areas have gradually shown an increasing trend, and the related mortality rate has also been climbing [5] [6]. This shows that for these patients, the sensitivity of carbapenem antibiotics has a downward trend.

There are many reasons for the increase in drug resistance, and some studies suggest that overexposure may be one of the important factors. A prospective study in Greece showed that frequent use of carbapenems and polymyxins and a longer treatment course were factors influencing carbapenem antibiotic resistance, and polymyxins was an independent risk factor for multiple drug resistance (Multidrug-resistant, MDR) [7]. Recently, the resistance of non-fermenting bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* has increased by years. Particularly, the sensitivity of carbapenems has decreased significantly. The emergence of some pan-resistant strains is of more concern.

Tigecycline belongs to a new type of glycyclcycline antibacterial drug. Its mechanism is similar to that of tetracycline antibiotics. After administration, it can bind to bacterial 30S ribosomes to prevent transfer RNA from entering, thereby effectively inhibits peptides chain formation, interrupts bacterial structure and makes it difficult for bacteria to perform certain functions, which ultimately exerts antibacterial effect and inhibits bacterial reproduction. Tigecycline has a strong binding ability to ribosomes. After injection, about 22% of the drug will be excreted in the urine, with an average elimination half-life of 27 h. The antibacterial spectrum is very broad, mainly including *Acinetobacter baumannii*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Aeromonas hydrophila*, *Citrobacter klebsiella*, and *Klebsiella pneumoniae*. These pathogens are highly sensitive to Tigecycline and have obvious therapeutic effects.

For critically ill patients with sepsis and septic shock in surgical ICU, tigecycline treatment can significantly reduce the mortality rate [8]. Especially in sepsis patients with multi-drug-resistant bacteria infection, tigecycline is an important antibiotic. A meta-analysis from 15 studies showed that tigecycline could increase clinical treatment inefficiency and mortality [9]. However, some studies suggested that the increased mortality caused by failure of tigecycline treatment

may be related to the low dose of tigecycline [10]. A recent study comparatively analyzed the effects of tigecycline and other antibacterial drugs in the treatment of complex intra-abdominal infections, and found that the short-term prognosis of the two groups of patients was similar, suggesting that tigecycline is one of the options for patients with complex intra-abdominal infections [11].

5. Limitations

Our study results are limited by small patient numbers and data from single hospital, but our results suggest that early TGC use may have significant economic benefits with similar mortality. Additional research is warranted to further demonstrate the value of early TGC therapy in patients hospitalized with cIAIs in China.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Transcatheter Aortic Valve Dislocation in Left Ventricular Outflow Tract with Successful Repositioning Using “Double Snare” Technique

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Abstract

Background: Transcatheter aortic valve implantation (TAVI) is a widely used treatment of severe aortic stenosis. Implantation of a self-expanding valve into a dense calcified aortic annulus can be challenging and may result in device malposition and malfunction. **Aim:** The aim of our case report is to present a novel technique of transcatheter aortic valve dislocation treatment. **Case presentation:** An 86-year-old woman with severely calcified aortic valve underwent TAVI using a 27-mm self-expanding Portico valve (Abbott Vasc, USA). In the last phase of implantation, the valve dislocated deep into the left ventricular outflow tract resulting in significant paravalvular regurgitation and patient instability. Repositioning of the valve with a single snare was ineffective because of severe aortic ring calcifications. A novel “double snare” technique was applied and the valve was successfully repositioned upward with an excellent anatomic and haemodynamic result. **Conclusion:** “Double snare” technique can be an effective strategy for repositioning of deeply implanted self-expanding transcatheter aortic valves. It represents an efficient bailout strategy in case of single snare approach failure, especially in cases of severe aortic ring calcifications.

Keywords

Aortic Valve, Transcatheter Aortic Valve Replacement, Complications, Aortic Valve Stenosis

1. Introduction

Transcatheter aortic valve implantation (TAVI) is a widely used treatment of aortic stenosis. Prosthesis dislocation immediately after TAVI deployment is a

rare complication and is usually a result of prosthesis-annulus mismatch associated with too high or too low implantation, ejection of the device by an effective ventricular contraction during deployment or lack of significant calcifications for prosthesis anchoring [1] [2] [3]. Deployment of self-expanding valves requires a slow release of tension that builds up in the delivery system. Caution is thus warranted since any undesirable motion from the patient or operator can lead to a dislocation [4]. Most frequently, the valve embolizes upward into the ascending aorta. In such case, upward snaring and repositioning of the embolized valve and placement of a second valve is the usual strategy [2]. In case of downward intra-ventricular valve dislocation, the situation is much more challenging with the final valve position being of utmost importance. Here, we present a case of transcatheter aortic valve dislocation in the left ventricular outflow tract (LVOT) with successful repositioning using a novel percutaneous approach.

2. Case Presentation

An 86-year old woman with arterial hypertension and osteoporosis was admitted for treatment of severe symptomatic aortic stenosis. Transthoracic echocardiography (TTE) showed normal left ventricular systolic function, impaired left ventricular diastolic function and a calcified trileaflet aortic valve with severe aortic stenosis (aortic valve area 0.7 cm², maximal velocity of 3.9 m/s, mean gradient of 42 mmHg and doppler velocity index of 0.25). Coronary angiogram showed normal coronary arteries. She was evaluated by the local heart team and TAVI was recommended due to her age and high operative risk (STS 6.2%). Computed tomography angiogram showed a severely calcified aortic ring and ascending aorta (**Figure 1**), an annulus area of 418 mm² and an average annular diameter of 23 mm, peri-meter 71 mm (**Figure 2**). We decided for an implantation of a Portico 27 mm valve (Abbott Vasc, USA) via right transfemoral approach.

Transcatheter aortic valve introducer was placed through the right femoral artery and a pig-tail catheter through 6F introducer in the left femoral artery. The aortic valve was initially crossed with a 0.0035-inch straight-tip wire that was later exchanged for a 0.0035-inch Amplatz SS (Boston Scientific, Burlington, Massachusetts) using an Amplatz left (AL) 1 catheter (Launcher, Medtronic). After a pre-dilatation with a Zelos PTA 22 × 40 mm balloon (OptiMed, Germany), a 27-mm self-expanding Portico valve (Abbott, Abbott Park, Illinois) was positioned across the aortic annulus and slowly released under fluoroscopic guidance. At the end of the valve opening the valve dislocated into the LVOT (**Figure 3**).

Low valve implantation resulted in severe paravalvular regurgitation leading to a drop in arterial pressure from 120/65 mmHg to 110/25 mmHg. With immediate right ventricular pacing at 110 bpm the diastolic pressure rose to 35 mmHg. In attempt to reposition the valve a 25-mm Amplatz Gooseneck Snare was introduced through the AL 1 6F guide catheter (Launcher, Medtronic)

through a contralateral femoral access and looped around the valve attachment post toward the greater curvature of the aorta. Snaring was ineffective as we obtained only a rotation of the valve frame. Therefore a second 25-mm Amplatzer Gooseneck Snare was introduced ipsilaterally through a cut AL 1 6F guiding catheter and looped around the valve attachment post towards the smaller curvature of the aorta. Even when using two snares there was not enough support for effective pulling. We decided to add support to the second snare with an AL 1 6F catheter. Both snares were shortened and fixed with a pean clamp (**Figure 4**).

We applied simultaneous pulling of both snares and AL 1 catheters (mother-in-child), the “double snare” technique. With exchange of tension from one snare to the other (by using steady moderate traction on one snare and progressive intermittent pulling on the other one) we were able to successfully retract and reposition the prosthesis (**Figure 5**).

The patient remained hemodynamically stable during the procedure and a rise in arterial pressure to 120/65mmHg was observed following valve repositioning. Targeted TTE showed normal prosthetic valve function, without paravalvular regurgitation. Aortogram demonstrated good valve position in the aortic root with no residual aortic regurgitation (**Figure 6**).

No tachyarrhythmias, conduction abnormalities or cerebrovascular complications were observed during the procedure and follow-up. At 1 year follow-up the patient had no complaints and denied dyspnoea or chest pain on exertion.

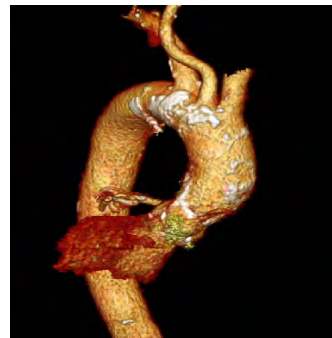


Figure 1. CT aortogram: severely calcified aortic ring and ascending aorta.

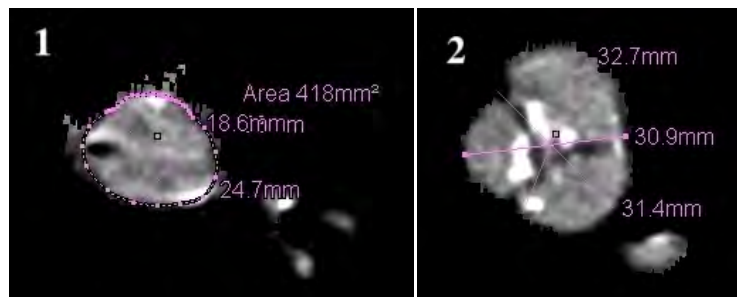


Figure 2. CT aortogram: 1) aortic annulus measurement, 2) aortic bulbus measurement.

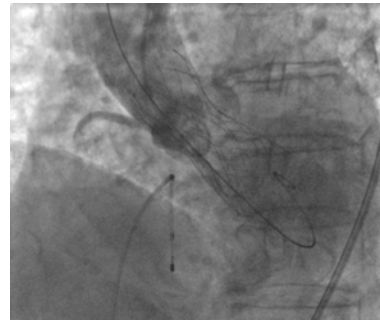


Figure 3. Portico 27-mm valve dislocation in the left ventricular outflow tract.

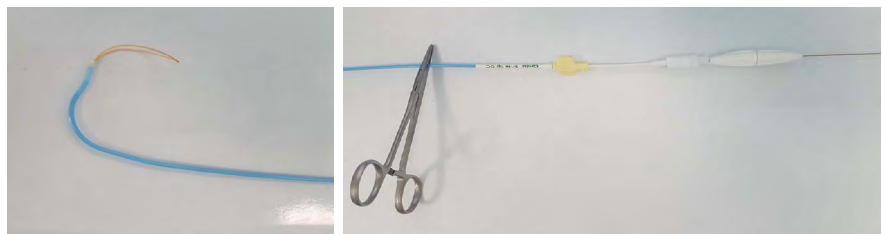


Figure 4. Snares introduced through AL 1 catheter and fixed with a pean clamp.

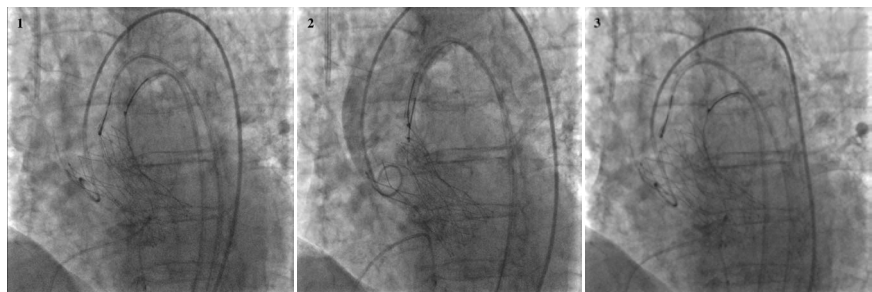


Figure 5. “Double snare” technique: two Amplatzer Gooseneck Snare were introduced through AL 1 6F catheters (mother-in-child) (1). With exchange of tension from one snare to the other the valve was successfully repositioned (2 and 3).

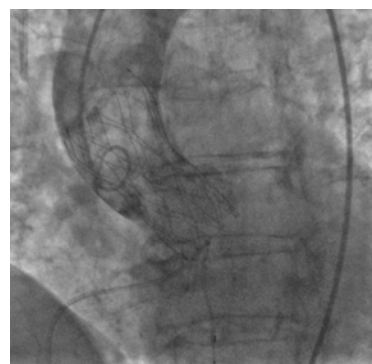


Figure 6. Final valve position with no residual regurgitation.

3. Discussion

Implantation of a self-expanding valve into a dense calcified aortic annulus can be challenging and may result in device malposition and malfunction. We pre-

sented a case of deep LVOT prosthetic aortic valve dislocation with successful repositioning using a novel percutaneous “double snare” technique. Very low LVOT valve positioning leads to severe aortic regurgitation, haemodynamic instability and potential need for cardiac surgery [5]. If mild sub-annular dislocation is suspected, balloon valvuloplasty with gentle pulling of the device into the ascending aorta can be an acceptable and relatively safe repositioning strategy [4]. Recently the use of snares has been proposed via radial or transfemoral access as a bailout option for cases of severe valve dislocation. The procedure carries a high risk of failure due to difficulties in correct valve repositioning [4] [6] [7] [8]. There have been several case reports of snaring maneuvers described in the literature. Ponangi *et al.* reported [7] a successful use of a single snare technique for a downward dislocated Portico valve with a 25-mm Amplatzer Goose-neck Snare. However, there were no significant calcifications of the aorta present which could aggravate the repositioning procedure. Similarly, a single snare repositioning of the CoreValve system (Medtronic, Dublin, Ireland) with the use of a 35-mm Gooseneck snare was reported by Vavouranakis *et al.* [9]. Furthermore Beute *et al.* [4] managed to reposition a CoreValve system (Medtronic, Dublin, Ireland) and a newer CoreValve Evolute Pro valve (Medtronic, Dublin, Ireland) with the use of a 6F EN Snare (Merit Medical System, South Jordan, UT, USA). In all previous cases the single snare technique was described as technically demanding but feasible. A technique with two snares with additional right radial access has also been proposed but not used [7]. Failure of the single snare technique in our complex case of Portico valve dislocation in the LVOT led us to use a novel, double snaring technique with two snares. The low valve dislocation was probably a result of anatomical irregularities and improper implantation steps. As severe calcifications of the aortic ring can complicate proper valve positioning the operator tried to prevent upward valve migration with gentle pushing towards the LVOT which resulted in inadvertent downward valve dislocation. Firstly, we haemodynamically stabilized the patient with ventricular pacing at 110 bpm. Attempts of repositioning the valve using the single snare technique were unsuccessful. Furthermore, the use of two snares looped around the valve attachment post was inefficient, probably due to severe aortic calcifications. The pulling strength of both snares (“double snare” technique) was improved by AL 1 catheter support (mother-in-child). Pulling force could also be improved by introducing a second snare through a right radial artery and attaching it to the smaller valve curvature attachment post. However, we decided for a different strategy and insisted on bifemoral approach. With the exchange of tension from one snare to the other we were able to retract the prosthesis towards the ascending aorta to an excellent final position at the level of the natural aortic valve.

4. Conclusion

It is seldom necessary to reposition a self-expanding transcatheter aortic valve

following deployment. However, when needed, few options are available to snare the valve in order to achieve proper positioning. To our knowledge, we are the first to describe a transcatheter aortic valve repositioning using two snares. The “double snare” technique may be used as an effective repositioning strategy for deeply implanted transcatheter self-expanding aortic valves, especially in cases of severe aortic ring calcifications and ineffective single snare techniques.

Disclosures

There are no relationships with industry related to this article.

Informed Consent

The patient discussed in the following case has given an informed consent.

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None.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Efficacy Analysis of Glucocorticoids in the Treatment of Allergic Purpura in Tibetan Children

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Abstract

Background: Henoch Schonlein Purpura (HSP) is a common immune-related allergic disease in children. It is very important to understand the clinical features of this disease for doctors. **Objective:** To explore the clinical efficacy of glucocorticoids in the treatment of HSP in Tibetan children at high altitude, and to analyze the possible causes of HSP in children at high altitude. The risk factors of the disease provide a reference for the treatment of HSP in children in high altitude areas. **Methods:** Selecting January 2015 to November 2020, 88 children diagnosed with Henoch-Schonlein Purpura in the outpatient and inpatient departments of the People's Hospital of Bomi County, Tibet Autonomous Region were the subjects of the study. Its gender, age of onset, season of onset, predisposing factors, allergy history, first symptoms, clinical manifestations, laboratory examinations, etc., perform retrospective analysis. **Results:** Among 88 children with allergic purpura, 55 were boys, accounting for 62.5%, and 33 were girls, accounting for 37.5%. Men have more cases than women. All have clinical manifestations of purpura of the skin, among which 35 cases have obvious triggers, of which the above there were 26 cases of respiratory infections, 6 cases of dietary factors, and 3 cases of contact with allergic substances. Simple skin type: 18 cases, accounting for 20.45%; Abdominal type: 6 cases, accounting for 6.82%; 2 male cases, accounting for 33.33%; 4 female cases, accounting for 66.67%; Articular type: 8 cases, accounting for 33.33%; Renal type: 2 cases, accounting for 2.27%; 54 cases of mixed type, accounting for 61.36%. After glucocorticoids, the rashes disappeared, no any adverse reactions. **Conclusion:** Allergic purpura in children

*Zhang-Xiangyu, Nima Zhaxi and Zhang-Shunde contributed equally to this work. They are the co-first authors.

is more common in school-age children, and upper respiratory tract infection is the main predisposing factor. Skin purpura is the main clinical manifestation, often associated with lower extremity joint swelling and pain. There is no significant difference in the efficacy and course of the disease between intravenous and oral treatment. Therefore, clinicians should strictly grasp the indications of glucocorticoids to reduce the occurrence of complications.

Keywords

Plateau, Tibetan, Children, Glucocorticoids, Allergic Purpura

1. Introduction

HSP is a systemic vasculitic disease which is common in children, and one of the systemic vasculitis, mainly with capillary vasculitis as the main pathological change, and its pathological change is extensive aseptic capillitis. It is accompanied by edema and congestion [1] [2]. The non-thrombocytopenic purpura, arthritis or joint pain, abdominal pain, gastrointestinal bleeding and nephritis are the main clinical manifestations. The common age of onset is 7 - 14 years old, and it is rare in infants under 1 year-old [3] [4]. Its etiology and pathogenesis are complex. The mechanism is not clear, and the incidence of the disease has been increasing year by year in recent years. At present, the clinical treatment methods are still mainly anti-allergic and symptomatic treatment. But severe cases are often accompanied by gastrointestinal tract, and kidneys injuries and other organ injuries [5] [6]. It requires clinicians to adopt appropriate diagnosis and treatment plans in time. Current research mostly focuses on plains. The treatment plan and clinical characteristics of children with HSP are the main ones. There is still a lack of relevant data on the treatment of HSP in children with high altitude Tibetans, and there is insufficient reference for clinical diagnosis and treatment. This study focuses on retrospective analysis of the 88 cases of HSP children treated in the Department of Pediatrics of the People's Hospital of Bomi County, Tibet Autonomous Region from January 2015 to November 2020, and provides recommendations for the treatment of HSP in the plateau area.

2. Clinical Data and Methods

2.1. Inclusion Criteria [7]

1) Age 1 - 16 years old, native Tibetan children of plateau; 2) Meet the diagnostic criteria of HSP; 3) Do not combine with other types of purpura (such as blood Small plate reduced purpura) and other blood system diseases (such as leukemia); 4) The clinical data is perfect.

2.2. Exclusion Criteria [7]

1) Congenital dysplasia, hepatosplenomegaly, systemic lupus erythematosus; 2) Recent severe systemic infection, primary kidney disease, such as kidney Glomerulonephritis; 3) Recently took glucocorticoids or other immunosuppressive agents.

2.3. Treatment Methods

All 88 children with Henoch-Schonlein purpura were treated with glucocorticoids, antihistamines, vitamin C and calcium, and their condition improved. Children were given oral or intravenously injected with dexamethasone (Huanan Pharmaceutical Group Co., Ltd., Guangdong, China, State Drug Approval Document Number: H44024469) at 0.25 mg/(kg·d). The drug was gradually reduced to stop.

2.4. Efficacy Criteria

Healed: Skin purpura subsides, and other symptoms disappear; Significant effect: Most skin purpura subsides, and symptoms are significantly reduced; Effective: Skin purpura partially subsides, and the symptoms have improved; ineffective: skin purpura recurs, and other symptoms aggravate.

2.5. Statistical Processing

Application SPSS 25.0 software for processing. Counting data is expressed as a percentage, measurement data is expressed as $\bar{x} \pm s$, $P < 0.05$ is statistically significant.

3. Results

3.1. General Situation

Among 88 cases of Henoch-Schonlein Purpura, 55 were boys, accounting for 62.5%, and girls: 33, accounting for 37.5%. Men had more cases than women. The results are shown in **Table 1**. The age of onset is 1 to 16 years old, with 1 infant, accounting for 1.14%; 22 cases from 5 to 7 years old, accounting for 25%; 44 cases were 8 to 12 years old, accounting for 50%; 21 cases were 13 to 16 years old, accounting for 23.86%. The results are shown in **Table 2**.

3.2. Clinical Feature

Among the 88 children with Henoch-Schonlein purpura, the simple skin type: 18 cases, accounting for 20.45%, including 15 males, accounting for 83.33%, females 3 cases, accounting for 16.67%; abdominal type: 6 cases, accounting for 6.82%, 2 male cases, accounting for 33.33%, 4 female cases, accounting for 66.67%; 8 cases of articular type, accounting for 9.1%, of which 4 were male, accounting for 50%, and 4 were female, accounting for 50%; renal type: 2 cases, accounting for 2.27%, and There are 2 males, accounting for 100%, 0 females,

accounting for 0%; 54 mixed cases, accounting for 61.36%, of which 32 are males, accounting for 59.26%, 22 cases were female, accounting for 40.74%. The results are shown in **Table 3**.

3.3. Performance of Skin Damage

All 88 children with allergic purpura had clinical manifestations of skin purpura, among which 35 cases had obvious triggers, among which the upper respiratory tract infection. There were 26 cases of infection, 6 cases of dietary factors, and 3 cases of contact with allergic substances. From the point of view of the distribution of purpura, most of them involve double under. The limbs are distributed symmetrically, followed by the hips and upper limbs. The back of hands, feet, trunk and face are rare. It may be accompanied by a sensation of itching. In severe cases, it may be accompanied by angioedema, purpura or hemorrhagic maculopapular rash of various sizes, different shapes, and pressure. The color does not fade, and sometimes it can be fused into a piece. The time for the rash to resolve varies depending on the condition of the disease, mostly ranging from 5d - 7 days (**Figure 1**).

3.4. Treatment Time

88 cases of children with Henoch-Schonlein purpura according to the course of the disease: 60 cases within 10 days of treatment, 26 cases within 10 - 15 days, and 2 cases were more than 15 days. For example, the results are shown in **Table 4**. Among them, 36 children were treated with intravenous glucocorticoids, 29 cases were treated for ≤ 10 days, and 10 - 15 days accounted for 5 cases, 2 cases were more than 15 days or more, the results are shown in **Table 5**. 52 children were treated with oral corticosteroids, and the treatment was less than 10 days, Among 31 cases, 10 - 15 days accounted for 21 cases, and ≥ 15 days 0 cases. The results are shown in **Table 6**.

Table 1. Sex of 88 cases of Henoch-Schonlein purpura.

Gender	Number of cases	Percentage (%)
Male	55	62.5
Femal	33	37.5

Table 2. Age of onset of 88 cases of Henoch Schonlein purpura.

Age	Number of cases	Percentage (%)
Infancy (<1 years old)	1	1.14
Preschool (5 - 7 years old)	22	25
School age (8 - 12 years old)	44	50
Puberty (13 - 16 years old)	21	23.86

Table 3. Treatment time of 88 cases of Henoch-Schonlein purpura.

Days	Number of cases	Percentage (%)
Simple skin type	18	20.45
Abdominal type	6	6.82
Articular type	8	9.1
Renal type	2	2.27
Mixed type	54	61.36

Table 4. 88 cases of allergic purpura treatment time.

Days	Number of cases	Percentage (%)
≤10 days	60	68.2
10 - 15 days	26	29.5
≥15 days	2	2.3

Table 5. 36 cases of intravenous glucocorticoid treatment time.

Days	Number of cases	Percentage (%)
≤10 days	29	80.6
10 - 15 days	5	13.9
≥15 days	2	5.5

Table 6. Treatment time of 52 cases of oral corticosteroids.

Days	Number of cases	Percentage (%)
≤10 days	31	59.6
10 - 15 days	21	40.4
≥15 days	0	0

**Figure 1.** After treatment, the child's rash subsided.

4. Discussion

In recent years, the prevalence of allergic purpura in children has been increasing. The pathogenesis is mainly immunological abnormalities and humoral immune abnormalities. It also involves cellular immunity with the participation of inflammatory cells, cytokines and inflammatory mediators. There are microvascular and interstitial in renal pathology damage. Non-thrombocytopenia and palpable skin purpura are necessary conditions for the diagnosis of HSP, and the rash is not the only phenotype in all children. Some children have joint pain or abdominal pain as the first symptoms, which can be as long as two weeks without rash [8]. Therefore, it is often easy to cause misdiagnosis. For example, when some children often have lower limbs or ankle joint swelling and pain as the first symptom, parents think it is caused by falls or sprains [9], or some children have purpura nephritis. When symptoms such as hypertensive encephalopathy will occur, if treatment is delayed [10] [11]; even when HSP abdominal type has not yet appeared skin purpura or has appeared but has not been detected, it is misdiagnosed as acute For acute abdomen such as appendicitis, laparotomy is performed. The symptoms of abdominal pain in children cannot be relieved or further aggravated, causing a series of complications and increasing the difficulty of follow-up treatment [12]. Therefore, clinicians must be vigilant for children with unexplained abdominal pain before the appearance of typical skin purpura, provide auxiliary examinations if necessary, and be cautious in laparotomy to avoid misdiagnosis that may increase the pain and damage the health of the child.

At present, there is no specific treatment plan for HSP, and comprehensive treatment is still the mainstay. Adrenal corticosteroids are added to those with severe gastrointestinal symptoms and joint swelling and pain, and those with nephropathy or rapidly progressive nephritis are treated with methylprednisolone shock treatment [13] [14]. For HSP treatment, it is necessary to strictly grasp the indications, to improve the clinical prognosis of children to the greatest extent, and to actively give immunosuppressive treatment and support symptomatic treatment [15]. In addition, the study also found that some children have kidney damage, and the degree of kidney damage is critical to the prognosis. The increase in urine microprotein excretion can be earlier than urine routine or urine protein quantitative examination, which is helpful for the early diagnosis of occult kidney damage [16] [17]. This study shows that among 88 allergic purpura cases, 55 are boys, accounting for 62.5%, and 33 are girls, accounting for 37.5% of men have more cases than women. The age of onset ranges from 1 to 17 years old. There is 1 case of infants and young children, accounting for 1.14%; 5 to 7 years old 22 cases were aged 8 to 12 years, accounting for 25%; 44 cases were 8 to 12 years old, accounting for 50%; 21 cases were 11 to 16 years old, accounting for 23.86%. Among them, the simple skin type: 18 cases, accounting for 20.45%, of which 15 cases are male, accounting for 83.33%, and 3 cases are female, accounting for 16.67%; Abdominal type: 6 cases, accounting for 6.82%, 2 male cases, accounting for 33.33%, 4 female cases, accounting for 66.67%; articular type 8 cases, accounting for 33.33%, including 4 males, ac-

counting for 50%, 4 females, accounting for 50%; kidney type: 2 cases, accounting for 2.27%, including 2 males, accounting for 100%, 0 females, accounting for 0%; 54 mixed cases, accounting for 61.36%, including 32 males, accounting for 59.26%, females 22 cases, accounting for 40.74%. All children have clinical manifestations of skin purpura, of which 35 cases have obvious triggers, of which the above. There were 26 cases of respiratory infections, 6 cases of dietary factors, and 3 cases of contact with allergic substances. From the distribution of purpura, it affects both lower extremities and is symmetrically distributed. Secondly, it can affect the buttocks and upper extremities. The back of hands, feet, trunk and face are less common. Sometimes purpura may also be accompanied by itching, in severe cases it may be accompanied by angioedema, purpura or hemorrhagic maculopapular rashes of various sizes and shapes. It is different and does not fade under pressure. Sometimes it can be fused into a piece. The time for the rash to subside varies with the treatment of the condition, mostly ranging from 5d - 7 days. Among them, 60 cases were treated within 10 days, 26 cases were treated for 10 - 15 days, and 2 cases were more than 15 days. Among them, 36 children were static. Glucocorticoid treatment, 29 cases were treated for ≤ 10 days, 5 cases were 10 - 15 days, 2 cases were ≥ 15 days, 52 cases were children with oral glucocorticoid therapy, 31 cases were treated within 10 days, and 21 cases were treated within 10 - 15 days, confirmed that there was no difference between intravenous and oral corticosteroids in the curative effect and course.

5. Conclusion

In summary, Henoch-Schonlein Purpura is a common and frequently-occurring disease in children, and can involve multiple systemic systems. Factors are related. The age of onset of allergic purpura in our region is mostly 8 - 12 years old, male > female; mixed purpura is common; simple skin is second; most of them have no cause for onset; there is no significant difference in curative effect and course of disease between intravenous and oral treatment, so clinicians should strictly grasp the indications of glucocorticoids to reduce the occurrence of complications. Due to the small number of observations and short time in this study, its overall long-term efficacy needs to be further confirmed in a multi-center, large sample, prospective clinical double-blind randomized controlled study.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Well Controlled Blood Pressure in Turkish Patients: How Many Drugs Are Required to Attain and Maintain the Blood Pressure Goal?

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Abstract

Background: This study aimed to determine the number of antihypertensive agents required to achieve optimal blood pressure (BP) in Turkish hypertensive patients. **Material and Methods:** Totally 400 hypertensive patients (114 males and 286 females) were enrolled. BP was measured by patients at home twice a day. The patients were called for controlling in every four weeks, and those who had BP < 140/90 were not followed-up. In patients with BP > 140/90 drug, doses were increased or another antihypertensive drug added and the patients were continued to be followed-up. **Results:** In the first follow-up (on the 4th week), 152 (38%) patients, including 35 (31%) men and 117 (41%) women, attained the goal BP. The mean duration of hypertension in single, double, triple, and quadruple treatment groups was 6.2 ± 5.0 , 6.8 ± 5.9 , 8.8 ± 5.4 , and 10.4 ± 6.6 years, respectively. In the beginning, the median number of agents used for each patient was 2.17. When the follow-up was concluded, the median of agents used for each patient was 2.72. **Conclusion:** Thirty-eight percent of participants had controlled hypertension in the first follow-up. Women had better BP control. The median number of agents required for attaining and maintaining BP goal was 2.72. More drugs are needed when hypertension gets longer.

Keywords

Blood Pressure, Antihypertensive Agents, Hypertension

1. Introduction

Hypertension is a major cause of morbidity and mortality, affecting almost every

organ system in the body. It is estimated that nearly one billion people are affected by hypertension worldwide [1]. Hypertension is associated with an increased risk for cardiovascular, cerebrovascular, and renal events [2] [3]. The Framingham Heart Study reported that the risk of major cardiovascular events increases with increasing severity of hypertension in all age groups [4]. Besides, Lewington *et al.* demonstrated that death from ischemic heart disease and stroke increases progressively starting from a systolic BP of 115 mm Hg and a diastolic BP of 75 mm Hg [5].

Practice guidelines for the management of hypertension recommend a BP goal of <140/90 mm Hg [6] [7]. More rigorous goals are recommended for patients with diabetes [6] [7] [8] and proteinuric chronic kidney disease [2] [7] [9]. However, despite the availability of several classes of antihypertensive drugs and several drugs in each class from which to choose, achieving BP goal is difficult in many patients.

The number of antihypertensive agents required to achieve optimal BP is unpredictable. It is difficult to find prospective studies aiming to determine the absolute mean number of drugs. Although some studies have information about the number of drugs used, this information is only presented as secondary data.

In this study, we aimed to examine the number of antihypertensive agents required to achieve optimal BP in Turkish hypertensive patients.

2. Material and Methods

In a total of 400 consecutive patients, previously diagnosed with essential hypertension, who attended the Medicana International Hospital Internal Medicine outpatient clinic between January 2016 and March 2017 were included in the study. The exclusion criteria included a history of notable cerebrovascular or cardiovascular disease within 6 months before the screening visit; abnormal serum electrolyte levels at screening (sodium < 135 mEq/l, potassium < 3.5 or >5.5 mEq/l); evidence of hepatic diseases (determined by any of the following: aspartate aminotransferase or alanine aminotransferase values greater than twice the upper limit of normal, a history hepatic cirrhosis); chronic kidney disease (determined by any of the following: a history of dialysis or a history of nephrotic syndrome and having an estimated glomerular filtration rate < 50 ml/min per 1.73 m² in the 3 months before screening); pancreatic disease or injury; uncontrolled, treated type 2 diabetes (glycosylated hemoglobin > 8.5%) and patients over 80 years of age.

Medication usage was assessed during the screening visit. Drug classes included angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers, calcium channel blockers (dihydropyridine and nondihydropyridine), diuretics (thiazide and potassium-sparing), alpha-adrenergic receptor antagonists (Doxazosin), and central-acting drugs (Rilmenidin).

The patients were questioned for age, duration of hypertension, educational status, smoking habit, and diabetes status. Standardized anthropometric mea-

surements (weight, height) were obtained on individuals in light clothing without shoes. Body Mass Index (BMI) was calculated as body weight divided by height squared (kg/m^2). Serum lipid levels (LDL-c, HDL-c, VLDL-c, and Triglyceride) were measured in all patients.

All patients measured systolic and diastolic BP at home using their digital or manual sphygmomanometers. Patients were trained in the BP measurement method and tested. BP measuring devices were checked for the accuracy. BP was measured by patients twice a day (in the morning, and the afternoon or evening). The patients were followed for 36 weeks.

The patients were called for controlling in every four weeks, and those who had BP $< 140/90$ were not followed-up for longer. In patients with BP $> 140/90$ drug doses were increased or another antihypertensive drug added and continued to be followed-up. We noted the number of agents used for each patient at the beginning of the study and when the follow-up was concluded.

We compared groups for the duration of hypertension in terms of the numbers of drugs used.

The data analyses were performed with SPSS version 20 software for Windows. Kolmogorov-Smirnov normality tests were applied to examine whether the data showed normal distribution or not. The comparison between men and women, with controlled hypertension at week four, was made via chi-square test. The comparison between groups for the duration of hypertension was made via independent sample's t-test. A value of $p < 0.05$ was considered to be statistically significant.

3. Results

A total of 400 patients, 114 males (28.5%) and 286 females (71.5%), were evaluated in the study (**Table 1**).

Among the patients, 103 (25.75%) were using monotherapy, 155 (38.75%) were taking two different classes of drugs, 115 (28.75%) were using three different classes of drugs, 25 (6.25%) were taking four different classes of drugs, and 2 (0.5%) were taking at least five different classes of drugs (**Table 2**).

The ratio of ACE inhibitors, ARBs, β -blockers, calcium channel blockers, diuretics, α -adrenergic receptor antagonists, and central-acting drugs were 60.75%, 28.0%, 21.75%, 33.5%, 59.0%, 4.75%, and 3.75%, respectively (**Table 3**).

In the beginning, the median number of agents used for each patient was 2.17. In the first follow-up (week four) 152 (38%) participants, including 35 (31%) men and 117 (41%) women, had controlled hypertension and their follow-up did not continue. The female patients had significantly better BP control ($p < 0.001$).

The numbers (proportion) of patients achieving the BP goal at weeks 8, 12, 16, 20, 24, 28, 32 and 36 were 193 (48.2%), 268 (67.0%), 297 (74.2%), 330 (82.5%), 342 (87.0%), 361 (90.2%) and 364 (91.0%), respectively (**Figure 1**).

Thirty six (9%) patients left the study before their follow-ups were completed.

Duration of hypertension in single, double, triple, and quadruple treatment groups were 6.2 ± 5.0 , 6.8 ± 5.9 , 8.8 ± 5.4 , and 10.4 ± 6.6 years, respectively. Duration of hypertension was longer in multiple drug groups (**Table 4**).

When the follow-up was completed and optimal BP control was provided the median number of agents used for each patient was 2.72.

Table 1. Demographic and baseline characteristics.

Variables	Group (n = 400)
Gender (n, %)	
Male	117 (29.25)
Female	283 (70.75)
Total	400 (100)
Age (years, mean \pm SD)	58.05 \pm 10.2
Education level (n, %)	
Illiterate	157 (39.25)
Literate	42 (10.50)
Primary school	181 (45.25)
High school-University	20 (5.00)
Duration of HT (years, mean \pm SD)	8.3 \pm 5.6
Diabetes presence (n %)	95 (23.75)
Smoker status (n %)	
Smoker	50 (12.5)
Non-smoker	350 (87.5)
Cholesterol (mg/dl)	218
LDL-c (mg/dl)	158
HDL-c (mg/dl)	42
VLDL-c (mg/dl)	33
Triglyceride (mg/dl)	193
BMI	30.93 \pm 3.56
BMI distribution (n, %)	
Normal weight	59 (15.75)
Overweight	153 (38.25)
Obese	169 (42.25)
Morbid obese	19 (4.75)

HT: Hypertension, BMI: Body mass index.

Table 2. No. of antihypertensive medications used among patients.

No of drug classes	Number	P% (SE)
1	103	25.75 (2.7)
2	155	38.75 (2.8)
3	115	28.75 (2.2)
4	25	6.25 (1.2)
5	2	0.65 (0.7)

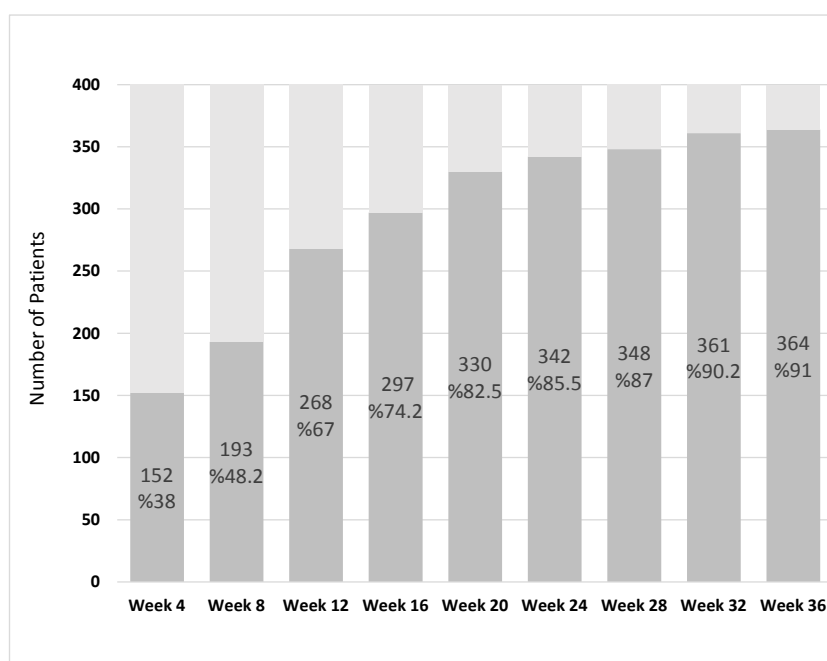
Table 3. Type of antihypertensive medications used among patients.

Antihypertensive medication class	Number	Percentage (SE)
ACEI	243	60.75 (2.8)
ARB	112	28.00 (1.7)
β -blocker	87	21.75 (3.1)
Calcium channel blocker	134	33.50 (3.2)
Diuretic	236	59.00 (2.5)
α -adrenergic receptor antagonist	19	4.75 (1.0)
Central-acting drug	15	3.75 (0.8)

ACE: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers.

Table 4. Comparison between groups regarding the duration of hypertension.

	Mono vs. double therapy	Mono vs. triple therapy	Mono vs. quadruple therapy	Double vs. triple therapy	Double vs. quadruple therapy	Triple vs. quadruple therapy
P	0.428	<0.001	0.001	0.006	0.006	0.213

**Figure 1.** Number (%) of patients achieving BP goal.

4. Discussion

Although the risks associated with hypertension are known and the array of effective antihypertensive medications available, the control of BP remains suboptimal. Even in controlled randomized trials, where patient motivation and physician expertise are ensured, it has been difficult to achieve optimal BP [10].

In our study 152 (38%) participants reached the goal BP in the first follow-up. Hypertension control rates are in the average of those obtained in five European countries in men (31% in Turkey for values ranging from 14.3% in Spain to 39.7% in England) and is little higher in Turkish women (41%) than values ranging from 19.5% in Sweden to 40.5% in England [11]. In the US, 1999-2004 data from the National Health and Nutrition Examination Survey showed that the BP control rate in hypertensive subjects was 29.2% + 2.3% in 1999-2000 and 36.8% + 2.3% in 2003-2004 [12]. The control rates are not better in the rest of the world and vary considerably between countries and regions, and also vary within countries by age, gender, race/ethnicity, socioeconomic status, education, and quality of health care [13] [14]. Among higher risk populations with diabetes mellitus or chronic kidney disease (CKD), the proportion of uncontrolled patients is higher too. Of NHANES participants with CKD, only 37% and only 25% of participants with diabetes were having controlled BP < 130/85mm-Hg [15] [16].

Our findings showed also better BP control in women (41% vs. 31%). Data on the association of gender with hypertension control have been conflicting. In NHANES III (1988-1994), rates of awareness and control among hypertensive cases were significantly higher in women compared with men [15] [17]. However, in the 1999 to 2004 NHANES, there was no significant difference between men and women as a result of significant increases in treatment and control rates in men [18]. But many studies either in Europe [19] [20] or in the US [21] or other countries showed a better BP control in women [22]. Possible reasons for this could be a higher awareness and compliance, low alcohol intake, and higher health concern.

In the beginning of our study the median number of agents used for each patient was 2.17, but when the follow-up was completed and optimal BP control was provided the median number of agents used for each patient was 2.72. A study that analyzed the number of antihypertensive drugs used in different clinical trials reported that the median of agents used for each patient was 2.8 [23] [24] [25].

The majority of hypertensive patients need more than one antihypertensive agent to achieve BP targets. Numerous clinical trials conducted during the 1990s found that most hypertensive patients (including those considered to have a higher cardiovascular risk) required two or more medications to achieve BP goals [23] [26] [27]. In a recent randomized, double-blind study conducted on 2271 patients with stage 2 hypertension even in the triple therapy arm, BP control was achieved only by 71% of patients [28]. These results indicate that mul-

tiple-drug therapy is required in most patients with hypertension.

Current hypertension guidelines acknowledge that two or more antihypertensive agents are necessary for the majority of patients to reach BP goals associated with reduced risk of cardiovascular events [6] [7] [29]. The JNC-7 report suggests starting with two antihypertensive drugs in those patients with a systolic BP greater than 20 mmHg over the BP goal and/or greater than 10 mmHg over the diastolic goal [7]. European guidelines suggest combination therapy as a first step when initial BP is at least 160/100mmHg or when cardiovascular risk is high [6]. In this regard, the 2009 reappraisal of the European Guidelines on hypertension management recommends a more individually tailored approach for the management of hypertension, especially in high-risk patients [30].

Classically, guidelines recommended “start low, go slow”. This meant that treatment should be initiated at low doses and with slow increases. But, several trials have shown that when the titration of drugs is very gradual, patients are at risk of presenting cardiovascular outcomes before BP goals are obtained, especially in those with diabetes or previous cardiovascular disease [31] [32].

Besides, guidelines recommend the selection of antihypertensive agents with different mechanisms of action to enhance the BP-lowering effect [6] [7]. The fact that hypertension is caused by interacting multifactorial mechanisms means treatment will be more effective if the drugs have different mechanisms of action [6]. Each constituent drug can neutralize counter-regulatory mechanisms activated by the other [33]. In addition, different pathways leading to elevated BP can be affected [6].

We also report a significant correlation between the duration of hypertension and the requirement for more drugs to achieve BP goals. Duration of hypertension in patients using multiple medications was longer. The need for higher dosage and more medication with the extension of the duration of hypertension is a common observation. Many questions arise about this subject. In fact, antihypertensive drugs are limited in terms of variation. Could the continuous effect of the same medication molecules on the same receptors cause a change in the receptor after a while? Could the non-response to the treatment be owing to the ineffectiveness caused by duration? Is a good BP control sufficient reason not to change the treatment? Would a change in medication from time to time be thought just to overcome resistance? Even though it is not a strong antihypertensive drug (but a different molecule) the benefit of adding spironolactone in reducing BP supports this thought. Recent trials have shown the benefit of adding spironolactone to the baseline strategy in RH patients [34] [35].

The present study has several limitations. Laboratory parameters were not routinely evaluated after the initiation of the study. Our study was not designed to test for effects on clinical outcomes. In the follow-ups of patients, we have preferred daily BP measuring at home, instead of periodically measuring BP in the office. Since all the patients had already been diagnosed with hypertension before and, most of them possessed a BP measuring device and a small percen-

tage of the patients acquired a measuring device via friends and relatives, which affected our decision accordingly. Moreover, either themselves or other persons at home, all the patients had experience in measuring BP. We checked the devices that were brought to us, but we cannot claim that all the devices were checked. Even though some setbacks occurred in daily measurements and making notes of BP, the patients made a satisfactory effort in this regard. The fact that the study was done in a metropolis like Istanbul, with understandable reasons, made it difficult for the patients to come for regular follow-ups. Therefore, the planned 24-week patient follow-up process was extended to 36 weeks.

5. Conclusion

More than 50% of hypertensive patients require two or even more drugs for the adequate control of their BP. To attain and maintain goal BP, using multiple drugs, changes in medications and more aggressive strategies should not be avoided. More drugs are needed when hypertension gets longer.

Ethical Statement

The study has been conducted and concluded with the Ethics Committee Approval (date 01.18.2016, decision no: 007) of our institution Biruni University, School of Medicine, Medicana International Hospital.

Informed consent was obtained from all participants; for illiterate participants, informed consent has been given from those authorized to represent them.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Erratum to “PECS Block Provides Effective Postoperative Pain Management for Breast Cancer Surgery—A Retrospective Study”, [International Journal of Clinical Medicine, 2017, 8, 198-203]

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<https://doi.org/10.4236/ijcm.2017.83019>) unfortunately contains some mistakes. The author wishes to correct the errors in pain management tools, method, and figures.

Our article had some mistakes in pain management tools, method, and figures. The followings are the list of errata and correct figures.

[List of Errata]

	TRUE	FALSE
P.198 2nd line of Abstract	total or partial mastectomy	modified radical mastectomy
P.199 10th line of Materials and Methods		
P.202 4th line of Conclusions		
P.198 7th line of Abstract		
P.199 6th line of Materials and Methods	numeric rating scale	visual analog scale
P.202 1st line of Conclusions		
P.199 last line	numeric rating scale (NRS)	visual analog scale (VAS)
P.200 7th line of Result		
P.201 1st line of Discussion	NRS	VAS
P.202 12th from top		

Continued

P.200 3rd line of Table 2	12	11
	35	27
P.200 3rd line of Table 2	0.0013	0.016
P.198 7th line of Abstract		
P.199 7th and last line of Materials and Methods	0, 0 - 4, 4 - 6, 6 - 12, 12 - 24 hours	0, 1, 2, 4, 6, 12, 24 hours
P.200 5th line		
P.202 1st line of Conclusions		

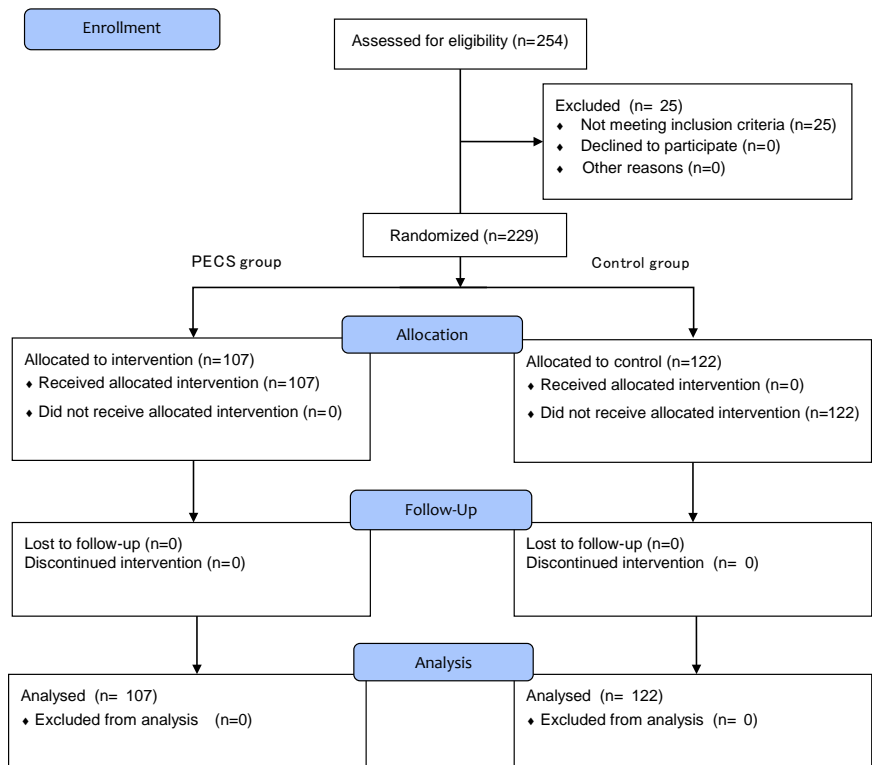


Figure 1. Flowchart of this study.

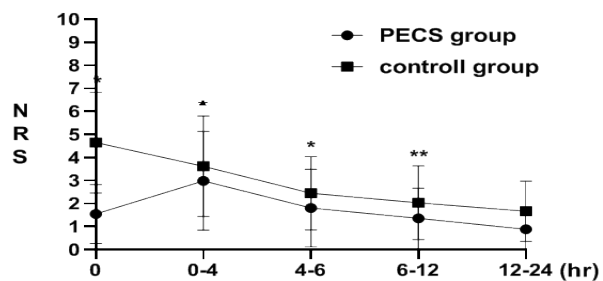


Figure 2. Postoperative NRS score at 0 - 4, 4 - 6, 6 - 12, 12 - 24 hours postoperatively. *P < 0.01; **P < 0.05.

***Raoultella planticola* Bacteremia-Induced Fatal Septic Shock and Sepsis-Induced Coagulopathy in a Patient with Pancreatic Cancer: A Case Report and Literature Review**

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Abstract

Background: *Raoultella planticola* is a gram-negative rod-shaped bacterium commonly found in water and soil and considered to be a rare and possibly underestimated cause of severe human infection. Its presence should be suspected in older patients with a history of cancer, immune suppression and recent exposure to traumatic injuries or invasive medical procedures. **Case presentation:** A 78-year-old male with a history of hypertension was diagnosed with pancreatic adenocarcinoma. Whipple procedure (pancreaticoduodenectomy) was performed afterwards. On the 8th day of surgery, the patient was admitted to our tertiary ICU with septic shock. His initial Sequential Organ Failure Assessment (SOFA) score was 12 with predicted mortality 95.7%. Empirical antibiotic therapy with colymycin, meropenem and teikoplanin was administered immediately and two sets of blood cultures were obtained. Patient developed refractory septic shock despite the addition of vasopressin and the patient's condition continued to deteriorate. Patient died on the third day of sepsis. His blood culture was positive for *R. planticola*, which was identified using the VITEK-2 biochemical identification system. **Conclusions:** Clinicians should be aware of fatal unusual infections in immunocompromised patients.

Keywords

Antibiotic Resistance, Bacteremia, Sepsis

1. Introduction

Raoultella planticola is a gram-negative rod-shaped bacterium commonly found

in water and soil and considered to be a rare and possibly underestimated cause of severe human infection [1]. It was previously described as *Klebsiella planticola* and *K. trevisanii*; relatively recently these two were combined into single species in 1986, i.e., *K. planticola*, based on DNA-DNA homology. In 2001, *K. planticola* was renamed *R. planticola* based on 16SrRNA and rpoB gene sequencing [2].

Although *R. planticola* is mainly an aquatic and soil bacterium, it has been clinically isolated from human sputum, stool, wounds, and urine. Its presence should be suspected in older patients with a history of cancer, immune suppression and recent exposure to traumatic injuries or invasive medical procedures. The frequent involvement of the biliopancreatic tract suggests the importance of the gut flora as a bacterial reservoir in clinically relevant infections. Herein, we report a *Raoultella planticola* induced fatal sepsis in an immunocompromised patient with pancreatic cancer.

2. Case Report

A 78-year-old male with a history of hypertension was diagnosed with pancreatic adenocarcinoma. Due to significant mass effect on the biliary tract, jaundice and epigastric pain chemotherapy was planned. Whipple procedure (pancreaticoduodenectomy) was performed afterwards. On the 8th day of surgery the patient became febrile and hemodynamically unstable. Patient was admitted to our tertiary ICU with septic shock. On admission to our unit blood pressure was 70/30 mmHg, heart rate was 135 bpm; oxygen saturation was 72; body temperature was 38.4°C. Patient was intubated. Thoracoabdominal examination showed tenderness in the epigastrium and bilateral reduced breath sounds. Chest x-ray revealed bilateral lung infiltrates (Figure 1). Laboratory tests showed marked elevation of c reactive protein (CRP) (260.5 mg/dl; normal range <6 mg/dl) and procalcitonin (18.13 ng/ml; normal range <0.05 ng/ml). Complete Blood Count evaluated white blood cell 36,470/ μ L with 89.7% neutrophils and platelet count of 47,000. Coagulation tests (Aptt 66.2 sec, PT 24.2 sec, INR 1.88, D dimer 5.59 mcg/ml) supported sepsis induced coagulopathy (Table 1). His initial Sequential Organ Failure Assessment (SOFA) score was 12 with predicted mortality rate was 95.7%.



Figure 1. Bilateral pulmonary infiltrates on chest x-ray.

Table 1. Scoring for the diagnosis of sepsis-induced coagulopathy.

Category	Parameter	0 point	1 point	2 points
Prothrombin time	PT-INR	≤1.2	>1.2	>1.4
Coagulation (×10 ⁹ /L)	Platelet count	≥150	<150	<100
Total SOFA	SOFA four items	0	1	≥2

Diagnosed as sepsis induced coagulopathy when the total score is 4 or more with total score of prothrombin time and coagulation exceeding 2. Total SOFA is the sum the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA). The score of total SOFA is defined as 2 if the total score exceeded 2. INR, international normalization ratio; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment.

Noradrenaline infusion was initiated to support blood pressure following adequate fluid resuscitation. Empirical antibiotic therapy with colymicin meropenem and teikoplanin was administered immediately and two sets of blood cultures were obtained. Acute kidney failure and deep metabolic asidosis developed with potassium levels of 6.7 mEq/L and bicarbonate level of 8 mmol/L. Despite the initiation of dextrose and insulin infusion potassium levels remained high and the patient had an episode of ventricular tachycardia (VT). Hemodiafiltration with citrate anticoagulation was started on day 2 of admission. Patient developed refractory septic shock despite the addition of vasopressin and the patient's condition continued to deteriorate. Patient died on the third day of sepsis. His blood culture was positive for *R. planticola*, which was identified using the VITEK-2 biochemical identification system. The strain was susceptible to both colymicin and meropenem. The results of antimicrobial susceptibility testing are summarized in **Table 2**.

3. Discussion

R. planticola is an aquatic, botanical and soil organism that does not typically cause invasive infections in humans. Raoultella species produce histidine decarboxylase and have been implicated in scombroid (histamine) fish poisoning, but the clinical significance of this organism in humans has not been characterized. *R. planticola* is found to have similar pathogenetic features as Klebsiella species. Klebsiella spp. are associated with severe infections in hospitalized and immunocompromised patients, including bacteremias, pneumonias, and urinary tract infections, and have been estimated to cause between 3% and 7% of all nosocomial infections.

The first case report of *R. planticola* infection was described by Freney *et al.* in Lyon, France, of 69-year-old patient with *R. planticola* bacteremia who was admitted to an intensive care unit 9 days following a mitral valve replacement and was treated with cefotaxim and tobramycin [3].

In the past few years, number of *R. planticola* infections, including infections with *K. planticola* and *K. trevisanii* were reported which included cholecystitis, urinary tract infections, bacteremias, central line infection, soft tissue infections,

pancreatitis, cholangitis, and pneumonia [4]-[9]. These infections mainly occurred in immunocompromised patients with conditions such as cancer and hematological malignancies, and those post-transplant and/or with comorbidities including diabetes and alcoholic cirrhosis.

Chun *et al.* summarized 20 cases of *R. planticola* bacteremia, six of which were polymicrobial infections; half of those failed to recover [10]. Although most of the *R. planticola* isolates published in literature are susceptible to carbapenems, carbapenem-resistant *R. planticola* cases have been reported resulting in unfavorable outcomes [11] [12]. The known mechanism of carbapenem resistance in *R. planticola* is production of carbapenemases, including class A-lactamase (KPC), class B metal-lactamase (IMP-8, NDM-1), and class D-actamase (OXA-48).

Zuberbuhler *et al.* reported the first case of conjunctivitis caused by *R. planticola* in a 58-year-old woman [13]. There was no known contact with the soil or water in this patient. It was a mild ocular infection and treated with the antibiotic eye drop. After this eye infection episode, the same organism was detected in the blood. Young Jun Cho *et al.* reported a case of pneumonia caused by *Raoultella planticola* in a 52 years old patient with severe left ventricle dysfunction which was treated with piperacilin/tazobactam and levofloxacin [14].

Table 2. Results of antimicrobial susceptibility testing of *Raoultella planticola* isolated strain.

Name of antimicrobial substance	VITEK 2 result EUCAST interpretation
	R
	R
	R
Cefazolin	I
Cefuroxime	S
Gentamicin	R
Ciprofloxacin	S
Trimethoprim-Sulphamethoxazole	R
Ceftazidime	R
Ertapenem	R
Amikacin	R
Tazobactam Piperacillin	S
Ceftriaxone	S
Meropenem	S
Colistin	R
Ampicillin	R
Tigesiklin	S
Cefoxitin	S
Cefuroxime Axetil	R
	S
	R
	R

R resistant, S sensitive, I intermediate Results of antimicrobial susceptibility testing (AST) was done by using Vitek biochemical identification system in Memorial Ankara Hospital, Ankara, Turkey. Results were interpreted by using European Committee on Antimicrobial Susceptibility Testing (EUCAS).

Yumoto T. *et al.* reported a first case of fatal septic shock due to *R. planticola* bacteremia after flame burn injury. Patient's blood culture was positive for *R. planticola*, which was susceptible to both piperacillin/tazobactam and meropenem. The patient died due to refractory septic shock and subsequent multiple organ failure on day 12 of antibiotic treatment [15].

Cases of *Raoultella* infections can occur in many organ systems (e.g. urinary tract, gastrointestinal tract, respiratory tract) or at surgical sites. Bacteraemia, osteomyelitis, meningitis, cerebral abscess, mediastinitis, pericarditis, conjunctivitis, mandibular osteomyelitis and otitis caused by *Raoultella* have also been reported [16] [17]. Reported cases of gastrointestinal, and specifically biliary, infections with *Raoultella* are often depicted as affecting mainly individuals with an altered immune system either by a malignant condition or a chronic disease. Nonetheless, although the majority of reported cases are susceptible to standard antibiotic regimens, the emergence of multi-drug resistant strains may pose a serious risk to debilitated patients, and thus requires due consideration to further prevent increased virulence, especially in frail individuals.

Here we described a case of refractory sepsis caused by *Raoultella planticola* in a patient with history of cancer on current chemotherapy and recent abdominal surgery. The patient's gastrointestinal tract has probably been colonized with *R. planticola* and the leakage of intestinal luminal contents and gut flora after anastomosis insufficiency was the likely route of the infection. Even though, *R. planticola* as a sole pathogen had been isolated from blood cultures in the present case, intestinal bacterial translocation could also accelerate the patient's development of refractory septic shock. In the present case, empiric administration of colymicin, meropenem and teikoplanin had been initiated prior to the development of septic shock and isolated organisms were susceptible to both colymicin and meropenem. To the best of knowledge this report is the first description of a fatal septic shock caused by *R. planticola* with multidrug resistance (MDR) in Turkey. As limited data is available regarding this pathogen and its virulence, the mechanism of its pathogenesis in the present case with poor outcome remained unclear. We cannot assert whether the clinical course was associated with *R. planticola* bacteremia; however, it may have played a critical role in the development of fatal septic shock. Further research regarding its virulence is necessary.

4. Conclusion

We reported a rare case of fatal sepsis caused by *Raoultella planticola* in a patient with pancreatic cancer on current chemotherapy and recent abdominal surgery. This paper contributes to the growing body of research on the negative effect of the *R. planticola* bacteria on immunocompromised patients by significantly increasing the likelihood of antibiotic resistance and septic shock, thus resulting in fatal outcomes. As limited data is available regarding this pathogen and its virulence, our paper aims to highlight the importance of further research on this subject.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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