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Volume 5 • Issue 2 • July 2022 ISSN 2591-7609(Print) 2591-7617(Online)

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## Journal of Advances in Medicine Science

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# Journal of Advances in Medicine Science

Volume 5 Issue 2·July 2022

International Standard Serial Number: ISSN 2591-7609 (Print)

ISSN 2591-7617 (Online)

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## **Contents**

- 1      Discussion on the Challenges Surrounding Anti-microbial Resistance, Using Relevant Case-study Examples**  
Yiqun Wang
- 8      Thoracic Endovascular Aortic Repair for Type B Aortic Dissection**  
Yanqin Ruan   Haofer Li   Chang Liu
- 14     Cancer Rehabilitation, A New Discipline Based upon Multidisciplinary Collaboration**  
Shan Su

# Discussion on the Challenges Surrounding Anti-microbial Resistance, Using Relevant Case-study Examples

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## ARTICLE INFO

### *Article history*

Received: 31 March 2022

Revised: 7 April 2022

Accepted: 24 July 2022

Published Online: 31 July 2022

### *Keywords:*

Anti-microbial resistance

State intervention

Interest structure

Case studies in the Global North and the Global South areas

## ABSTRACT

The advent of antimicrobial drugs has made a huge contribution to human society, but their commodity nature has given rise to behaviors such as abuse and overuse, leading to the emergence of resistance to antimicrobial drugs and other hazards. Nowadays, the structure of interests formed by various stakeholders in the market circulation of antimicrobial agents has become unbalanced, and government intervention as a breakthrough still faces many challenges. This paper discusses the AMR challenges of government intervention under the interest structure in the context of case studies in the Global North and the Global South areas from the point of view of human health in terms of stagnant R & D processes for novel antimicrobial drugs, a profit-oriented neoliberal atmosphere that mismatches production trends of antimicrobial drugs with market demand, the prevalence of private institutions lacking effective regulation, incomplete government interventions, and the difficulty of pursuing the WHO strategic plan on antimicrobial resistance, etc.

## 1. Introduction

Since the advent of antimicrobial drugs, they have not only made great contributions to human society but also brought serious hazards such as drug resistance which was defined by WHO as a phenomenon that ‘bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines’<sup>[1]</sup>. With the spread of drug resistance over all the world, a post-antibiotic era in which there are no medicines available will emerge as it has become increasingly difficult and costly to treat infections

and antimicrobial tend to be less effective. According to a 2016 estimate by a UK economist O’Neill, the number of deaths caused by drug resistance will exceed 10 million by 2050 if effective actions are not taken. Meanwhile, the World Bank and the Food and Agriculture Organisation of the United Nations (FAO) forecast in their research that in 2050, there would be a 1.1% to 3.8% decrease in the annual global GDP<sup>[2]</sup>. The WHO has declared antimicrobial resistance to be one of the top ten global public health threats to humanity with the misuse and overuse of antimicrobial drugs being one of the primary drivers<sup>[1]</sup>.

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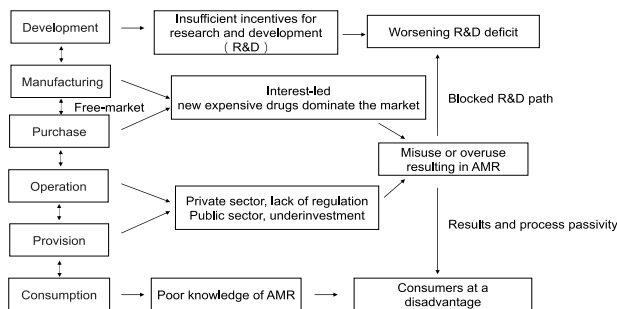
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DOI: <https://doi.org/10.30564/jams.v5i2.4441>

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Ultimately, antimicrobials circulate in the market as a unique commodity. According to the nature of the product, the use of antimicrobial drugs is divided into six stages, including development, manufacturing, purchase, operation, provision, and consumption<sup>[3]</sup>. In this process, an interest structure is formed through the checks and balances between the various stakeholders at each link. However, the imbalance of interests and the absence of outside intervention in advance lead to market failure, antimicrobial proliferation, and uncontrolled drug resistance (Figure 1). Necessarily, a breakthrough is supposed to be government intervention.

As a result, this article aims to discuss the challenges of AMR in state intervention under the interest structure only from the point of view of human health (other areas of use including food-production, agricultural, aquaculture and so on). The first section describes the current issues of state involvement in the changing dynamics of interest relations at national and international levels through the six aspects mentioned above, and contrasts them by referring to case studies in the Global North and the Global South areas. The second section summarises the limitations of the paper including the problems of government interference itself. Last but not least, based on the challenges identified, several recommendations are made to tackle AMR in the context of national interventions.



**Figure 1.** The Relationship Between Imbalance of Interests and AMR.

Modified after<sup>[3]</sup>.

## 2. Challenges

### 2.1 Development Stage

At the international level, there is no explicit division of labour in each country. The rapid growth of anti-microbial resistance levels in countries including Brazil, Russia, India, China, and South Africa (BRICS) accounted for three-quarters of a 36% increase in the consumption of antimicrobials in 71 countries from 2000 to 2010<sup>[4]</sup>. Although a report has shown that the British government

recently confirmed a financial examination of economic issues pertaining to antimicrobial resistance and a strategy to promote and facilitate the development and production of new generations of antimicrobials, the situation remains critical. In the 1990s, almost 20 companies were active in antimicrobial development around the world. At present, only GlaxoSmithKline and AstraZeneca are still among the world's pharmaceutical firms with antimicrobial testing programs<sup>[5,6]</sup>.

In order to alleviate the global crisis of AMR and the shortage of antimicrobial drugs, the key point of the 2014 Commission chaired by the former Goldman Sachs economist Jim O'Neill was to stimulate antimicrobial researches and innovations with active incentives<sup>[7]</sup>. Nevertheless, hurdles or obstacles remain<sup>[8]</sup>. Firstly, in terms of incentives, pharmaceutical companies are gradually abandoning antimicrobial research teams in favour of fields that may not be 'easier' to explore but certainly have better economic returns as the process of discovery is time-consuming and expensive<sup>[5]</sup>. For example, compared with less than 50 antimicrobial products, almost 800 new drugs were produced in 2014 in the field of oncology<sup>[6]</sup>. Secondly, the financial assistance offered may be overdue or the determination of the appropriate amount of bonus could be difficult and eventually, all risks are borne by governments or other investors<sup>[9]</sup>.

As for the current regional policies such as the Generating Antibiotics Incentives Now (GAIN) Act in the USA, and the Innovative Medicines Initiative (IMI) in Europe, the economic stimulus packages are inadequate and burdensome, even though initiatives have been suggested to boost the production channels for new antimicrobials<sup>[5,9]</sup>. For instance, the GAIN Act does not address antimicrobial stewardship measures<sup>[10]</sup>. Without the effective management of new antimicrobials, they are mostly used as a last resort therapy, which is impossible to obtain benefits for market exclusivity<sup>[11]</sup>. In the absence of sufficient usage of new antimicrobials, consequently, the effective life of new antimicrobials was shortened, and the reward impact of the GAIN Act was decreased due to the resistance condition aggravated by the abuse of antimicrobials<sup>[8]</sup>. Only if push and pull strategies operate together in the drug development environment will the best incentives be accomplished.

### 2.2 Manufacturing and Purchase Stages

With regard to AMR, different political parties have their respective positions. Three types of welfare states are recognized, including liberalism, social democracy, and nationalism, among which neo-liberalism is characterized by the highest level of commodified services that



are extremely distinctive and wide in scope and advocates less interference from the state. Therefore, interfering in strategies to minimize AMR in a neoliberal environment faces many challenges.

Although the role of the free market is emphasised in the neoliberal theory, the absence of external intervention is likely to cause severe consequences in the case of antimicrobial resistance as with the initial commercialisation of penicillin and many other antimicrobial compounds. In the 1940s, a vast number of pharmaceutical companies participated in the development of antimicrobials and the price of unpatented medications such as penicillin plummeted as funding grew. With the great demand for penicillin daily products, such as toothpaste, makeup, and other forms of consumer necessities, pharmaceutical firms have expanded the market under the guise that penicillin could not only cure bacterial infections but also benefit healthy people by preserving the efficacy of removing daily germs. After successfully inventing and patenting new antimicrobials, they increased their investment in the pharmaceutical industry and raised the price of these antimicrobials, as well as their manufacturing volumes regardless of the need. As a consequence, in the 1960s, many needless medications emerged in the market, resulting in a pattern that lasted until antimicrobial research programmes dried up in the 1980s when the pharmaceutical industry turned its focus to other more lucrative drugs<sup>[12]</sup>.

Neoliberalism probably provides the overarching philosophy for the analysis of these economic developments in relation to AMR, affecting the restricted or counter-productive role of governments in facilitating actions that effectively regulate AMR<sup>[12]</sup>.

Furthermore, the relationship between the industry output and the market demand is not completely exploited in neo-liberalism to tailor production according to changes in the market demand. One successful case is the ban on the use of antimicrobials on cattle by Namibia after its European consumers refuse to eat food-borne meat antimicrobials. It is a rare example of Namibia's prompt modification of its approach to market demand so as to sustain its sales market and reduce its AMR<sup>[13]</sup>.

### **2.3 Operation and Provision Stages**

Based on their ownership, major stakeholders in operation and provision stages can be divided into two categories, namely the public and private health sectors. What needs to be made clear is that private clinics and doctors act as operators and providers in the private system, while in the public system, the government acts as an operator and the public health sector as a provider.

The last two decades have witnessed the tremendous expansion of the private health care sector, especially

in South Asia where 80% of patients were expected to receive treatment in private hospitals and in India where 93% of health facilities were provided in private sectors<sup>[14]</sup>. Despite services provided by private sectors for individuals whose needs cannot be met by public organisations, there is a lack of effective regulation in private sectors when compared with the public health sector, especially in Low- and Middle-Income Countries (LMICs), which constitutes a severe threat of AMR<sup>[15]</sup>. Firstly, differences in the quality of clinics have widened gaps in access to health services<sup>[16]</sup>. In most South Asian countries such as Pakistan and Bangladesh, few structures or tools are available for tracking and controlling private sectors, leading to the fact that active institutions are operated by untrained providers<sup>[14]</sup>. Secondly, it is a normal phenomenon that untrained or inexperienced individuals run pharmacies because of the limited control over the qualification for the sale of specific types of drugs, which directly leads to misdiagnosis, confusion, or inadequacy. Thirdly, commercial companies prefer to store a vaster array of antimicrobials than municipal hospitals without the desire to indiscriminately administer or prescribe them. In addition, the sale of antimicrobials on the internet as a form of online privatisation is the same case. One survey showed that without prescriptions of antimicrobials, a third of the 138 separate vendors listed as antimicrobials suppliers were selling them. Fourthly, doctors with the lowest credentials were found to have the lowest fees in general. However, they saw the largest number of vulnerable patients at the risk of infectious diseases, including Tuberculosis (TB), HIV, and Malaria<sup>[14]</sup>. Fifthly, the poor quality of medicines and the profit margins between various clinics intensify the pressure for options, leading to a flood of substandard and spurious medicines into the market. According to the statistics, the annual sales of falsified and adulterated pharmaceuticals in Peru and Columbia were about \$66 million and \$60 million, respectively<sup>[15]</sup>. In accordance with the above five points, it can be concluded that private organisations lacking monitoring and management systems are more likely to have issues in the diagnostic process that may form an anti-microbial resistance vicious circle (Figure 2).

The public health care sector faces multiple challenges caused by the local political structure, economic status, and social patterns. First and foremost, universal health promotion strategies, namely Infection Prevention and Control Interventions (IPCIs) proposed by WHO, have gained success in some domains in LMICs. For example, washing hands with soap in Karachi, Pakistan has not only halved diarrhea and acute respiratory infections but also decreased the occurrence of pustules that would require

antimicrobials by 30%<sup>[15]</sup>. However, the implementation of such strategies remains difficult as there is a frequent lack of access to even simple mechanisms, as well as a poor empirical base to justify their incorporation into such healthcare contexts<sup>[17]</sup>. Furthermore, government investment in infrastructure is far from being adequate. In spite of the importance of water and water-related devices for alleviating the transmission of AMR bacteria, basic clean water, sanitation, and hygiene facilities are not well-established in parts of developing countries to cut off AMR's environmental transmission pathways<sup>[18,19]</sup>. For example, open defecation is still occurring in many heavily populated areas such as India. More industrialised countries such as the United States and the UK are facing ageing facilities and the demand for more sophisticated and sustainable water treatment technologies<sup>[18]</sup>.

## 2.4 Consumption Stage

In order to reduce AMR, WHO presented an international action plan in 2015, one of the strategic objectives of which is 'to improve awareness and understanding of antimicrobial resistance', and steps have been taken by several nations, such as the European Antibiotic Awareness Day campaigns<sup>[20,21]</sup>. However, surveys (Table 1) of the public's knowledge and perceptions about AMR from four typical countries (Sweden, USA, Japan, Nigeria) revealed that there were still many obstacles in the consumption process of antimicrobials in both the Global North and the Global South areas. Despite the limitations of the surveys due to the sample size and respondent bias, they still have a reference value.

At first, consumers had poor knowledge of the appropriate use of general antibiotics.

They did not know when antibiotics should be used. In Japan, for example, only 22% of respondents recognised that antibacterial medications could not kill viruses and 45.5% of them obtained antibiotics due to the cold<sup>[22]</sup>. In the United States, almost 40% of respondents felt that antibiotics were the best way to treat cold symptoms and the proportion was 13.4% in Sweden where AMR was low<sup>[23,24]</sup>.

They did not know how to choose the right antibiotics. According to the Nigerian report, people tended to purchase and use the same antibiotics that had cured their previous diseases<sup>[25]</sup>.

They did not know how to use antibiotics correctly. For example, about 26.1% of Nigerian participants avoided taking antibiotics when they felt better instead of taking all them as instructed<sup>[25]</sup>. Also, 23.6% of Japanese participants reported the halt or adjustment of their antibiotic doses on their own<sup>[22]</sup>.

Next, storing antibiotics were more common in developed countries with a 31% storage rate in Nigeria compared to 12% in Japan<sup>[22,25]</sup>. Preserving antibiotics could be a temptation of self-use (e.g., self-treatment, avoidance of flu) but improper storage and expired antibiotics may lead to allergic reactions and increase the possibility of sharing them with others.

Besides, the persistent absence of information by patients will produce an unfair interaction with doctors. As mentioned above, people could rely on professors who might be more susceptible to external factors such as pharmaceutical firms to prescribe profit-related or counterfeit drugs<sup>[26]</sup>.

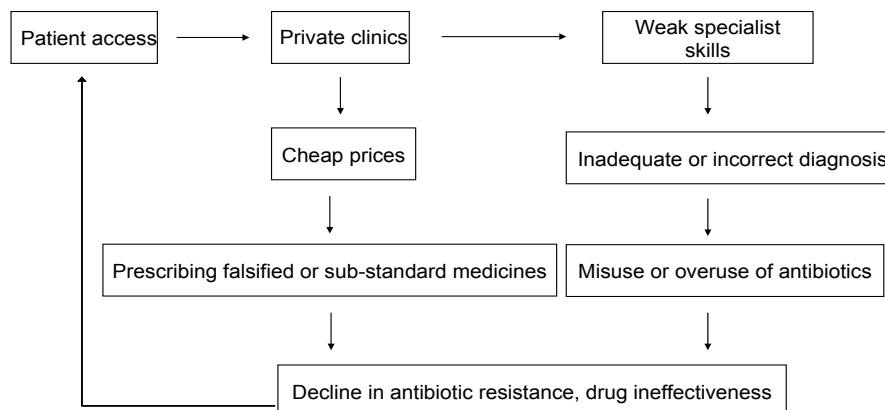


Figure 2. An Anti-microbial Resistance Vicious Circle



**Table 1.** Surveys from Four Countries of Public's Perceptions and Knowledge about AMR

Country	Swedish	America	Japan	Nigeria
Characteristics	Global North low AMR	Global North	Global North	Global South
Subjects of Survey	public	public	public	public
Number of participants	1426	215	3390	482
Agree that antibiotics cannot effectively fight against viruses (%) (right statement)	77%	70%	22%	
Agree that antibiotics can effectively fight against cold and flu (%) (wrong statement)	13%	less than 25%	three-quarter (75.4%)	44%
Store antibiotics (%)			12%	31%
Level of knowledge of the relevant terms	29.50% of interviewees are with accurate knowledge.		4 out of 10 interviewees had heard the term 'AMR'.	8.3% of interviewees are with accurate knowledge; 7.3% of interviewees had heard the term 'AMR'; 56.45% of interviewees had heard the term 'antibiotic resistance'; 46.9% of interviewees had heard the term 'drug resistance'; 17% of interviewees had heard the term 'AMR'.
Use over the counter (OTC) antibiotic drugs (%)			3%	2%
The most common source of information about AMR		Television and the Internet	TV news or newspapers (25.7%) doctors (19.1%).	doctors/nurses (50%) pharmacists (31.3%) specific campaigns (8.5%) media (9.8%)

### 3. Conclusions

This article has discussed the challenges of AMR in state intervention under interest structure from six perspectives (developing, manufacturing, purchasing, operating, providing, consuming) based on the use of antimicrobial drugs.

Owing to a lack of consistency in the government's external division of labor and inadequate domestic economic recovery measures, the research and development process of new antimicrobials has stagnated.

A free market between production and purchase was established in a neo-liberal atmosphere, and the principle of benefit was encouraged above all else. However, the AMR proved to be worse and worse without government interference, making clever use of the relationship between production trends and market demand.

In recent years, private clinics have become more prev-

alent as a cornerstone of the operating phase, but the lack of effective government regulatory policies and institutions, particularly in countries with low and medium incomes, has led to a vicious circle of untrained or inexperienced providers mixing and creating AMR.

The government, as an operator, uses interventions such as policy implementation and the distribution by the public health sector of basic services such as vaccines and sanitation to minimize the spread of infectious diseases in public systems, but this remains difficult to do in the near term due to discrepancies between countries.

Countries have used social marketing ads to fulfill the WHO 2015 strategic plan to 'improve awareness and understanding of antimicrobial resistance', but a review of surveys from four typical countries reveals that there is still a long way to go to meet customers with AMR expertise.

In order to achieve checks and balances in the interests

of society as a whole, the government, as the most powerful mediator in the whole process, should limit the intentions of abusive subjects by fostering anti-abuse subjects and provide awareness and intelligence to support the acts of anti-abuse subjects by partially or completely opening up information channels.

It should be noted that this paper has been primarily concerned with the point of view of human health; what is needed in the future directions are cross-national studies involving strategic policy analysis of plants and animals to provide more possibilities for addressing anti-microbial resistance.

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# Thoracic Endovascular Aortic Repair for Type B Aortic Dissection

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## ARTICLE INFO

### Article history

Received: 28 April 2022

Revised: 9 May 2022

Accepted: 24 July 2022

Published Online: 31 July 2022

### Keywords:

Aortic dissection

Interventional therapy

Indications

Complications

## ABSTRACT

The incidence of aortic dissection (AD) is estimated to be 1 in 100,000 per year. The onset and progression of AD are rapid. Failure to receive appropriate treatment might lead to death in a short time. Even following active treatment, patients might develop low cardiac output syndrome, severe infection, and hemorrhage, which lead to death. Interventional therapy is a surgical method that has been widely used in Stanford type B AD recently. It is characterized by minimal invasiveness, low incidence of postoperative complications, and low cost. This article will review the interventional treatments for AD and will guide the selection of treatment options.

## 1. Introduction

Aortic dissection (AD) is a fatal vascular disease that occurs when blood leaks through an intimal tear in the aorta, passes into the artery wall and eventually forms a dissected hematoma, where true lumens (TLs) and false lumens (FLs) expand along the long axis of the artery <sup>[1]</sup>. The occurrence of AD is mainly associated with hypertension, which induces long-term oxidative stress in the arterial wall, resulting in cystic degeneration or necrosis of the elastic fibers, and the formation of dissection <sup>[2]</sup>. If

AD is not diagnosed or treated appropriately, the early (within 1 h) fatality rate of patients with AD could reach 1%. Timely surgical treatment and the administration of medications significantly improved the survival rate of patients with AD, with a decrease in the case fatality rate from 27% to 18% <sup>[3]</sup>. Stanford type B AD includes dissections that originate in the descending thoracic aorta, abdominal aorta, and iliac artery, which account for 25%–40% of all AD cases. Approximately 75% of type B AD is noncomplicated AD <sup>[4]</sup>. Thoracic endovascular repair of

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DOI: <https://doi.org/10.30564/jams.v5i2.4671>

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the thoracic aorta (TEVAR), which is known as thoracic aortic interventional therapy, is a minimally invasive surgical method that is used for the treatment of critically ill patients with AD and is superior to open surgery in some aspects<sup>[5,6]</sup>. Due to the advances in medical technology and equipment, TEVAR has been applied gradually for the clinical treatment of Stanford type B AD. This article will review the interventional treatments for Stanford type B AD and will provide guidance on the selection of interventional therapies.

## 2. Indications and Contraindications of Interventional Therapy

In interventional therapy, endovascular stents or covered endovascular stents are commonly used to close the tear and FLs, and therefore, restore the patency of the TLs. Aortic intima fenestration and stent implantation are performed to restore blood perfusion in ischemic areas<sup>[7]</sup>. Interventional therapy is suitable for patients with chronic heart failure, chronic kidney insufficiency, and chronic pulmonary insufficiency, and those who have previously been treated with thoracotomy<sup>[8]</sup>. The indications for interventional therapy for patients with early-stage AD are: (1) duration of chronic type B AD > 3 weeks and (2) length of the neck hemangioma is > 1.5 cm<sup>[9]</sup>. Due to the advances in medical equipment and technology recently, the indications for interventional therapy have changed. Patients who are diagnosed with acute type B AD with possible aortic rupture, branch organ ischemia, aortic aneurysm formation, intractable severe pain, or hypertension might qualify for interventional therapy.

The optimal treatment for acute type B AD remains controversial. Some researchers found that the early and medium-term mortality of patients with thoracic aortic disease that were treated with interventional therapy was lower than those who received other treatments, in particular, conservative medical treatment. Therefore, currently, the indications for TEVAR for the treatment of AD are: (1) rupture and bleeding of a dissected aorta; (2) diameter of the dissected aorta increases rapidly ( $\geq 10$  mm/year); (3) ischemia occurs in vital aortic branches; (4) persistent and unrelieved pain; (5) formation of intramural hematomas and aortic ulcer; and (6) formation of an aneurysm with an approximate diameter of 50–60 mm<sup>[10]</sup>.

Although TEVAR has been widely used to treat AD, it is not recommended for patients with systemic infection, an inappropriate vascular approach, or inadequate anchoring area.

## 3. The Main Surgical Approaches in Interventional Therapy

TEVAR procedures mainly include aortic covered stent

implantation, aortic fenestration, chimney technology, and branch stent technology. Aortic covered stent implantation was first performed in Argentina in 1990 to treat abdominal aortic aneurysms. Percutaneous transluminal aortic stent implantation was first used in 1994 to treat thoracic aortic aneurysm and descending AD. In this surgery, a covered stent is placed in the TLs to block the rupture of the dissection, reduce the blood flow through the FLs, induce thrombosis, and decrease the pressure in the FLs, and therefore, decrease the risk of aortic dilatation and rupture. In addition, the expansion of the TLs improves branch vascular perfusion and stabilizes the dissection. The aortic stent implantation shortens the operation time and reduces trauma, and significantly decreases the incidence of complications and mortality in patients with AD<sup>[11]</sup>. Zhou et al.<sup>[12]</sup> investigated the effect of stent-graft implantation for the treatment of patients with acute or subacute Stanford type B AD. The clinical data for 38 patients (31 males, 7 females) who presented with Stanford type B AD and received TEVAR treatment were retrospectively analyzed, which included 22 cases in the acute stage and 16 cases in the subacute stage. The average diameter of the TLs and FLs within the dissection before and after TEVAR, and the maximum aortic diameter, were measured. Seven patients (18.4%) had endoleaks following treatment. There were no perioperative deaths in this cohort. The results of computed tomography angiography at baseline showed that there was no significant difference in the maximum aortic diameter, or the diameter of TLs or FLs before TEVAR between the acute and subacute groups ( $p = 0.193$ ,  $p = 0.301$ , and  $p = 0.067$ , respectively). After TEVAR treatment, significant differences were observed in the maximum aortic diameter and the diameter of FLs between both groups ( $p = 0.005$  and  $p = 0.012$ , respectively), but not in the diameter of TLs ( $p = 0.069$ ). The diameter of the TLs increased, and that of the FLs in the acute and subacute groups decreased significantly following TEVAR ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ , and  $p = 0.007$ , respectively). The maximum aortic diameter in the acute group significantly decreased ( $p < 0.001$ ), but no significant changes were observed in the subacute group ( $p = 0.121$ ). These findings suggested that the short-term prognosis for patients who received TEVAR in the acute stage was similar to that of the subacute group, although better outcomes were observed in patients with acute AD.

In aortic fenestration, the fenestration position and fenestration diameter of the branch arteries are determined by imaging examination. Holes and fenestrations are made on the inner membrane to separate TLs and FLs, decompressing the hypertensive FLs, and therefore, restoring blood supply. Aortic fenestration is used to increase



the length of the stent; therefore, the anchoring area of the stent has a better fit on the aortic wall<sup>[13]</sup>, which makes it suitable for AD patients with complications, such as visceral or lower limb ischemia. In addition, fenestration is performed in patients with ischemic manifestations, such as gastrointestinal ischemia, acute renal failure, claudication, or pulseless limbs<sup>[14]</sup>. Fenestration relieves ischemic symptoms in approximately 85%–93% of patients, stabilizes AD, and increase the time for elective surgery or stent intervention, and therefore, improves the prognosis of patients with AD<sup>[15]</sup>. Kuo et al.<sup>[16]</sup> evaluated the efficacy and safety of a handmade fenestrated stent-graft over an aortic stent graft to preserve the left subclavian artery (LSA) in TEVAR. A total of 32 patients with various thoracic aortic pathologies were included. There were 24 patients (75.00%) with AD, 5 patients (15.63%) with thoracic aortic aneurysm, and 2 patients (6.25%) with penetrating aortic ulcer. One patient (3.13%) required re-TEVAR due to the endoleak and sac expansion from previous TEVAR for a thoraco-abdominal aneurysm. They were treated with TEVAR, in which handmade fenestration over a thoracic aortic stent-graft was used for the LSA. TEVAR on zone 2 landings with single fenestration for the LSA was performed in 26 patients (81.25%); TEVAR on zone 1 landing with double fenestration for LSA and left common carotid artery was performed in 5 patients (15.63%); TEVAR on zone 1 landing with single fenestration for the LSA and a chimney graft for the left common carotid artery was performed in 1 patient (3.13%). The technical success rate, defined as the successful alignment of fenestration to the LSA, was 93.75%. At a mean follow-up of 17.3 months, four cases of endoleak and two cases of stent graft-induced new entry were observed; three of them were treated endovascularly. The ability to preserve blood flow in the LSA using a handmade stent-graft fenestration might justify the use of TEVAR in emergency cases. In addition, fenestration surgery can be used as adjuvant therapy in emergency treatment or stent implantation to reduce the incidence of ischemic complications. Recently, fenestration and branch endovascular stent implantation have shown promising clinical results for the treatment of branch vascular ischemia.

During transluminal therapy that uses the chimney technique, the vital branch vessels, such as the LSA, are intentionally or inadvertently covered due to the inadequate anchoring area. Bare stents and covered stents are often anchored together to preserve the branch vessels<sup>[17]</sup>.

This technique was first proposed by R. K. Greenberg and then applied to TEVAR. The chimney technique is not performed as a routine surgical approach for complex Stanford type B AD, it is used in patients who cannot tolerate hybrid surgery or open surgery, or in an emergency<sup>[18]</sup>. Since this technique preserves vital branch vessels and maintains the blood supply to vital organs, it might replace bypass or open vascular repair in the near future. Zhao et al.<sup>[19]</sup> analyzed the effects of different chimney techniques that were applied to different positions on the aortic arch and provided guidance to reduce the complications from chimney thoracic endovascular aortic repair (cTEVAR). In this study, 234 patients with AD that involved the arch branches were treated with cTEVAR. There were 156 cases (66.7%) with single chimney (SC), 48 (20.5%) with double chimney (DC), and 30 (12.8%) with triple chimney (TC). A total of 342 chimney grafts were used. The results showed that all chimney grafts were successfully implanted, and no migration or occlusion was observed during follow-up. The postoperative mortality rate was 1.7% (4/234) and the occurrence of cerebrovascular events was 1.3% (3/234). In addition, 75 cases (75/234, 32.1%) had type I intimal leakage during the operation. The leakage in 27 patients (27/75, 36.0%) disappeared during follow-up; 33 patients (33/75, 44.0%) had stable FLs; 15 (15/75, 20%) had FLs expansion and were successfully treated with endovascular embolization. Patients with a proximal tear that was located in zone 0 had a higher instant endoleak rate than those with the tear located in zones 1, 2, and 3 ( $p = 0.041$ ,  $p = 0.042$ , and  $p = 0.009$ , respectively). Patients with TC had increased instant endoleak than those with SC ( $p < 0.001$ ) and DC ( $p = 0.012$ ). However, during follow-up, there was no significant difference in instant endoleak between the groups. These data showed that the SC technique achieved satisfactory results.

A retrospective study on 234 patients with aortic arch disease was performed to evaluate the feasibility, effectiveness, and safety of chimney, fenestration, and in situ fenestration techniques<sup>[20]</sup>. Among them, 126 patients received cTEVAR (98 cases with SC, 24 cases with DC, and 4 cases with TC); 102 patients (102/234) were treated with surgical fenestration (92 cases with single fenestration, 9 cases with double fenestration, and 1 case with double fenestration and innominate arterial chimney); the remaining 6 received in situ acupuncture fenestration. The indications included AD (99/234), aortic arch aneurysm

(60/234), penetrating aortic ulcer (72/234), and re-intervention (3/234). There were five early all-cause deaths. The technical success rate was 99.6% and the patency rate of all branches was 99.6%. There were 15 cases with type Ia intestinal leakage; 14 cases (11.1%) in the chimney group and 1 case (1%) in the table fenestration group. Five patients underwent re-intervention. The median follow-up for all patients was 28 months (range: 16–41 months), which indicated that chimney, table fenestration, and needle fenestration techniques were feasible, effective, and safe methods for the treatment of aortic arch lesions.

The Castor branched aortic stent, which was produced in China in June 2017, is a new type of thoracic aortic stent that has been used globally. This stent has a unique integrated structure, which better fits with the blood vessels of Chinese patients and shows improved stability and a low risk of long-term displacement. It allows precise positioning, separates TLs and the FLs, and avoids the use of hybrid technique and staged operation to reduce the pain of patients. The origin of the LSA can be intentionally covered by a stent-graft to provide an adequate proximal landing area during the endovascular repair of the Stanford B AD. Jing et al.<sup>[21]</sup> retrospectively analyzed 73 patients with Stanford type B AD who were treated with the Castor stent-graft in 11 tertiary hospitals in China. There were 50 cases with acute AD (<2 weeks [68.5%]) and 23 cases with chronic AD (>2 weeks [31.5%]). The results showed that the surgical success rate was 97% (n = 71/73). Two of the failures were caused by partial occlusion of the branches of the stent-graft. Four patients had intraoperative endoleaks (type Ia: n = 2, type B from the LSA: n = 2) and the endoleak rate was 5% (n = 4/73). One patient died in the hospital and the rest had no major complications. The mortality rate within 1 year of post-operative follow-up was 5% (n = 4/73) and the mortality rate within 6 years was 7% (n = 5/73). The cause of death in two patients was unknown. The deaths of three patients were not related to the aorta. Two patients had a new breach at the proximal or distal edge of the stent-graft and underwent endovascular repair. The branches where the Castor stent was deployed were partially occluded in 6 patients, and the follow-up patency rate of the branches was 93% (n = 63/68). In two cases with intraoperative endoleaks that were not treated, the endoleaks disappeared during follow-up. These findings suggest that endovascular treatment that used the Castor single-vessel stent graft was an easy-to-operate, safe, and effective treatment

option for TBAD patients whose stents needed to be anchored near the origin of the LSA. The intraoperative reconstruction of the LSA resulted in a better blood supply and fewer complications.

#### 4. Complications of Interventional Therapy

The complications from interventional therapy include internal leakage, distal new rupture, stent displacement, vascular injury, and thrombus exfoliation. Internal leakage, which is the most common complication, occurs when the covered stent implantation in the aorta does not completely isolate the aneurysm cavity from the arterial blood flow<sup>[22]</sup>. The incidence of internal leakage with stent treatment of AD was 3%–44%<sup>[23]</sup>, which was related to the physical condition of the patient, type of the stent, anatomical condition of the aortic aneurysm, and the experience of the operator. Approximately 50% of the internal leakage disappeared spontaneously. However, it might expand to form an aneurysm and could lead to the rupture of the aneurysm cavity. In this case, re-implantation of the stent is required.

Stent displacement is a common complication in interventional therapy that mainly occurs due to intra-aortic blood flow and pulsation after stent implantation. Stent displacement increases the risk of internal leakage and might cause serious consequences, such as aortic rupture. Therefore, during the operation, it is important to ensure that there is no dilation or lesion at the anchorage site of the aorta and stent<sup>[24]</sup>. To prevent stent displacement it is important to select an appropriate stent, the diameter of the proximal and distal stent should be 3 mm ~ 4 mm larger than the diameter of the hemangiomas, to avoid stent distortion and angulation<sup>[25]</sup>.

The incidence of new distal rupture is 3.4%–27.8% and the mortality rate is 26.1%<sup>[26]</sup>. When the length of the stent is >145 mm, the incidence of fracture significantly decreases. The oversizing area is closely related to the risk of stent-derived rupture. The stress between the stent and the aortic wall is the main factor that affects the distal aorta. To prevent distal rupture, lengthening the stent has been suggested, reducing the oversizing area, and the stress between the stent and the aortic wall, and protecting the edematous vascular wall in the acute stage<sup>[27]</sup>.

#### 5. Summary

The clinical significance of interventional therapy for the treatment of AD has been increasingly recognized.

Stent therapy could replace traditional surgical treatment in most cases. In addition, it could be performed in patients who cannot tolerate surgery. Due to the development of technologies and materials, the suture-free elephant trunk stent with artificial vessels and branch vessels has been used in type B AD with ascending and arch expansion. New stent materials, such as Ni-Ti alloy extruded stent and Ni-Ti memory alloy have been gradually used in clinical practice. New interventional guidance, such as visual guidance, virtual reality imaging technology, magnetic navigation guidance, and esophageal ultrasound guidance, shows the internal structure of the cardiovascular system and provides real-time monitoring for physicians during an operation. In addition, blood transfusion is not required in interventional therapy, which decreases the operation time and reduces operative morbidities and costs. The use of new dynamic imaging technology might facilitate the exploration of the morphology and dynamics of the aorta; therefore, new stents could be designed for patients with AD for a better prognosis.

## Funding

This study was sponsored by funds from the Chinese National Natural Science Foundation (No. 82060093).

## Disclosure of Interest

The authors report no conflicts of interest.

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# Cancer Rehabilitation, A New Discipline Based upon Multidisciplinary Collaboration

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## ARTICLE INFO

### *Article history*

Received: 20 August 2022

Revised: 27 August 2022

Accepted: 1 November 2022

Published Online: 8 November 2022

### *Keywords:*

Cancer rehabilitation

Therapy of natural immunology

Immune activation

Immune reconstruction

Immune response management

Cancer rehabilitation psychology

Cancer rehabilitation nutritional science

Cancer rehabilitation exercise physiology

## ABSTRACT

Cancer Rehabilitation is a new discipline, a combination of tumor medication, immunology, psychology, nutritional science and exercise physiology etc.. The core of cancer rehabilitation is the therapy of natural immunology, which aims at activating T-cells, and restoring the bone marrow function impaired during chemo-radiation therapy. Cancer rehabilitation seeks to achieve the gradual recovery of the immune system, which in turn hinders recurrence and metastasis. In addition, with the help of psychological consultation, nutritional and physical exercise guidance, cancer patients may have a better chance at managing the risk of recurrence and metastasis, extending life expectancy with an improved quality of life.

## 1. Introduction

Most cancer deaths occur in the process of cancer recurrence and metastasis after tumor surgery and chemoradiotherapy. It has become a comprehensive problem that needs to be solved urgently in the process of continuous treatment and postoperative rehabilitation. Regrettably, no effective method has yet been found that accomplishes postoperative comprehensive rehabilitation after chemoradiotherapy, while successfully reducing the risk of me-

tastasis, cancer recurrence, and significantly improving the survival rate and quality of life. After years of clinical exploration, the team of Dr. Su Shan from the Cancer Rehabilitation (Clinical) Research Center of Shanghai International Medical Center believes that the establishment of a multi-disciplinary and collaborative tumor rehabilitation system can ameliorate the side effects of chemoradiotherapy, reducing the chance of metastasis and cancer recurrence. It is of positive effect and significance to break

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DOI: <https://doi.org/10.30564/jams.v5i2.5231>

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the vicious circle of metastasis and recurrence—surgical chemoradiotherapy, re-metastasis and recurrence—re-operation and re-radiotherapy in the process of tumor treatment, and to improve the survival rate and quality of life of cancer patients.

## **2. Immune Recovery and Immune Reconstitution**

1) The recovery and reconstitution of the immune system is a core demand of postoperative patients and patients after chemoradiotherapy

According to the statistics of the World Health Organization, 19.29 million new cancer cases and 9.96 million deaths occurred globally in 2021. Among them, 37% of breast cancer patients and 42% of colon cancer patients chose chemotherapy. Chemoradiation has remained the primary method of clinical tumor treatment. However, it seriously damages the proliferation and the effector function of T cells during the treatment process, causing irreversible complications which are often fatal. This has long attracted the attention of the medical community<sup>[1]</sup>.

Myelosuppression is a common complication after tumor chemotherapy and radiotherapy. Most postoperative patients and patients after chemoradiotherapy have different degrees of myelosuppression. The CASPIAN study on the proportion of myelosuppression by various chemotherapeutic drugs showed that 52% of patients developed severe neutropenia after chemotherapy, along with platelet and hemoglobin abnormalities<sup>[2]</sup>. Myelosuppression damages the immune system, increases the probability of bacterial infection and the degree of complex bacterial infection, and causes cancer recurrence or metastases. A study on the damage to the lymphocyte system in breast cancer patients after chemoradiotherapy shows that the number of B cells, T cells, and NK cells drops significantly after approximately two weeks. The disruption of the proliferation and differentiation program of T cells further deactivates B cells, reaching a mere 5.4% in number before chemotherapy<sup>[3]</sup>. Since the fundamental mechanism of producing white blood cells is fatally damaged, further treatment for newly developed myelosuppression is required.

At present, the main clinical treatment for myelosuppression is granulocyte colony-stimulating factor, which targets hematopoietic progenitor cells that are functionally damaged, forcing their proliferation and differentiation. This treatment stimulates the precocious maturation of granulocytes and mononuclear macrophages and releases them into peripheral blood. The number of white blood cells in the peripheral blood appears normal, but it does not mean that the bone marrow itself has recovered. The whole treatment can be compared to killing the goose that

lays the golden eggs, because stimulation from external drugs does not guarantee normal functioning of the white cells. The cocktail of chemoradiotherapy and steroids for leukopenia, creates a vicious cycle of immune inhibition – stimulation – reinhibition – restimulation, up to the point when the immune system collapses completely.

An important site of lymphocyte homing to perform their effector functions, the mucosal system contains most immune cells of the human body. After tumor chemoradiotherapy, the mucosal system suffers extensive damage, especially for patients receiving head and neck radiotherapy, which often leads to mucosal inflammation and ulcerative lesions. A study by Henan Puyang People's Hospital on patients with nasopharyngeal carcinoma shows that more than 76% of patients develop Grade 3 to Grade 4 oral mucositis, mucosal congestion, erosion, and ulcer after radiotherapy<sup>[4]</sup>. Due to the destruction of the mucosal secretory glands, the patients no longer have saliva secretion in the mouth, causing xerostomia, dysphagia, bad breath, bleeding, and anorexia. Dysgeusia could still occur in patients five years after chemotherapy and radiotherapy, for whom eating anything is like chewing wax, and constant sipping of water is necessary to moisturize the throat.

Gastrointestinal mucosal damage after chemoradiotherapy commonly leads to digestive tract reactions like nausea, vomiting, constipation, diarrhea, and abdominal distension. He Haiyan, Zhu Jingci and others have conducted a survey and research report on gastrointestinal symptoms in 600 patients with tumor intravenous chemotherapy, with the conclusion that there is a 95% occurrence rate of gastrointestinal symptoms after chemotherapy, and that 87.5% of patients have developed multiple symptoms<sup>[5]</sup>. Due to the damage of the intestinal mucosa, the intestinal wall is diffusely thickened, the endocrine glands destroyed, and the reparative and regulatory functions of the immune system lost. According to a survey of more than 30,000 people by the Cancer Nutrition and Knowledge Treatment Committee of the Chinese Anti-Cancer Association, 40% to 80% of patients suffer from malnutrition to varying degrees, and about 20% of cancer patients directly die of malnutrition.

Human bone marrow is the organ where immune cells are produced, and T lymphocytes are the most important immune cells to recognize and eliminate cancer cells. Under normal circumstances, once tumor cells are generated, they are quickly detected by dendritic cells, which present them as antigen signals to T cells, inducing their activation. After T cells are activated, they continue to proliferate and differentiate into different types of effector T cells, including Tc cells that directly kill cancer cells,

and Th cells that help activate B cells. B cells activate and proliferate in a highly ordered and highly coordinated program between immune cells and immune cytokines, differentiate plasma cells and produce antibodies, which combine with various immune cells to kill cancer cells [6]. After the tumor patients receive chemoradiotherapy, however, the immune system fails to respond, disrupting and destroying the normal operating procedures of activation, differentiation, and proliferation of immune cells. The incapacitated immune system causes massive long-term immune escapes, which naturally lead to tumor recurrence and metastasis. The only solid solution to this problem is the restoration and reconstitution of the immune system, which fundamentally solves the problem of metastasis and recurrence.

2) The lack of immune reconstitution and recovery in current clinical treatment

Clinically, the same methods of surgery and chemoradiotherapy are used in both the initial and the later stages of tumor treatments, against cancer recurrence and metastasis. These repeated treatments cause havoc to the human immune system, almost destroying its function, and induce a high rate of metastasis and recurrence. According to the official data of the China Cancer Prevention Center, the tumor metastasis and recurrence rate is 69% within six months after chemoradiotherapy, and more than 60% of tumor patients die of metastasis, recurrence, and complications within five years [7].

Whether it is the initial treatment of the tumor or the repeated treatment of metastasis and recurrence, most chemotherapy regimens currently implemented in China still use traditional platinum-based chemotherapy drugs. This type of tumor chemical drug is expected to achieve anti-tumor effect by interfering with the synthesis of DNA in cells. Common radiotherapy inhibits and kills cancer cells by using rays of different energies to irradiate tumors, destroying the chromosomes of cancer cells. However, it remains an indisputable fact that no matter what the clinical treatment is, being chemo- or radiotherapy, collateral damage and destruction to immune cells are inevitable. Targeted therapy hopes to precisely affect tumor cells by using chemical drugs or radiopharmaceuticals that minimizes damage to normal cells. However, the results of clinical use are not satisfactory. The immune system is still vulnerable to damages from chemotherapy drugs or radioactive substances, and the rate of cancer metastasis and recurrence has not declined as expected.

CAR-T therapy shifts tumor therapy from killing cancer cells to using autoimmune cells to fight tumors. The T cells, recognized by the immunology community as an important type of cells to fight cancer, are cultured by in

vitro genetic modification technology and then reinfused to increase the number of T cells in the patient's body, replacing the T cells damaged by chemotherapy and radiotherapy. When the number of T cells is reduced, Tc cells cannot be normally activated to generate enough CTL to kill cancer cells. At the same time, when helper T cells are not activated to proliferate and differentiate, B cells remain dormant and would not produce antibodies to initiate a series of immune responses against cancer cells. After T cells proliferate, differentiate, and produce effects, dendritic cells are required to present tumor cells as antigens to T cells, inducing their proliferation and activation. Activated T cells will generate a series of complex but orderly immune responses against tumor cells. The clinical application of CAR-T immunotherapy [8] shows that T cells that are cultured and infused into the body trigger an immune storm in a disordered and uncontrolled state, resulting in treatment failure. Of 942 patients in the United States who received CAR T-cell therapy, 258 (27%) required admission to the intensive care unit, and 241 (26%) were included in the analysis. Intensive care unit admission was required within a median of 4.5 days (IQR 2–7.0) of CAR T cell infusion. The 90-day mortality rate was 22.4% (95% CI 17.1–27.7; 54 deaths). Grade 3–4 cytokine release syndrome was found in 50 of 200 patients (25%) within 1 day of admission to the intensive care unit, and grade 3–4 ICANS was found in 38 of 108 patients (35%). Seventy-five (31%) patients received life-saving treatment within 24 hours of admission to the intensive care unit, of which 65 (27%) were primarily on vasoactive drugs. Factors independently associated with 90-day mortality by multivariate analysis were frailty (hazard ratio 2.51 [95% CI 1.37–4.57]), bacterial infection (2.12 [1.11–4.08]), lifesaving treatment within 24 hours of admission (1.80 [1.05–3.10]) [9].

PD1 immunotherapy is currently an important means of tumor clinical treatment. The full name of PD-1 is “programmed death receptor 1”, which is an inhibitory molecule on T cell receptor protein. PD-L1 is a tumor cell surface protein, which once combined with T cell protein PD-1, activates the inhibitory function of T cells, stopping their proliferation and activation, resulting the apoptosis of T cells. As a result, the immune system naturally loses the function of monitoring and eliminating cancer cells. The role of the PD-1 antibody is to prevent the combination of PD-1 and PD-L1, so that T cells are normally activated under the action of tumor cell antigens, with their natural mechanism of killing cancer cells restored. However, some clinical application researchers have found that although this therapy shows good results in some patients, it is completely ineffective in others. The efficacy also

varies in different cancer types. For example, the effective rate is 40%-50% in melanoma, 50% in bladder cancer, and only 30% in cases of lung cancer, gastric cancer, esophageal cancer and liver cancer<sup>[10]</sup>.

It deserves attention that the current clinical treatment of chemoradiotherapy or immunotherapy is fundamentally incomprehensive and targeted. It can be used as the main method for the initial treatment of tumor patients. But these methods may cause the same damage in the continuous treatments after recurrence and metastasis. Under these clinical treatments, the immune system would still not recover healthily, and the risk of recurrence and metastasis would persist. If the health and function of the immune system are not restored, full recovery would be impossible. This has become a problem that cannot be ignored or avoided in the process of cancer rehabilitation and continuous tumor treatment.

### 3) Clinical application of immune recovery and reconstitution in the process of tumor rehabilitation

After 10 years of experimental research, Dr. Su Shan's team has conducted clinical cooperation with many hospitals in China to conduct experiments and research on immune recovery and immune reconstitution. A total of 743 cancer recovery patients of different ages, cancer staging, who completed different times of radiotherapy and chemotherapy were involved. Their conditions covered 13 types of cancer including lung cancer, breast cancer, uterine cancer, ovarian cancer, gastric cancer, liver cancer, pancreatic cancer, duodenal cancer, ampullary adenocarcinoma, colon cancer, rectal cancer, prostate cancer, and thyroid cancer. The self-developed "super polysaccharide factor" acted on T cell receptors with no toxicity and no side effects. It activated T cells and other immune cells, conducting high-frequency differentiation and proliferation in an orderly manner in safe mode to completely avoid immune storms. As a result, numerous healthy T cells (TC & TH) were produced, and their natural functions exerted. Most of the patients achieved good clinical continuous treatment and rehabilitation effects. Even in patients with clinically significant metastatic and recurrent lesions, after three to six months of immune reconstitution and recovery, the metastases no longer developed or gradually disappeared.

The development of "super polysaccharide factor" is based on the basic research on the immune effects of Chinese traditional precious herbs Qinghai Yushu and Tibet Nagqu Cordyceps sinensis by scientists from China, Japan and other countries. Chinese scientists have started the research and clinical application of Cordyceps sinensis in various diseases since the 1950s. In the 1980s, their research and application focused on the role of Cordyceps

sinensis on the human immune system. In the 1990s, the effect of Cordyceps sinensis on human immunity, whether in research or clinical application, reached a peak period, and most research reports and clinical data appeared. Zhou Rongrong, Wu Liying, Shu Jiahe found in the application of 75 cases of gastrointestinal malignant tumors after surgery and chemotherapy, that after one month of Cordyceps sinensis treatment, CD3, CD4, CD4\CD8 increased significantly, and CD8 decreased. This research demonstrates that Cordyceps sinensis can regulate the level of Th1\Th2. Wu Yihong and Wang Shi found in their research<sup>[11]</sup> on the immune function of 30 patients with cardiopulmonary disease that the number of T lymphocyte subsets had increased significantly, indicating that Cordyceps sinensis may activate the phagocytic function of macrophages through the immune regulation of the body, so that the disturbed various immune cells and cytokines can be restored to normal mutual regulation, increasing the lymphocyte count of the patients.

Based on the large amount of research and application data mentioned earlier, the team of Dr. Sushan used more advanced physical purification technology to obtain a "super product" that is 68 times more accurate than traditional purification technology. It is of low cost, high efficiency, non-toxic and has no side effects. The product, called "polysaccharide factor", has made a breakthrough in immune recovery and immune reconstitution in the process of cancer rehabilitation.

Lung cancer patient Q showed invasive adenocarcinoma in the biopsy of the left upper lobe mass on December 28, 2020. In the first stage of treatment, lung cancer was treated twice with the targeted drug of Icotinib. In the process of chemotherapy, however, bilateral lung metastasis was diagnosed. Due to the severe damage to the mucous membranes from chemotherapy, oral ulceration led to difficulty in eating. The patient suffered from a stomach pain which lasted for three months, sometimes the pain became so severe that the patient could not fall asleep or stop sweating. Constipation or dry stool became a problem only solvable using Glycerine Enema. His weight decreased from 83 kg to 72 kg. After the session of targeted therapy, however, bone metastases and liver metastases were found in reexamination. After the patient was admitted to the hospital on June 10, 2021, he often experienced severe stomach pain, nausea, vomiting, poor taste, no appetite, and dry stools. Immunity reconstitution rehabilitation with superpolysaccharide factor began after his admission. Since chemotherapy drugs remain in the body, it is not suitable for rapid activation of T cells. A small dose of super immune factors was used to activate T cells. The patient sweated heavily during sleep that

night, a symptom that disappeared after three days. Under the principle of controlling inflammation mediated by peptic ulcer, after a week, the sense of taste and appetite recovered, followed by regular intake of food, and regularized bowel movement. The stomach pain disappeared after ten days. Due to the patient's poor eating habits, the nutritional rehabilitation program is based on vegetable protein. His meal arrangement was changed to five times a day with smaller amount to reduce the burden on the digestive tract. After three months of immune reconstitution and recovery, the patient's weight returned to 79.5 kg. The report on September 21, 2021, showed that no obvious tumor lesions and metastases were found in both lungs. After the immune system gradually recovered, the dosage of super polysaccharide immune factors was increased, and the intensity and persistence of T cell activation strengthened. The report on April 19, 2022, showed low level of metabolism in the upper lobe of the left lung, accompanied by calcification, multiple small nodules in both lungs with low level of metabolism, and low level of metastatic metabolism on the fourth lumbar vertebra. Doctors considered these as the results from previous treatments, indicating that the tumor activity is basically inhibited.

Ovarian cancer patient Z, diagnosed with ovarian adenocarcinoma on June 29, 2020, underwent cytoreductive surgery, total hysterectomy, double adnexa, omentectomy, pelvic and abdominal implant foci resection, and lymphadenectomy. Two weeks of chemotherapy started on July 6, (paclitaxel liposome 240 mg + 400 mg of carboplatin). On September 9, it was found that the postoperative chemotherapy was ineffective, CA125 increased to 1250 U/mL, FDG metabolism increased, and possible peritoneal metastasis was considered. Chemotherapy was then repeated in September, October, and November, and the regimen was adjusted to paclitaxel 400 mg + lobaplatin 50 mg + bevacizumab 400 mg. During the re-examination in May 2021, it was found that CA125 increased again to 1800 U/mL, and FDG metabolism continued to increase. The examination results showed bone metastases, liver metastases, pleural effusion, and ascites, and another CTC exam indicated more than 15 polyploid cells. When she came to the hospital in October 2021, still on targeted drugs, the patient had developed pleural effusion and ascites. The results of the evaluation showed that multiple chemotherapy treatments had caused severe damage to major organs like kidneys, heart, and lungs. The immune reconstitution and recovery of patients with multiple chemotherapy and multiple recurrence and metastasis is a great challenge, which requires patience and care. The first stage of the immune reconstruction and recovery program involved three months of low-dose im-

mune factors, slowly starting T cells, and at the same time metabolizing part of the toxins produced by chemotherapy drugs slowly from the body. This was an important procedure to prevent these toxins from becoming antigens to activate T cells, causing immune system disorders and immune storms. The targeted drugs that had been taken were halved. The psychological intervention plan solved her insomnia with daily practices of mindfulness, visualization, and sleep counseling before going to bed. After three months, the hospital examination results showed that the metastases did not develop, and the indicators of various organs stabilized.

### **3. Psychotherapy and Counseling for Cancer Rehabilitation Patients and Their Families**

1) Cancer rehabilitation patients and families belong to a special group different from patients with other diseases

The psychology of cancer rehabilitation is different from social psychology, and different from the psychology of cancer. Cancer rehabilitation psychology deals with a group of cancer rehabilitation patients with special psychological states and special psychological needs. They are desperate, helpless, suspicious, infinitely magnifying their pain, and massively psychopathic. Cancer patients and their families suffer from long-term, persistent, post-cancer anxiety, differences in treatment plans, financial pressures, and so on. Understanding and mastering the special psychological status of recovered patients, as well as the psychological impact of family on patients, combined with effective psychotherapy, helps the patients bravely face disease and death. Eventually, cancer patients would be able to achieve self-realization, and to reintegrate themselves into family life and society. This is the important significance and clinical value of tumor psychological rehabilitation.

Psychotherapy data on 57 cancer rehabilitation patients showed that 91% of cancer rehabilitation patients had experienced psychological trauma of varying degrees, which can be divided into four stages: parent-child relationship trauma in childhood, emotional trauma in youth, career trauma in midlife, and the loss of children in old age. The diagnosis of cancer is the most traumatic event for cancer patients, and all these traumas are magnified infinitely by the patients. In the end, the patients are almost overcome by stress and despair.

Parent-child trauma in childhood will affect the life of some patients, and the trauma will be further exacerbated by the diagnosis of tumor. Z is a patient with rectal cancer. When she was a child, to attract her mother's attention from her younger brother, she used various ways to please her mother. She stayed in the vicinity of her mother and



told her various trivial things, which annoyed her mother instead, who was busy with housework. As a result, the mother-daughter relationship became estranged and distant. After she left home to study or work, she made many besties, all of whom became listeners of all her trivial stories. After being diagnosed with rectal cancer, the pain caused during the treatment process became the focus of her narrations, not only to all the doctors, and nurses she encountered in work, but also to strangers she met in the subway. Taking all her history into account, the psychological team of cancer rehabilitation set the focus of her psychotherapy program as addressing psychological trauma caused by motherhood in childhood. The psychological team arranged for her to call her mother once a day and tell her "I love you". For ten days, my mother listened silently on the phone and did not speak. Ten days later, the mother sobbed and cried on the phone, and said to her daughter for the first time "mommy loves you too". The mother learned about her daughter's psychological struggles and came to take care of her from her hometown, hoping to make up for her troubled childhood. With immune reconstruction and recovery, healthy diet, and exercise, after half a year, the patient's condition began to stabilize. All inspection indicators returned normal.

Emotional trauma from adolescence has a high incidence in cancer recovery patients. A patient with uterine cancer, who was doted on by her parents as a princess when she was young, met with strong opposition from her parents when she met her prince charming. To get revenge on her parents, she closed herself up for ten years, refusing to get married or falling in love. During that period, she often suspected that she had a tumor, even though each inspection suggested otherwise. Later, she married a handsome and talented gentleman, but still had not taken her life seriously until being diagnosed with uterine cancer. After being diagnosed with cancer, she made a romantic plan to find a fairyland-like place with her daughter, and to die quietly in her most beautiful clothes. She became obsessed with this idea of beautiful death and could not extricate herself from it. The psychological intervention plan is to collect the most handsome photos of her husband, to make a list of his talent. After three months of psychological rehabilitation, her husband was invited, and to her greatest surprise, she found her husband more handsome and charming than ever before. The patient's mood gradually calmed down. After completing her rehabilitation period in good spirits, she started a new life again.

The trauma of career failure, disappointment in life or the trauma of losing a child in old age bring difficulties to the treatment of cancer patients. What cancer psychological rehabilitation needs to do is to understand the psycho-

logical trauma of patients, to change their psychological state, and to meet their psychological needs. The goal is to reduce recurrence and metastasis, prolong survival period, and to achieve complete recovery, through cooperation with immune reconstruction and recovery and other clinical treatment methods.

2) Psychotherapy precludes emotional catharsis and emphasizes sunshine, hope and beauty

Active psychotherapy of cancer rehabilitation is based on mindfulness, inspiration, joy, and hope, and has positive significance for the recovery of tumor patients. The emotional catharsis advocated by social psychology is less encouraged in the psychotherapy of cancer rehabilitation. Cancer patients who have had traumatic experiences in different periods, once guided to vent out, would often mix old emotions with reality, flooding it with negative and even destructive emotions. They could find themselves trapped in negativity and unable to escape, aggravating the condition and making it difficult for rehabilitation psychotherapy. It is of positive clinical significance for tumor rehabilitation to encourage the patients to live in the sunshine, even if there is only one year, one month or one day left in the future.

Patient C has had a strong character since childhood. Born in a remote village, she studied to pass the entrance exam of a famous university. After graduating from university, she worked hard again and eventually succeeded in career. To make her children stand out, she gave up a happy family life in China and was adamant in taking her two children abroad, accompanying their study. When she returned to China five years later, she was greeted with a divorce letter from her husband. One week after the divorce, she felt tired, nauseated, and vomited. The hospital examination showed that she had developed advanced gastric adenocarcinoma, and her life expectancy was only three months. After chemotherapy, her body became very weak with high level of ascites. Report showed that the albumin level dropped to 29 g/L, and creatinine was 32% below normal value. The patient had been the backbone of the family since childhood, supporting her younger siblings to go to college. On top of her dilemma, her father and ex-husband came after her money, coercing her into making a will. During the psychological counselling after being admitted to the hospital, she finally broke down. She kept crying and said that they had never loved her, only asking for money, and that her mother had never even held her hand since she was a child. Psychotherapy uses a program of one-on-one psychotherapy and family counseling. The program first lets her love herself, and then lets her family love her. She bought herself beautiful clothes, and everyone took pictures of her to appreciate



her beauty. She was happy and said no one had ever appreciated her. She donated money, books, and computers to her alma mater in elementary school, asking the principal to bring the student representatives to the hospital to present flowers to her and pay tribute. She had a sense of value and purpose in life. Secondly, her mother was invited to accompany her, who also received psychological counseling. The atmosphere of love was gradually established, and the patient gradually calmed down. She cooperated very well with her treatments, and the immune reconstruction and recovery went very smoothly. After being discharged from hospital, psychological follow-up and family psychological counseling continued. The person who was originally sentenced with a life expectancy of only three months has continued to live on for nearly three years. Not only has she survived, but the longer she lived, the healthier she became.

3) Psychotherapy and psychological counseling with the theme of sunshine, beauty, and hope

A large part of group therapy in cancer psychological rehabilitation is carried out in the form of courses, most of which are derived from social psychology and then redeveloped to meet the needs of rehabilitation patients. The format of the curriculum is like that of Montessori child education, in which children achieve simultaneous growth, often unconsciously, through play. These courses also provide continuous and effective psychological intervention and psychotherapy for cancer patients through lively and fun games. With the theme of sunshine, beauty, hope and love, the direction of psychotherapy explores the happiness shared by all human beings, so that cancer patients can enjoy this happiness again and walk out of the shadow of disease and death.

The main course of cancer psychological rehabilitation is based on the theme of love and happy memories, the first of which being the happy memories of childhood. 90% of people have experienced the happiness of childhood, and even the least privileged have happy childhood experiences like catching fish in the river and fighting crickets. "Bright Stars in the Sky" is a curriculum based on traditional Chinese childhood stories, games, fun, food, and nursery rhymes. These lessons include origami, kicking shuttlecock, blowing bubbles, sewing sandbags, guessing charades, storytelling, paper cutting, etc. The second type of happiness is the memory of first love. First love, even if a secret one, is the purest and most beautiful form of love and would remain unforgettable. "There is a girl in the village named Xiaofang" is an interactive course designed in the form of afternoon tea meetings, allowing patients to quietly recall a bud of love buried in their hearts. The third one is the happy memories that

children and grandchildren bring to the elderly. "The Little Sun in Our Home" allows patients to tell the childhood stories of their sons, daughters, grandchildren and show their photos. Holding a birthday party for their grandchildren, celebrating the start of school or nursery school of their grandchildren, etc., are activities that are designed to integrate patients better into family activities.

Auxiliary Courses:

**Lifeline.** The purpose of the curriculum is to allow patients to review their life and clarify their life trajectory line by line. The curriculum includes personal line, children line, health line, parent line, career line, partner line, family line, friend line, etc.

**Mindfulness.** The setting of mindfulness courses is to train patients to look inside themselves, to consciously change some bad habits, and to improve a good concept of survival. These mindfulness courses include breathing, chewing, walking, meditating, smiling, sleeping.

**Living habits:** The purpose of the curriculum is to let patients learn some common sense of life and to love life. These lessons include folding T-shirts, folding socks, kitchen tidying, and room tidying. Some specialized courses also teach patients how to smile and how to be grateful.

#### **4. Nutritional, Physical Rehabilitation and Metabolic Therapy**

1) Establish nutrition formula and exercise mode through data measurement, and set exercise amount

For tumor nutritional rehabilitation, the priority is to avoid food with chemical pesticides and veterinary hormone residues, making organic and naturally grown vegetables and fruits the first choice. Nutritional formulas after chemoradiotherapy are divided into common formulas and individual formulas. When a group of patients are admitted, nutritional diagnoses are performed to determine the adaptive food and supplementary food for each individual patient. Based on the test data, the common adaptive food and personalized adaptive food are identified, forming the nutritional formula. For example, if the common adaptive food for 15 people is carrots, carrots for 15 people are implemented from the beginning of purchasing, and the nutritionist and the chef collaborate to develop the carrot menu. Meanwhile, if test result shows the demand of kelp for 2 people, that specific purchase will be implemented, and the nutritionist and the chef will jointly formulate a kelp menu for 2 people. In addition, the formulation of special meals is handled according to the special nutrition list prescribed by doctors.

Due to the form and intensity of most aerobic exercises, they are not suitable for most cancer patients. Research <sup>[12]</sup>

shows that a 6-minute set of simplified Tai Chi can achieve 65% of the target heart rate for 80% of the test subjects, while exercises on the treadmill take 12 minutes on average. Therefore, traditional Chinese Tai Chi and Baduanjin are more suitable for cancer rehabilitation patients. Aerobic exercises in gyms become only advisable after successful rehabilitation. It is also important to set the form of exercise based on where the various cancers occur. Rehabilitation patients with lung cancer use thorax and upper-limb exercises to enhance breathing and recover lung function. Rehabilitation patients with digestive tract tumors use abdominal exercises to enhance intestinal peristalsis and digestive function, restoring the function of digestive tract.

2) Metabolic therapy has successful clinical experience, but still not without defects

There are some successful cases of nutritional metabolic therapy in the current clinical application, but due to the complexity of cancer rehabilitation treatment, some rehabilitation patients lack comprehensive rehabilitation methods such as immune or psychotherapy, resulting in various complications, including loss of appetite, severe physical fatigue, and difficulty in eating or exercises. Isolated metabolic therapy is ineffective in most people and cannot be an independent rehabilitation method. The introduction of metabolic therapy into cancer rehabilitation requires a combination of means including immune reconstruction, psychotherapy, nutritional therapy, and physical exercises to comprehensively solve the problem of tumor microenvironment to control the development of cancer cells. Metabolism, as an important reference index, has positive significance for the control of cancer cells. Pancreatic cancer patient J, whose CTEC test before admission showed active cancer cells, with the number of tumors polyploid epithelial cells reaching 12, was diagnosed with abnormal glucose metabolism. After admission, the first round of immune reconstruction activated the T cells, restoring the function of other immune cells. This in turn affects the endocrine system, which, combined with psychotherapy and appropriate exercise, gradually stabilized his glucose metabolism. After three months, a second CTEC test showed fewer polyploid cells.

Covering many types of tumors and a large and diverse group of patients, cancer rehabilitation must be accomplished through multidisciplinary collaboration. The technical means of cancer rehabilitation, including immune reconstruction, psychotherapy, nutritional and physical metabolic therapy, need to be constantly researched and

updated to meet the needs of cancer patients. The theoretical study of cancer rehabilitation also calls for the continuous efforts of multidisciplinary experts. Cancer rehabilitation still has a long way to go.

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ISSN 2591-7609

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