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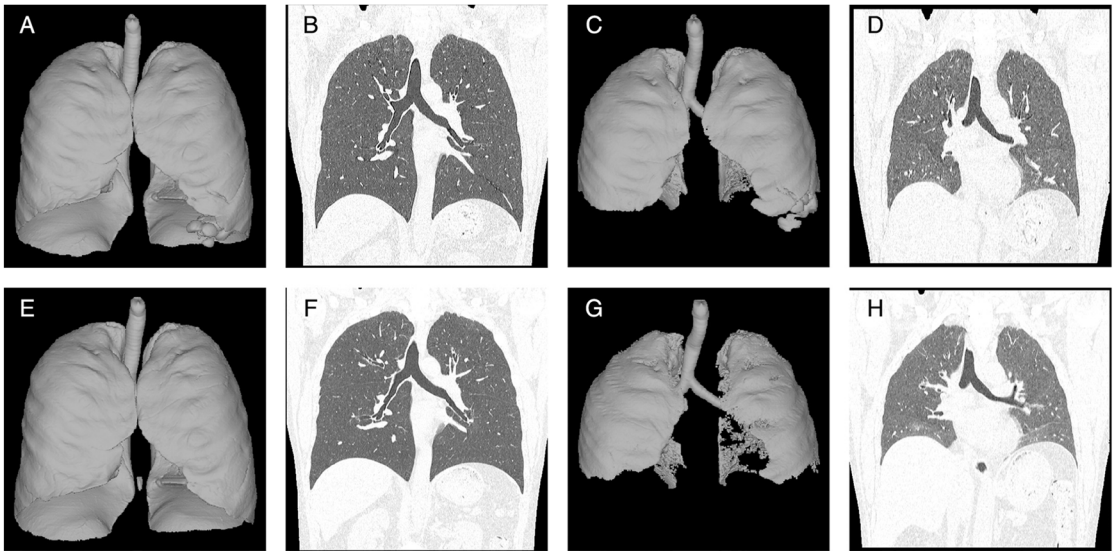

Lung capacity by virtual place in the inspiration and expiration. PAGE 99

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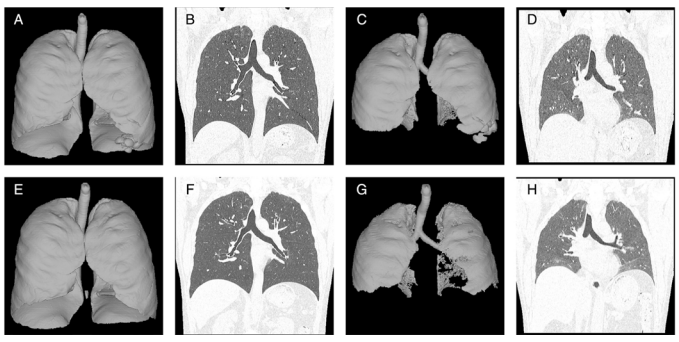

Lung capacity by virtual place in the inspiration and expiration. Upper row: Before BT; Lower row: After BT. BT, Bronchial Thermoplasty. (*Page 99*)

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Strategic approach for combating antimicrobial resistance (AMR)

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Abstract: During the past 70 years, there has been a continued incremental worsening of antimicrobial resistance (AMR) by a combination of abusing antimicrobials in humans and animals as well as insufficient research and investment for new antimicrobial agents. The current trend of worsening AMR is likely to result in increased mortality and morbidity, longer stays in hospitals and accelerated health care costs. It is estimated that the global mortality attributed by AMR could reach 10 million per year by 2050, which is a massive increase from the current estimated mortality of 700, 000 per year. The year 2014 was the turning point of more than a half century of AMR history, transforming it from technical issue to a political agenda. Major progress includes adoption of the Global Action Plan on AMR at the WHO World Health Assembly in May 2015, followed by completion of a National Action Plan in most parts of the world, enactment of the Global Antimicrobial Surveillance System (GLASS) in October 2015, launch of the World Antibiotic Awareness Week in November 2015, and G20 Leaders' commitment to create the AMR Global Collaboration Hub in July 2017. Moreover, a comprehensive program against AMR has been implemented in some countries, such as UK, USA, and Germany. The strategic approach through coordination led by WHO with relevant international agencies and other entities was one of the key enabling factors for sustained political commitment on AMR.

***Keywords*:** Antimicrobials, antibiotic resistance, drug resistance

Introduction

Antimicrobials are often regarded as one of the greatest inventions of human history. Since Dr. Alexander Fleming first discovered penicillin in 1928, it became one of the indispensable elements of modern medicine, not only treating infectious disease, but also for a wide range of medical interventions such as joint replacement, caesarian section and chemo-therapy for cancer. However, one of the first notable warnings of antimicrobial resistance (AMR) – formally referred as antibiotic resistance or drug resistance – was made in 1945 by Dr. Alexander Fleming, in his speech at the Nobel Lecture, he predicted that "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant" (*1*).

During the past 70 years, there has been a continued incremental worsening of AMR by a combination of abusing antimicrobials in humans and animals as well as insufficient research and investment for new antimicrobial agents (*2-4*). It is worth noting that different from other political agendas such as health emergencies that had specific outbreaks to induce political attention, the disease burden of AMR worsens only in an incremental manner (*5*). By 2014, the threat of AMR became gradually obvious among the science and medical community due to increased prevalence of sporadic drug resistant infection outbreaks in health care settings even among high income countries, as well as worsening of drug resistance among three major infectious diseases – HIV/AIDS, tuberculosis and malaria – in low- and middle-income countries (*6*).

Besides, although some of the infectious diseases are among the leading causes of disease burden in recent studies, such as lower respiratory infections, diarrheal diseases and neonatal encephalopathy, where a substantial portion of them are caused by AMR, AMR itself is not categorized as a disease in these studies and hence its direct burden is not measurable (*7*).

The same is true for risk assessment. While some of the infection related risks, such as unsafe sex, unsafe water, insufficient handwashing, and unsafe sanitation are identified as a factor to be calculated, AMR is not included as a risk factor (*8*). AMR is invisible both in terms of disease burden analysis and risk analysis.

The global political strategies of AMR control

It was since 2014 when AMR got due attention from the political circle, which enables the agenda to make remarkable progress in terms of policy formulation, resource mobilization and effective implementation

(*9*). This recent progress encompasses a wide variety of programs and initiatives, including adoption of the Global Action Plan on AMR at the WHO World Health Assembly in May 2015 (*10*), followed by completion of the National Action Plan in most parts of the world (*11*), enactment of the Global Antimicrobial Surveillance System (GLASS) in October 2015 (*12*), launch of the World Antibiotic Awareness Week in November 2015, and G20 Leaders' commitment to create the AMR Global Collaboration Hub in July 2017 (*13*). To catalyze and facilitate the required action with adequate financing and legal framework, the political process played a pivotal role (*14*).

In spite of its elusive nature, since 2014, AMR has emerged as one of the most prominent political agendas with the highest attention, discussed at G7 and G20 Summits as well as UN General Assembly High Level Meeting (*13,15-17*). This recent transformation of the agenda was phenomenal after more than half century of AMR history. While AMR has been technically discussed among science and health communities for more than half century with several problem-solving approaches proposed and tried, we could not deliver tangible results until recently.

AMR Global Action Plan

AMR Global Action Plan was adopted at the WHO World Health Assembly in 2015 and member states agreed to plan and finalize a national action plan in each country in the following 2 years (*11*).

This Global Action Plan contains five objectives (*18*): *i*) raising awareness; *ii*) surveillance; *iii*) reduce the incidence of infections; *iv*) optimal use of and access to medicine; and *v*) research & development of new antimicrobials and diagnostics.

While objective *iii* (reduce the incidence of infections) is not AMR specific because it would be achieved through immunization and infection prevention and control (IPC) programs, the other four objectives are AMR specific. It is notable that the planning of National Action Plans and programs for these four AMR specific goals has been implemented in the succeeding periods from 2015 to 2017 as shown in Figure 1.

The major actions include: *i*) National Action Plans have been planned and finalized in the following 2 years after the adoption of the Global Action Plan in May 2015 for around 130 countries, which covers more than 95% of the global population (*13*); *ii*) AMR Awareness Week was launched in November 2015, the first time in AMR history as a major public communication programs and continues since then; *iii*) AMR Global Surveillance System (GLASS) was launched in December 2015 to monitor the prevalence of AMR among major pathogens in clinical settings, where more than 40 countries across all continents have joined so far (*12,19*); *iv*) Roadmap on Global Framework for Development & Stewardship to Combat AMR was drafted in May 2017 for further elaboration (*20*); and *v*) AMR Research and Development Collaboration Hub was established in July 2017 (*13*).

During this implementation period from 2015 to 2017, there had been a constant issuance of political declaration by G7, G20 and UN General Assembly. All these political declarations reiterated its firm support for the Global Action Plan and committed to implementation of its objectives. This unprecedented level of rapid implementation of the technical outputs during this period could not be explained without this constant and repeated political declaration from the highest level (*14*).

The challenge of AMR control

Although development and spread of AMR is a natural

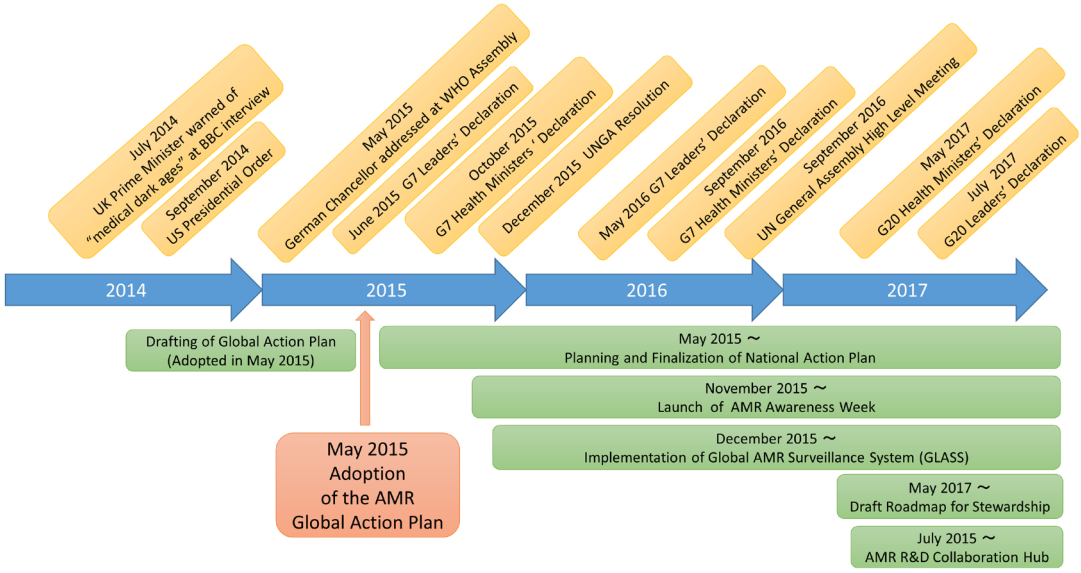

Figure 1. Key political milestones and technical implementations from 2014 to 2017.

phenomenon that occurs irrespective of human activities, massive and irrational use of antimicrobials are the major attributing factor for the current rapid spread of AMR (*21*). The use of antimicrobials is not well regulated in low- and middle-income countries, being accessible without prescription and not dispensed by qualified health professionals. Rampant contamination of substandard and falsified medicine into the supply chain of antimicrobials also contributes to spread of AMR among low- and middle-income countries (*7*).

In addition to its use for humans in clinical settings, far greater amounts of antimicrobials are currently consumed by the animal husbandry sector, including aqua culture. This massive usage is not only for treatment or prophylaxis of food animals, but also growth promotion purposes as well (*22,23*).

This under-regulated massive use of anti-microbials both in human and animal sector contributes to the spread of AMR on the global scale, combined with lack of adequate investment on research and development for new medicines. It poses a risk of returning ourselves to an era akin to before Fleming.

The current trend of worsening AMR is likely to result in increased mortality and morbidity, longer stays in hospitals and accelerated health care costs. According to a study initiated by UK Prime Minister David Cameron, the global mortality attributed to AMR could reach 10 million per year by 2050, which is a massive increase from the current estimated mortality of 700, 000 per year (*7*). This would impact not only health but also political and socio-economic stability of the globe (*24*).

The strategy of AMR control: from technical issue to a political agenda

The year 2014 was the turning point of more than half century of AMR history, transforming it from technical issue to a political agenda. Prime Minister of UK David Cameron, President of the United States Barack Obama and German Chancellor Angela Merkel played a key role (*25,26*).

On July 2, 2014, Prime Minister Cameron appeared on a BBC interview for the first time on this issue. In this broadcast, he said the world could soon be "cast back into the dark ages of medicine" and "if we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work, and we are cast back into the dark ages of medicine where treatable infections and injuries will kill once again". Prime Minister Cameron also revealed in this broadcast that he discussed the issue in June 2014 with US President Barak Obama and German Chancellor Angela Markel in Brussels, saying that "it's good that Britain is taking the lead on this issue to solve what could otherwise be a really serious global health problem".

It was successfully relayed to US President Barak Obama. President Obama issued an executive order on September 18, 2014 on Combating Antibiotic-Resistant Bacteria (*25*). This executive order states that "the rise of antibiotic-resistant bacteria represents a serious threat to public health and the economy" and "combating antibiotic-resistant bacteria is a national security priority". Based on this recognition, it contains a comprehensive program against AMR, that encompasses establishment of an oversight and coordination mechanism within the government led by the National Security Council, launch of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, improved antibiotic stewardship, strengthening national surveillance efforts for resistant bacteria, preventing and responding to infections and outbreaks with antibiotic-resistant organisms, promoting new and next generation antibiotics and diagnostics, and international cooperation.

The introduction of the AMR agenda by two political leaders – Prime Minister David Cameron and President Barack Obama – in 2014 was perceived as somewhat abrupt as is often the case with the initial stage of any agenda. There was a need for adequate political follow up to keep the momentum. As a strategy to broaden the commitment, it would be desirable for this follow up to be made by different leaders or entities. After the introduction of the agenda into the political arena by UK and US, this follow up role was made by Germany, as the president of G7 in 2015. This German G7 Summit meeting in June 7-8, 2015 was the first time in history for a group of heads of state and heads of government to make a declaration on AMR (*15,16*) (Previously, it was described as "antibiotic resistance", but starting from this political document, the wording became "antimicrobial resistance (AMR)" to broaden the concept, which became the standard wording thereafter).

This political document states that "Antimicrobials play a crucial role for the current and future success of human and veterinary medicine. We fully support the recently adopted WHO Global Action Plan on Antimicrobial Resistance. We will develop or review and effectively implement our national action plans and support other countries as they develop their own national action plans. We are strongly committed to the One Health approach, encompassing all areas – human and animal health as well as agriculture and the environment. We will foster the prudent use of antibiotics and will engage in stimulating basic research, research on epidemiology, infection prevention and control, and the development of new antibiotics, alternative therapies, vaccines and rapid point-of-care diagnostics. We commit to the annex (Joint Efforts to Combat Antimicrobial Resistance) as we develop or review and share our national action plans".

In conclusion, the level, frequency and density of the politicization on AMR during the period from 2014 to 2017 was unprecedented as a health agenda. This has been the key element in facilitating the recent technical outputs. AMR has successfully maintained

political momentum because it is not considered as a mere health issue, it is also a matter of national security, economic growth, social stability, food security and a key determinant for the attainment of Sustainable Development Goals (SDGs). This strategic broadening of the scope of the agenda, through coordination led by WHO with relevant international agencies and other entities was one of the key enabling factors for sustained political commitment on AMR. As observed for AMR, politicization, though not an end in itself, is an effective tool for implementing the output, which could ultimately deliver the expected outcome, in terms of health improvement and mitigation of its socio-economic impact.

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G20 Okayama Health Ministers' Meeting: lessons learned and way forward

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Abstract: The third G20 Health Ministers' Meeting was held in Okayama, Japan on October 19-20, 2019. The authors were involved in the decision making of the substantial issues of this meeting including theme setting, schedule management, facilitating the discussion, and preparation for the ministers' meeting. Here, we summarize our lessons of experience from hosting G20 Okayama Health Ministers' Meeting as: *i*) Utilizing the occasion of existing major health related meeting to gain efficiency; *ii*) Collaboration with other G20 tracks such as finance can function as a tool to facilitate inter-sectoral collaboration within other G20 members; *iii*) Two-day Health Working Group before the ministerial meeting provides sufficient time for negotiation of the declaration text; and iv) Inclusion of residents and representatives of the host city provides great opportunity to create G20 legacy. Such an experience of Japanese policymaking is rarely shared in English and the lessons learned from our experience shall provide meaningful advice for Saudi Arabia colleagues who are to hold the next G20 Health Ministers' Meeting as well as for the preparation of other G20 ministerial meetings.

***Keywords*:** G20, Japan, UHC, aging, AMR, health emergency, nutrition

Introduction

On October 19-20, 2019, the third G20 Health Ministers' Meeting was held in Okayama, Japan. The authors were involved in the decision making of the substantial issues of the G20 health track which led to this meeting including theme setting, schedule management, facilitating the discussion, and running the ministers' meeting. We were also involved in the negotiation of the first ever joint session by the Health and Finance Ministers as well as the health component of the G20 leaders' declaration. Such an experience of Japanese policymaking is rarely shared in English and the lessons learned from our experience shall provide meaningful advice for Saudi Arabia colleagues who are to hold the next G20 Health Ministers' Meeting as well as for the preparation of other G20 ministerial meetings.

Reviewing the progress of G20 Health Ministers' Meeting

The first G20 Health Ministers' Meeting was held under the German presidency in Berlin in 2017. Given the rising interest in health emergency preparedness starting from the Ebola outbreak in West Africa (*1*), the meeting's main focus was global health crisis management (*2*). The discussion was taken over from the G7 Health Ministers' Meeting in Kobe in 2016, which placed a strong emphasis on health emergencies as well. The German G20 Health Ministers' Meeting included a first-ever tabletop simulation exercise participated in by health ministers from the G20 members which focused on core issues in global health crisis management including communication, collaboration, contributions, coordination, and compliance (*3*). The following G20 presidencies, Argentina and Japan, took over this unique feature to involve ministers in simulation exercises. Another major achievement of the 2017 G20 health track was the launch of the Global AMR Research and Development (R&D) Hub. The initiative, which aims to expedite R&D of new antibiotics through cross-sectoral collaboration, emerged from a call from the G20 Leaders (*4*).

Under the Argentina presidency in 2018, it inherited most of the main themes in the German presidency (Figure 1). The main themes included antimicrobial resistance (AMR), malnutrition, health system strengthening, and health system responsiveness (*5*).

Malnutrition, in particular, focused on childhood overweight and obesity. In Latin America, childhood overweight and obesity have been an alarming problem as researched in a systematic review (*6*). This was a good example to show how high-level global dialogue could cast light on emerging regional public health issues. A simulation exercise featuring AMR was also performed in the G20 Health Ministers' Meeting in Argentina. Through the opportunity, the G20 health ministers cultivated their practical knowledge and skills to combat resistant pathogens.

In 2019, the Japanese presidency adopted several main pillars: the achievement of universal health coverage (UHC), response to population aging, management of health risk and health security, and AMR (*7*). As a country that achieved UHC nearly 60 years ago in 1961, Japan has identified UHC as a priority in global health. Regarding aging, it was a new theme for the G20 health ministers to discuss. As the World Health Organization (WHO) projected, we are experiencing global population aging at its fastest pace (*8*). Being the most advanced country in the world on aging, Japan was responsible for playing an important role to lead the discussion with G20 members. The summary of major themes and timeline of the G20 Health Ministers' Meeting found in Figure 1 and Table 1 provides an overview of key outcomes for each meeting by major themes.

Process of G20 Okayama Health Ministers' Meeting and lessons learned

The preparation process for the Okayama meeting started from summer 2018 as we started our internal discussion on the theme of the meeting. Following this internal discussion, we presented the theme to the G20 members in January 2019 and had 4 rounds of Health Working Group discussions on the leaders' declaration health section as well as the ministers' declaration (see Figure 2 for G20 health track schedule). Alongside the Health Working Group discussion, we closely collaborated with our foreign ministry regarding the leaders' declaration and finance ministry regarding the G20 Shared Understanding on the Importance of UHC Financing in Developing Countries which was the output for the Joint Session of Ministers of Finance and Health. The following sections describe the details of *i*) setting the theme, *ii*) managing the schedule of Health Working Groups and other relevant meetings, *iii*) facilitating the G20 member discussion, and *iv*) preparing for the G20 Health Ministers' Meeting and the lessons learned (Table 2) through this process.

Setting the theme

In identifying the main pillars of discussion, we put importance both on the continuity from the previous presidencies and accommodating new agenda. We also needed to consider the diversity of G20 members, which includes both developed countries and emerging economies and select the themes which are relevant for all G20 members.

Since the late summer of 2018, we had an internal discussion in the government. As the Leaders' summit was to be held before the Health Ministers' Meeting, we needed to align the discussion in the Health Working Group and the Sherpa track. Therefore, we worked together particularly with the Ministry of Foreign Affairs. We also had close collaboration with the Ministry of Finance, as the Joint Session of Ministers of Finance and Health was to be held in the margin of the Leaders' Summit. After internal coordination among those ministries, the Ministry of Foreign Affairs sent an issue note on health, which showed the three main

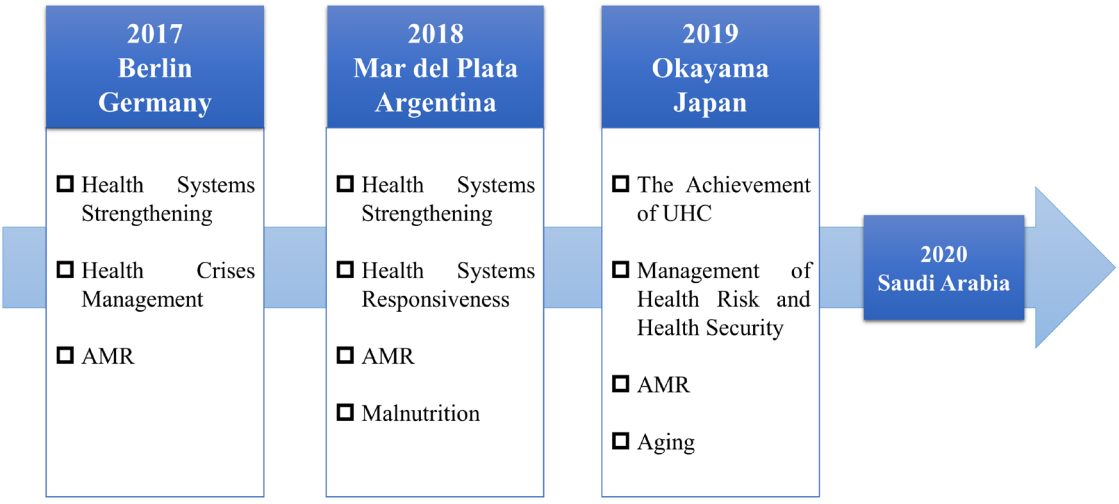

Figure1. Names of host cities, time-line and major themes of G20 Health Ministers' Meetings are listed in chronological order. Key pillars discussed in Berlin in 2017, including health systems strengthening, health risk management, and AMR, have been taken over by the subsequent presidencies. Malnutrition and response to population aging are unique themes discussed in Mar del Plata and Okayama. *Abbreviations*: AMR, antimicrobial resistance; UHC, universal health coverage.

Table 1. Major themes and key outcomes in the G20 Health Ministers' Declaration

Items	2017, Germany	2018, Argentina	2019, Japan
UHC/HSS	• Appreciate the establishment of the UHC2030. • Request for reliable evidence base and appropriate indicators to monitor progress. • Encourage investment in building a skilled and motivated health workforce.	• Encouraged investment in building the health workforce. • Encouraged sharing best practices of e-health including effective policy design and implementation.	• Promote use of data and digital technologies. • Highlight the importance to build institutional capacity, including human resources for developing health policies. • Work with Finance Ministers and relevant stakeholders for financial sustainability.
Aging	–	–	• Affirm active and healthy aging as priority. • Commit to develop and implement multi-sectoral national action plans on dementia.
AMR	• Highlight the importance of the R&D initiatives to examine push and pull mechanisms. • Commit to create an AMR National Action Plan and aim to implement them by the end of 2018.	• Welcome the establishment of the Global AMR R&D Hub and encourage investment in R&D.	• Encourage investment in R&D and reaffirm the need to further examine practical market incentives. • Enhance implementation of policy measures to prevent infections and stewardship of antimicrobials.
Health Emergency	• Highlight the need for monitoring and evaluation measures of IHR implementation and the importance of implementing IHR, including building core capacities within the context of HSS.	• Encourage member states to contribute to the CFE. • Emphasize the need for multi-sectoral preparedness efforts.	• Encourage WHO to broaden donor base for the CFE and contribute to it.
Nutrition	–	• Commit to take action to tackle malnutrition, with a particular focus on childhood overweight and obesity, including through enhanced inter-sectoral efforts.	• Acceleration of efforts to enhance nutrition in the framework of the UN Decade of Action on Nutrition (2016-2025).

Note: Names of host cities, time-line and major themes of G20 Health Ministers' Meetings are listed in chronological order. Key pillars discussed in Berlin in 2017, including health systems strengthening, health risk management, and AMR, have been taken over by the subsequent presidencies. Malnutrition and response to population aging are unique themes discussed in Mar del Plata and Okayama.
Abbreviations: AMR, antimicrobial resistance; HSS, health systems strengthening; UHC, universal health coverage; UHC2030: International Health Partnership for Universal Health Coverage 2030.

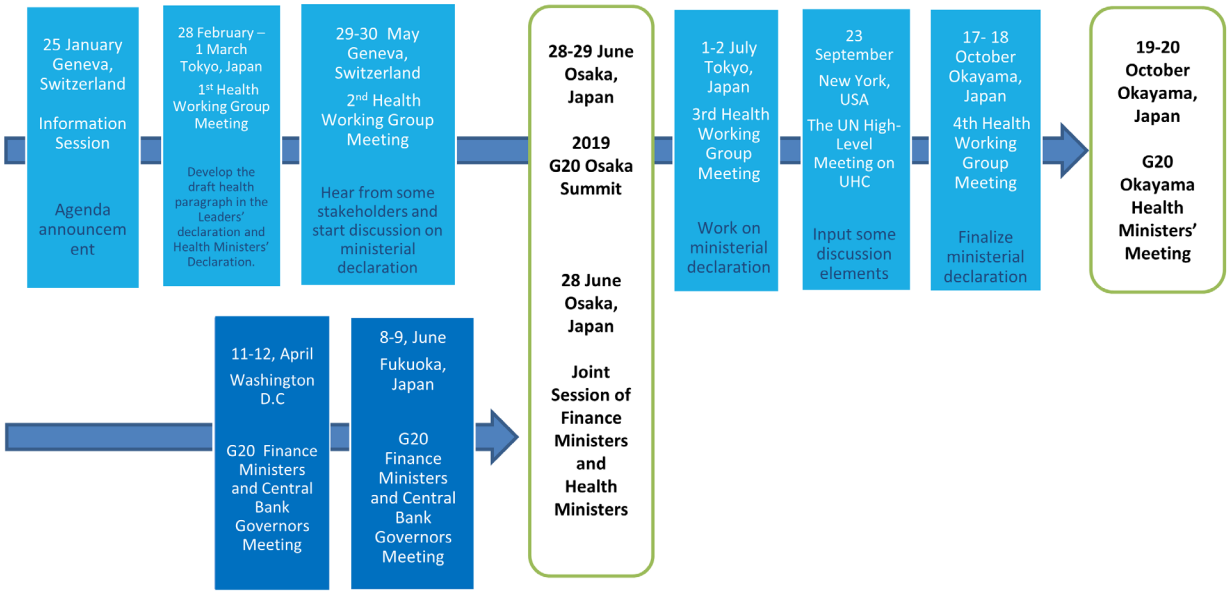

Figure 2. 2019 G20 health track schedule.

Table 2. Lessons learned from our experience of hosting G20 Okayama Health Ministers' Meeting

Items	Lessons learned
Lesson 1	Utilizing the occasion of existing major health related meeting is the key to facilitate efficient G20 member discussion.
Lesson 2	Collaboration with other G20 tracks such as finance can function as a tool to facilitate inter-sectoral collaboration within other G20 members.
Lesson 3	Two-day Health Working Group before the ministerial meeting provides sufficient time for negotiation of the declaration text.
Lesson 4	Inclusion of residents and representatives of the host city provides great opportunity to create G20 legacy.

pillars, on December 20th 2018 to G20 members.

Following the practice of Argentina, we hosted an information session in the margin of the WHO's Executive Board (EB) meeting in January. We explained our idea on the agenda and way forward to the Health Ministers' Meeting, which were both supported by G20 members. Utilizing the occasion of existing major health-related meetings, such as the EB meetings, was effective in gaining efficiency as many health experts from the capital were present (*Lesson 1*).

Managing the schedule of Health Working Groups and other relevant meetings

The first Health Working Group was held from January 31 to February 1, 2019 in Tokyo. We had an intensive discussion on the agenda and received valuable input from G20 members, invited countries and international organizations to develop the draft health paragraph in the Leaders' declaration and Health Ministers' Declaration.

The outcome of the Joint Session of Ministers of Finance and Health was coordinated through the finance track. Ministry of Finance in each G20 member country had coordination with its health counterpart and made input into the outcome document of the Joint Session of Ministers of Finance and Health with "one voice". This process facilitated a dialogue between the Ministry of Finance and Health within each country. Thus, the process of developing the outcome, "G20 Shared Understanding on the Importance of UHC Financing in Developing Countries" has functioned as a tool to enhance inter-sectoral collaboration between finance and health sector in each G20 country (*Lesson 2*).

Based on the discussion in the first Health Working Group, the draft paragraphs on health in the Leaders' Declaration were developed and discussion by the Sherpas started in May. The discussion continued until the day of the Leaders' Summit. Finally, the Leaders' declaration including 4 paragraphs on health was agreed upon. The health paragraphs which consist of UHC, responses to aging, health risk management, and health security and AMR guided further discussion in the Health Working Group.

The discussion on the Ministers' declaration started in May. We hosted the Second Health Working Group from May 29 to 30, 2019 in Geneva at the margin of the World Health Assembly (WHA). It was also very efficient to utilize the occasion of WHA for the same reason as the information session in January. We hosted the 3rd Health Working Group from July 1 to 2, 2019 in Tokyo, just after the Leaders' Summit and the Joint Session so that participants can attend both meetings with one trip to Japan. As we highlighted as our 1st lesson, in order to have an efficient process, the presidency needs to consider how they can host meetings to which G20 members can easily attend.

Facilitating the G20 member discussion

From the beginning, each member supported the themes and contributed to constructive discussion. Especially, the support from Troika countries, Argentina and Saudi Arabia was valuable for facilitating the discussion.

While fully considering existing agreements such as Political Declaration for the UN High-Level Meeting on Universal Health Coverage, WHA resolutions, G20 Leaders' communique, and the shared understanding by the G20 Finance and Health Ministers, our discussion centered on points that should be agreed upon and implemented by G20.

Emphasis was placed on dialogue with health-related engagements groups such as C20 (Civil Society) and T20 (Think Tank), as these dialogues have been employed by the previous G20 Presidency. Their inputs as a form of policy proposals and in person discussion at the 2nd G20 Health Working Group facilitated our discussions and was effective to incorporate various opinions of stakeholders into our final deliverables.

Another emphasis was collaboration with the Global AMR R&D Hub which is one of the legacies from the G20 German presidency. This collaboration resulted in the workshop held at the occasion of the 2nd Health Working Group Meeting, providing G20 participants with the current landscape of AMR R&D and the importance of deepening discussions on AMR.

When we reached the 4th Health Working Group, we had agreed on majority of the text thanks to the intense e-mail based communication in August and September. At the final 4th Health Working Group Meeting, constructive cooperation among countries

enabled smooth and efficient discussion. We considered that two days (not one day) of the final meeting provided sufficient time for G20 members to consult with their headquarters during the first and second day which contributed greatly to smooth consensus building. This two-day Health Working Group before the ministerial meeting could be a good example method for future multi-lateral negotiation (*Lesson 3*).

Running the G20 Health Ministers' Meeting

Representatives from G20, invited countries and international organizations, including 9 Ministers, attended the Ministers' Meeting and the number of delegates amounted to 157. After the active discussion chaired by Mr. KATO Katsunobu, Minister of Health, Labour and Welfare who shared Japan's experiences and commitments relevant to themes, the Okayama Declaration of the G20 Health Ministers was adopted. Particularly, responses to population aging was first included as one of the main pillars in the G20 Health Ministers' Declaration and we believe that this new commitment will mobilize active policy responses in all G20 members and generate global momentum on this important issue.

Alongside the discussion by Ministers and representatives, we invited representatives from the host city, Okayama. Mr. OMORI Masao, Mayor of Okayama City, made a presentation to show their local efforts to extend healthy life expectancy. The representatives from local high school students presented their recommendations to G20 on women and children's health. Local elementary school students cordially welcomed delegations at the meeting venue. These involvements by the host city impressed the delegates and became a valuable legacy for the community. Collaborations with the host city was a key to the success of the meeting (*Lesson 4*).

Following the practice of previous presidencies, we had a simulation exercise on the 2nd day of the Health Ministers' Meeting. The theme was public health response to a health emergency during a mass gathering: according to a fictitious scenario and questions which request political decision, participants had a lively discussion facilitated by moderators, Dr. SUZUKI Yasuhiro, Chief Medical & Global Health Officer of the Ministry of Health, Labour and Welfare and Dr. KURANE Ichiro, former Director-General of National Institute of Infectious Diseases. The topic was relevant to all G20 members which often host large scale gatherings.

Way forward

The G20 presidency for 2020 is succeeded by Saudi Arabia. We would be very pleased if our lessons and experiences discussed in this article are useful for their preparation of the next G20 Health Ministers' Meeting.

Besides G20 meetings, we would like to highlight two upcoming meetings. Regarding UHC, which was one of the major topics of the G20 Okayama Health Ministers' Meeting, Prince Mahidol Award Conference (PMAC) 2020/UHC Forum 2020 to be held from January 31st to February 2nd in Bangkok will provide a great opportunity to follow up on the Okayama declaration and call for further concrete actions including developing a PHC-based health system, strengthening health financing and investing in promoting innovations of health technologies.

Moreover, the importance of collaboration between finance and health authorities was strongly emphasized in the shared understanding by the G20 Finance and Health Ministers. To keep this momentum, the Asian Development Bank (ADB), WHO, and the Government of Japan plan to coorganize a ministerial-level symposium on May 3rd 2020, at the time of the 53rd Annual Meeting of ADB's Board of Governors in Incheon, Republic of Korea.

We expect the above mentioned meetings would be a good occasion to call for further concrete actions, building upon strong global political commitments we shared at the G20 Okayama Health Ministers' Meeting.

Statement

Views expressed in this article are written in authors' individual capacity and does not represent any organization.

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National Action Plan on Antimicrobial Resistance (AMR) 2016-2020 and relevant activities in Japan

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Abstract: Antimicrobial-resistant bacteria that are spreading all over the world have caused significant problems. While these problems are becoming bigger, the development of new antimicrobials has remained stagnant, and some essential antimicrobials for treatment may be depleted in the near future. This is a significant problem that may jeopardize the sustainability of healthcare itself. In Japan, the National Action Plan on Antimicrobial Resistance was established in April 2016. Based on the five strategic objectives set out in the World Health Organization's Global Action Plan on Antimicrobial Resistance, and by adding a 6th objective of international cooperation as a Japanese unique goal, the goals, strategies and specific actions of each of these six fields are presented. This Action Plan is significantly characterized by setting numerical targets as a performance index to be achieved by 2020.

***Keywords*:** Antimicrobial resistance (AMR), surveillance, monitoring, prevention, public awareness, international cooperation

Introduction

Antimicrobial-resistant bacteria are spreading globally and have become a problem. However, while the issue of antimicrobial resistance (AMR) is becoming more significant, the development of new antibiotics has stagnated. It is estimated that if no countermeasures are taken, 10 million people will annually die of AMR by 2050, which would largely exceed the number who die of cancer. To establish a sustainable healthcare environment, we have to take countermeasures against AMR now to ensure the continuous use of antibiotics in the future.

At the World Health Assembly in May 2015, a Global Action Plan to tackle AMR was endorsed. All member states are urged to develop and establish a national action plan on AMR within two years. In Japan, the National Action Plan on Antimicrobial Resistance was released in April 2016 (*1*). Japan's National Action Plan on Antimicrobial Resistance 2016-2020 includes "International Cooperation" as a unique 6th pillar additionally set in reference to the 5 pillars of the Global Action Plan, and a goal, strategy and countermeasures have been set for each area (Figure 1).

Current status and challenges of antibiotic treatment in Japan

The use of antibiotics in Japan is not particularly higher compared to that in Europe or the USA. However, in Japan oral antibiotics account for 92.4% of the total daily usage, and consists of third generation cephalosporins, macrolides and fluoroquinolone derivatives, which are so-called broad-spectrum antibiotics. Therefore, it is considered that the problem in Japan is the use of such broad-spectrum oral antibiotics (*1*). Higashi, *et al*. examined the national prescription database for the period from January to March 2005 and reported that approximately 60% of patients with non-bacterial upper respiratory tract infections were given antibiotics. The breakdown of the prescriptions was third generation cephalosporins (46%), macrolides (27%) and quinolones (16%) in descending order of frequency, and were prescribed more often at clinics than hospitals (*2*).

Antibiotics may be prescribed to patients with the common cold for the purpose of pneumonia prophylaxis. Regarding this, a study was conducted to investigate how many patients with acute respiratory tract infection, including those with the common cold, need to be treated with antibiotics to prevent one patient from developing complications including pneumonia (*3*). The results showed that one case of complications could be prevented if 4,000 patients with acute respiratory tract infection would be given antibiotics. Considering the cost of antibiotics prescribed to 4,000 patients and the risks of adverse drug reactions and resistant bacteria, the prophylactic use of antibiotics to

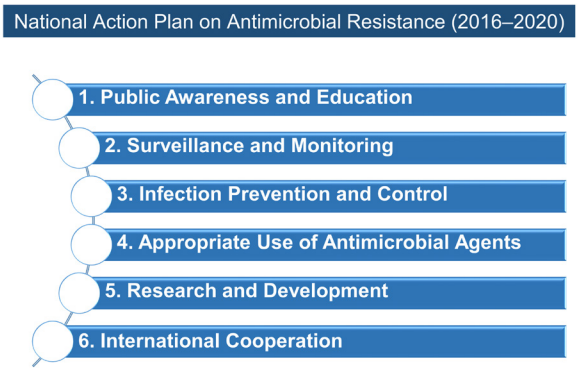

Figure 1. Six areas and their Goals for Japan's National Action Plan on Antimicrobial Resistance (AMR). Japan's National Action Plan on Antimicrobial Resistance (AMR) 2016-2020 includes "International Cooperation" as a unique 6th pillar additionally set in reference to the 5 pillars of the Global Action Plan.

prevent complications is not recommended because the demerits outweigh the benefits.

Background and Outline of the Ministry of Health, Labour and Welfare (MHLW) "Manual of Antimicrobial Stewardship (1st Edition)"

Under these circumstances, Japan first decided to promote the appropriate outpatient handling of conditions that do not normally require antibiotic treatment such as viral upper respiratory tract infections and infectious enteritis. To achieve this, appropriate medical handling has to be promoted based on an official guideline. Therefore, the MHLW compiled "Manual of Antimicrobial Stewardship (1st Edition)" (*4*). This manual is mainly created for healthcare professionals who provide consultations to outpatients. It targets patients who are of school age and older and who do not have concomitant diseases. The covered diseases are acute respiratory tract infections and acute diarrheal diseases, for which it is considered that unnecessary antibiotics are generally used based on the above-mentioned study. Children aged 5 years and under, babies and infants are excluded from the manual because particular clinical conditions need to be considered in such cases. Highly complicated cases that require an expert's judgement are also excluded from the manual, including those with concomitant diseases. For cases that are not covered by the manual, it is necessary to refer to the existing guidelines of academic societies or to consult experts.

Acute respiratory tract infection is a concept that includes acute upper respiratory tract infections (acute upper respiratory tract inflammation) and acute lower respiratory tract infections (acute bronchitis). For those conditions, such terms as the "common cold" *etc.* are generally used. Among these terms, "common cold" is used with various meanings from "acute upper respiratory tract infections" to "acute lower respiratory

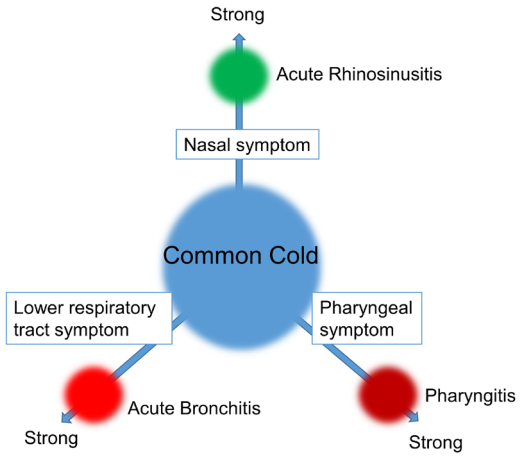

Figure 2. The four disease types of acute rhinosinusitis, acute pharyngitis and acute bronchitis (extracted from MHLW "Manual of Antimicrobial Stewardship (1st Edition)"(*4*). The common cold is an acute viral respiratory tract infection in which symptoms of all three areas, namely, nasal symptoms (nasal discharge, nasal congestion), pharyngeal symptoms (pharyngalgia) and lower respiratory tract symptoms (cough, sputum) present "simultaneously" and "at a similar level", regardless of whether pyrexia is present or not. MHLW, Ministry of Health, Labour and Welfare.

tract infections". In addition, patients often describe acute pyrexia, malaise and various feelings of being unwell as "I caught a cold". Therefore, when a patient presents with the complaint of "I caught a cold", it is important to examine the condition in detail, because a significantly wide range of diseases should be considered.

Viruses account for approximately 90% of the causative organisms of acute respiratory tract infections, and include the rhinovirus and coronavirus. Bacteria are involved in only a limited number of cases of acute respiratory tract infections, and in such cases, acute pharyngitis is mostly caused by group A β-hemolytic streptococcus (GAS) and acute bronchitis by Mycoplasma or Chlamydophila.

The American College of Physicians provides a useful classification to differentiate cases of acute upper respiratory tract infections that require antibiotics from those that do not (*5*). It classifies acute respiratory tract infections into four disease types, namely, the common cold (nonspecific upper respiratory tract inflammation, ordinary common cold), acute rhinosinusitis, acute pharyngitis and acute bronchitis, based on the three areas of symptoms such as nasal symptoms (nasal discharge, nasal congestion), pharyngeal symptoms (pharyngalgia) and lower respiratory tract symptoms (cough, sputum). In this manual explanations are also given based on this classification (Figure 2). The common cold is an acute viral respiratory tract infection in which symptoms of all three areas, namely, nasal symptoms (nasal discharge, nasal congestion), pharyngeal symptoms (pharyngalgia) and lower respiratory tract symptoms (cough, sputum) present "simultaneously" and "at a similar level", regardless of whether pyrexia is present or not.

In the natural clinical course of the common cold, slight fever, malaise and pharyngalgia develop in the beginning, followed by nasal discharge and nasal congestion, and then by cough and sputum. Around the third day after onset the symptoms peak, and overall the symptoms subside in 7 to 10 days after the onset. However, coughing often remains for about three weeks with the common cold, and physicians should be aware of this. However, even if coughing persists, it does not necessarily mean that the clinical condition requires an antibiotic. On the other hand, if symptoms worsen as a deviation from the natural course, or in case of the re-exacerbation of once-subsided symptoms, the complication of secondary infection should be considered. This manual recommends that antibiotics should basically not be given to any acute respiratory tract infections if there are no complications. For example, this manual recommends not to give antibiotics to patients with the common cold.

Knowledge, awareness and attitude of the public towards AMR

To control antimicrobial-resistant bacteria, it is necessary to encourage public understanding of the threat of AMR and to change the way antibiotics are handled. Concerning public awareness of AMR, an awareness survey of 3,390 people in Japan was conducted (*6*). The results of the survey indicated that 46.8% and 40.6% of respondents, respectively, believed that the following statements were correct: "antibiotics kill viruses" and "antibiotics are effective against the common cold and influenza", while 38.8% of all respondents were aware that antibiotics may cause adverse reactions. This figure was lower than that found with a preceding survey conducted in European Union countries in 2016 (Special Eurobarometer 445) (*7*). The results indicated that enlightenment on AMR is an urgent task in Japan. In the UK and Northern European countries, the effectiveness of such measures as active campaigns targeting the general public have been revealed.

Our "Antibiotics Awareness Survey 2018" conducted on 721 people nationwide in Japan revealed that many patients could not distinguish antibiotics from other medicines intended to control symptoms such as antipyretics or from antivirals. In addition, when the respondents were asked what medicine they would like to be prescribed for the common cold, the most common answer was an antitussive, followed by an antipyretic, medicine that suppresses nasal discharge, and antibiotics followed as the fourth most common answer (*8*). The above-mentioned Special Eurobarometer 445 revealed that accurate knowledge of AMR has been spreading among the public over time (*7*). The joint committee of the Japanese Society of Chemotherapy and the Japanese Association of Infectious Diseases conducted a nationwide questionnaire survey of clinic physicians in February last year, and 50.4% of the respondents stated that when a patient with a common cold or his/her family requests an antibiotic to be prescribed, "I would prescribe (an antibiotic) if they are not convinced by my explanation" (*9*). There is also a study that revealed that physicians tend to feel that "the patient wishes to receive an antibiotic" when a patient is not convinced by the treatment options the physician offers. These facts indicated that there are often gaps between patient's desire and physician's considerations, and that antibiotics are prescribed as a result.

Courteous explanation to patients will change the medical care for acute respiratory tract infections

In this context, an effective explanation to patients is drawing attention. It is known that accurate explanations to patients with acute respiratory tract infections increase their satisfaction. Giving only dismissive explanations such as "It is a viral infection. There are no effective treatment options available" or "You don't need antibiotics" could cause dissatisfaction. Positive explanations such as "I will prescribe medication to alleviate your symptoms" or "Lukewarm drinks will ease your nasal congestion" tend to be better accepted. When comparing three ways of explaining; positive explanation alone, dismissive explanation alone and both types of explanations, the patients who were given both types of explanations received fewer prescriptions of antibiotics and showed a higher level of satisfaction.

Since there is great concern about whether it will be possible to change medical practice, we hereby present some encouraging facts. First, there is a study with positive results for Japan. The study was conducted on 3,390 people in Japan, and 58.9% answered that the knowledge they acquire about antibiotics and AMR will change their behavior (*8*). This percentage is much higher than that seen in a similar study conducted in Europe. This result indicates that there is a high probability that people in Japan will change their behavior by acquiring knowledge. Therefore, we, as healthcare professionals must carefully consider how information should be delivered to individuals when conducting awareness-raising activities. Second, when Japan's medical fee was revised in April 2018, additional fee points were set out to support the appropriate use of antibiotics for pediatric patients. Last, we would like to introduce a preceding study. The study was conducted during a four-month period from October 2004 among physicians from 5 clinics in Japan on 691 adults with acute respiratory tract infections (excluding influenza) without underlying diseases. The breakdown of conditions included nonspecific upper respiratory inflammations in 80%, acute rhinosinusitis in 2%, acute pharyngitis in 13% and acute bronchitis in 5%. It was reported that when the physicians conducted examinations and treatment of those patients in accordance with the American College

of Physicians guideline, 5% required antibiotics at the time of the initial consultation, and 2% needed antibiotics later (*10*).

It is possible to change people's mindset and medical practice if it is supported by medical fee revision. These facts showed that Japan's environment is considerably favorable to achieve changes of the examination and treatment practice of acute respiratory tract infections.

Research and Surveillance: Introduction of Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)

To accurately present the current AMR situation in Japan and to ensure measuring the progress of the action plan, appropriate statistics are essential. In the future, AMR countermeasures must also be promoted in hospitals, clinics and other healthcare settings than hospitals, such as facilities for elderly people and in the home care setting. Data sharing in these places will also be required.

Japan has a surveillance system that monitors the status of AMR and healthcare-associated infections called Japan Nosocominal Infections Surveillance (JANIS) (*11*). This in principle is the inpatients data from medical institutions with inpatient wards. In addition, Japan Antimicrobial Consumption Surveillance (JACS) was established by the Science Research Grant Project that serves as the database of antibiotics consumption in hospitals (*12*). Besides establishing these systems, owing to the efforts made by our pharmacists in Japan, it is now possible to calculate the standardized usage of antibiotics at many medical institutions.

One common problem with the conduct of surveillance is the burden placed on the individuals who are in charge. Developing a surveillance method that lowers the burden on healthcare professionals is possible by digitalization and automation of data collection and analysis by using available healthcare information such as electronic medical charts and NDB. It is necessary to carefully consider the way the surveillance is conducted. For example, regarding the appropriate use of antibiotics, surveillance was conventionally conducted based on the consumption of antibiotics at each medical institution. However, it is difficult to determine whether antibiotics are used appropriately based only on their consumption levels. To evaluate the appropriate use of antibiotics, we also need another surveillance that investigates the appropriate use of the antibiotics as such, and that means to collect indicators of the process and outcomes of medical practice for infectious diseases.

Therefore we have the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE), which is a platform for surveillance data of infectious disease countermeasures (Figure 3).

The most significant characteristic of J-SIPHE is that it imports the information returning from JANIS to

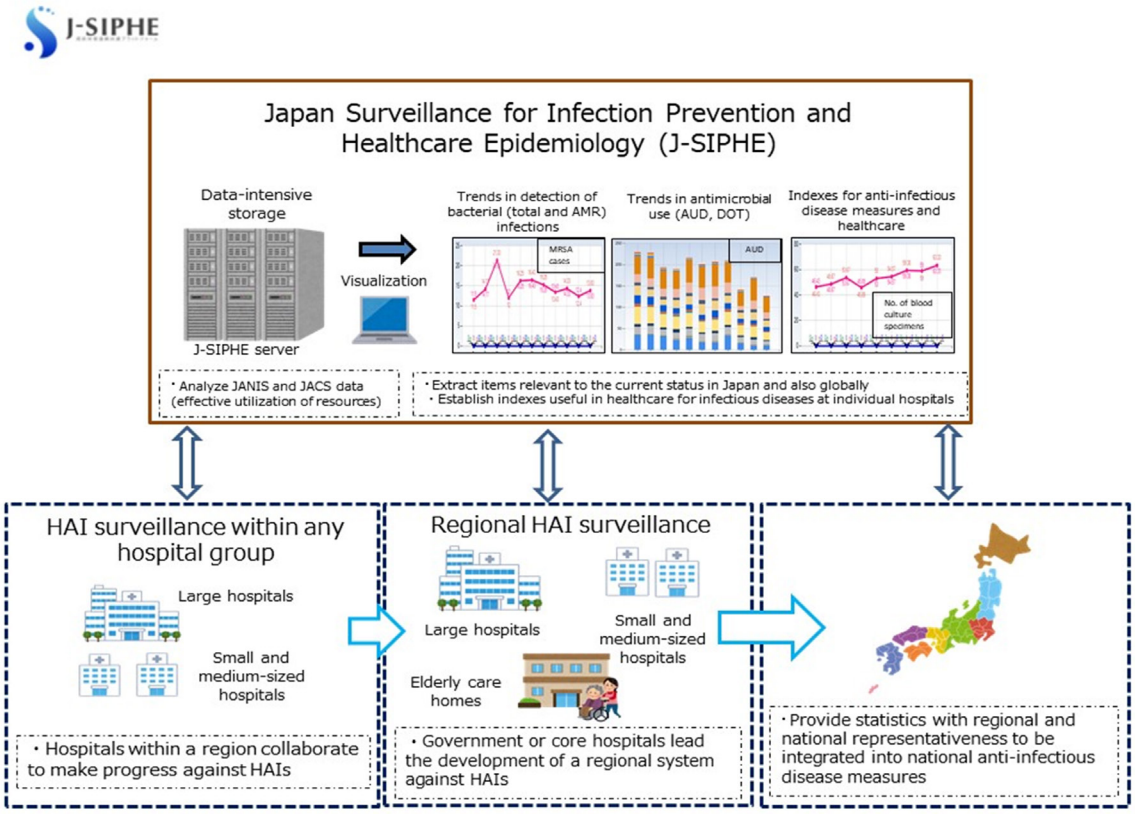

Figure 3. Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE). The Japan Surveillance for Infection Prevention and Healthcare Epidemiologyh is a platform for surveillance data of infectious disease countermeasures.

Table 1. Target value of antibiotics usage and drug resistant organism*

Index	2020 (Target Value)**
Proportion of penicillin-resistance in Streptococcus pneumoniae from CSF sample	≤ 15%
Proportion of penicillin-resistance in Streptococcus pneumoniae from samples other than CSF	
Proportion of fluoroquinolone resistance in Escherichia coli	≤ 25%
Proportion of methicillin resistance in Staphylococcus aureus	≤ 20%
Proportion of carbapenem resistance in Pseudomonas aeruginosa (Imipenem)	≤ 10%
Proportion of carbapenem (Meropenem) resistance in Pseudomonas aeruginosa	≤ 10%
Proportion of carbapenem (Imipenem) resistance in Escherichia coli	≤ 0.2%
Proportion of carbapenem (Meropenem) resistance in Escherichia coli	≤ 0.2%
Proportion of carbapenem (Imipenem) resistance in Klebsiella pneumoniae	≤ 0.2%
Proportion of carbapenem (Meropenem) resistance in Klebsiella pneumoniae	≤ 0.2%

*Data extracted from Japan's National Action Plan on Antimicrobial Resistance 2016-2020 (*1*). **Proportion of resistant isolates of specific indicator microorganisms in humans (%).

each medical institution and the data in the same format as that registered to JACS. It also collects data that have already been collected at each medical institution as part of nosocomial infection measures and/or the promotion of appropriate antibiotics use, and presents the data in an easily understandable manner for individuals who are in charge of the implementation of such measures. Another significant point is that these data can be shared with other medical institutions. J-SIPHE allows sharing of data within a randomly formed group of medical institutions. J-SIPHE started full-scale operations in January 2019.

Progress and challenges of the AMR action plan: Trend of antibiotics use

The AMR action plan sets numerical targets (Table 1). We now investigate the progress and challenges.

In the action plan, it is stipulated that use must be reduced to less than 2/3rds of that in 2013. An interim report of sales volumes of antibiotics in the medical care setting has become available. The sales volume for 1,000 individuals times the daily sales volume (DDD/1,000 inhabitant days = DID) was calculated by correcting the volume of the antibiotics, the WHO Defined Daily Dose (daily use by a person weighing 70 kg). The total sales volume of antibiotics was 14.9 DID in 2013, 14.5 DID in 2014, 14.6 DID in 2015, 14.6 DID in 2016, 13.8 DID in 2017 and 13.3 DID in 2018, showing a 10.7% reduction in 2018 compared to 2013 (*13*). However, the use of injectable antibiotics increased slightly during the same period of time.

The use of antibiotics in the dental care setting has also been revealed. The AMR clinical reference center tabulated the use of antibiotics that were prescribed in the dental care setting for the period from 2013 to 2016 by using the National Database of Health Insurance Claims and Specific Health Checkup of Japan (NDB), and disclosed it. It revealed that the usage of antibiotics in the dental care setting was less than 1/10th that in the medical care setting, that oral antibiotics accounted for a significant majority, and that other β-lactam antibiotics than penicillin were most frequently used (*14*).

In the process of implementing the action plan, the use of antibiotics in medical care in Japan has been revealed (*15*). Major peaks of the use of oral and injectable antibiotics lie in pediatric care for those aged 0 to 9 years and in geriatric care for those aged 70 years and older. However, it is characteristic of Japan that there is another low peak seen in those aged from 30 to 34 years. People around these ages tend to have a low possibility to be affected by diseases that require antibiotics. Therefore, it is assumed that there is some situation in which those people would require antibiotics. In addition, another study calculated the total use of antibiotics stratified by age for children aged 15 years and younger (*16*). Among these children aged from 0 to 15 years, the highest total use of antibiotics was found among those aged 1 year. Immunity is not fully developed in children around that age and they are considerably susceptible to acute respiratory tract infections including the common cold. The above-mentioned results are therefore considered to reflect such a tendency. The use of injectable antibiotics is particularly characteristic. The highest use of injectable antibiotics is seen among those aged 85 years and older (*15*). It is considered that when people of this age contract an infection, they are more frequently hospitalized and then receive treatment with injectable antibiotics.

It is considered a favorable trend that the total sales volume of antibiotics had decreased by 10.7% by the end of the third year of the five-year action plan. However, close investigation of the causes of the slight increase in the use of injectable antibiotics is necessary. When the appropriate use of antibiotics is promoted, it is occasionally observed that the use of antibiotics actually increased in medical institutions. This is considered because the dosage and regimen are followed appropriately. Injectable antibiotics are mainly used for inpatients. Promotion of the appropriate use of injectable antibiotics for inpatients shows actual difficulties due to the various individual inpatient conditions. For example, a decrease in oral antibiotics use can be promoted by a

clear strategy such as "to reduce the administration of unnecessary antibiotics". However, since the conditions of inpatients vary, it is not an easy task to identify unnecessary administration of antibiotics. In the future, specified measures need to be taken by defining the meaning of "appropriate use" in detail and clarifying the target population for the appropriate use of antibiotics. Regarding the evaluation index, discussion is needed on whether use should be continued or another index be employed

Progress and challenges of the AMR action plan: Trend of resistant bacteria

With regard to the trend of resistant bacteria, Nippon AMR One Health Report (NAOR) 2018 (*17*) stated that "In Japan, the carbapenem resistance rate in Enterobacteriaceae, particularly Escherichia coli and *Klebsiella pneumoniae* remained below 1% during the observed period, despite its global increase in humans. Likewise, the proportion of vancomycin-resistant enterococci in humans remained less than 1%. Penicillin resistance (non-susceptibility rate) in Streptococcus pneumoniae also has been on the decline in recent years. While the criteria for assessing carbapenem resistance in Pseudomonas aeruginosa changed in 2014, the resistance rate was trending downward". On the other hand, it is also reported that "The rate of resistance against the third-generation cephalosporins and fluoroquinolones among Escherichia coli, however, was increasing. Although the percentage of methicillin-resistant Staphylococcus aureus (MRSA) has been declining in recent years, levels remained high" (*17*). Furthermore, the prevalence of fluoroquinolone-resistant *E. coli* (%) was compared between humans and animals using JANIS, which involves surveillance of the medical care setting and the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), which comprises nationwide monitoring of resistant bacteria involved in the livestock care setting. The results showed that although fluoroquinolone-resistant *E. coli* remained at a low level in the livestock care setting during the period from 2011 to 2015, it has been increasing in the human medical care setting year after year (*18*).

The possibility of transmission of resistant bacteria between humans and animals has been discussed (*19*). However, the prevalence in humans has been demonstrating an upward trend year by year compared to that in animals, which indicates that there is a unique situation in the human area and that the issue has not been resolved yet. Concerning this issue, further epidemiological research is necessary to explain the situation, and interventions based on the results are necessary.

Prepare for "import of resistant bacteria" *via* healthcare practice

A man aged 84 years was hospitalized in Cairo due to septic shock while staying in Cairo during his 15-day trip to Turkey and Egypt. His condition improved after receiving intensive care and he was transferred to the Center Hospital of the National Center for Global Health and Medicine. As it is well known that resistant bacteria are highly prevalent in countries surrounding the Mediterranean Sea including Egypt, specimens such as feces were investigated. The examination identified *Klebsiella pneumoniae* exhibiting a MIC of 4 μg/mL of imipenem, a carbapenem antibiotic. Further investigation revealed that this bacterium was *Klebsiella pneumoniae* that produced the enzyme OXA-48, which inactivates carbapenems (*20*). It is also known that there was an outbreak of this bacterium in European countries, particularly in the Mediterranean Sea area. Based on such factors as quarantine of the patient right from the start and efforts of healthcare professionals, no secondary or horizontal infections occurred. Since then, screening tests have been performed on all patients who had undergone health consultations or were hospitalized overseas within the previous one-year period. The results have revealed that approximately more than half of the patients had some resistant bacteria that required quarantine of the patient (*21*). In recent years, outbreaks of resistant bacteria that were brought from overseas have occurred in medical institutions nationwide one after another. The import of resistant bacteria through healthcare practice is a problem for the entire country of Japan. The Disease Control and Prevention Center developed and disclosed a guideline to prevent the import of such resistant bacteria (*22*).

Conclusion

In Japan, the Action Plan on AMR released in April 2016 prompted a vigorous debate, not only because of its high-level goals, but also because provided guidelines would significantly change the conventional concept of medical care. Three years have already passed since it was implemented, and there are areas that have steadily shown results. On the other hand, it became clear that there are areas that have hardly shown improvement such as fluoroquinolone-resistant and third-generation cephalosporin-resistant *E. coli*. To solve these issues, it is not adequate to take approaches only from the medical care point of view, and it is necessary to clarify the structure of problems from the One Health approach, and set effective countermeasures accordingly. We have also learned that the issue of resistant bacteria is inherently a fundamental problem of the healthcare/medical care system itself. Therefore, from this point onwards, we should not regard the issue of resistant bacteria only as a problem that is limited to the area of infectious diseases, but as a problem of the entire healthcare system, and eventually the entire society.

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Emerging and re-emerging infectious diseases in Japan: epidemiology and infection prevention measures

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Abstract: In recent years, emerging and re-emerging infectious diseases, such as the Ebola virus disease and Middle East Respiratory Syndrome (MERS), have been frequently reported. In this review, we summarize the representative outbreaks of emerging and re-emerging infectious diseases since 2000 and outbreaks of various infectious diseases that have occurred around the world and in Japan. Moreover, the emerging and re-emerging infectious diseases that could develop in Japan are also summarized. Especially, for mosquito-borne infectious diseases, viral hemorrhagic fever and severe fever with thrombocytopenia syndrome, and avian Influenza and MERS, the disease features, routes of infection, and infection prevention measures are reviewed in this article. Healthcare workers are at high risk of infection, and therefore, a sufficient understanding of disease features and routes of infection and the appropriate infection prevention measures are needed to increase self-protection.

***Keywords*:** Emerging and re-emerging infectious diseases, standard protective equipment, standard preventive measures

Introduction

In recent years, emerging and re-emerging infectious diseases have been frequently reported, causing concern. Table 1 shows representative outbreaks of emerging and re-emerging infectious diseases since 2000 and outbreaks of various infectious diseases that have occurred around the world and in Japan.

As factors that cause these emerging and re-emerging infectious diseases increase in a population, such as ecosystem changes, weather/climate changes, economic development and land use, development in scientific technology and industry, and increases in travelers, the susceptibility of individuals, especially those who are poor or not vaccinated, to infectious diseases increases. In particular, the number of travelers has been increasing since World War II; and today, as many as 1.1 billion people travel between countries per year. The trend is similar in Japan, wherein approximately 17 million Japanese citizens travel abroad and 28 million foreigners visit each year. Due to this background, Japan cannot do anything regarding the emerging and re-emerging infectious diseases and is in a situation where emerging and re-emerging infectious disease could occur at any time within the country. The development of dengue fever in Japan in 2014 (*1*) is one such incidence.

Emerging and re-emerging infectious diseases that could develop in Japan include those shown in Table 2. Based on the routes of infection, major emerging and re-emerging infectious diseases are divided into mosquito-borne infectious diseases, tick-borne infectious diseases, respiratory infectious diseases caused by droplet transmission, and viral hemorrhagic fever transmitted by contact with blood/body fluids.

Mosquito-borne infectious diseases

Mosquito-borne infectious diseases include dengue fever, chikungunya fever, Zika virus infection, and yellow fever. All are infectious diseases that are prevalent in tropical/subtropical regions and are transmitted by *Aedes* mosquitoes, such as *Aedes aegypti* and *Aedes albopictus*. In Japan, *Aedes albopictus* mosquitoes are distributed across wide areas, excluding Hokkaido, and an outbreak that originates from an individual with an imported infectious disease can occur within the country.

Dengue fever is an infectious disease that is caused by the dengue virus, which belongs to the genus *Flavivirus*. An estimated 390 million people are infected with dengue fever worldwide every year (*2*). Among Japan's imported infectious diseases, most individuals are infected in Southeast Asia and South Asia. The incubation period is 3-7 days, and the fever has a typical course of 5-7 days. In addition to fever, headache and

Table 1. Outbreaks of major emerging and re-emerging infectious diseases since 2000

Emerging and Re-emerging Infectious Disease	Year of Outbreak	Country/Area
SARS	2004	China, Taiwan, Singapore, *etc*.
H1N1 influenza	2009	From Mexico spread worldwide
MERS	2012	Middle East
H7N9 influenza	2012	China
Ebola virus disease	2013	Guinea, Sierra Leone, Liberia, *etc*.
Chikungunya fever	2013	Central and South America
Dengue fever	2014	Japan
MERS	2015	South Korea
Zika virus infection	2015	Central and South America
Pest	2017	Madagascar

MERS, Middle East respiratory syndrome.

Table 2. Emerging and re-emerging infectious diseases that can develop or have developed in Japan

Major Route of Infection	osquitoes	Ticks	Droplets	Blood/Body Fluids
Disease	Dengue fever Chikungunya fever Zika fever	SFTS Emerging relapsing fever Anaplasmosis	MERS Avian influenza (H5N1, H7N9)	Viral hemorrhagic fever (Ebola hemorrhagic fever)
Route of invasion into Japan	Imported infections	Community-acquired infections	Imported infections	Imported infections
Transmission within Japan	Humans→Mosquitoes →Humans	Ticks→Humans	Humans→ Humans Birds→Humans	Humans→ Humans
High-risk individuals	Individuals living in cities	Individuals exposed to wooded areas	Healthcare workers Poultry-rearing individuals	Healthcare workers
Medical treatment institution	Medical institutions across the country	Medical institutions across the country	Medical institutions designated for specific/type 1/type 2 infectious diseases	Medical institutions designated for specific/type 1/type 2 infectious diseases

joint pain are common, and symptoms of muscle pain, diarrhea, and nausea/vomiting may occur.

Chikungunya fever is an infectious disease caused by the chikungunya virus, which belongs to the *Togaviridae* family. There are approximately 10 cases of imported infections per year in Japan, which is less compared to dengue fever. However, the disease is rampant: an outbreak also occurred in Central and South America in 2013, and chikungunya virus infections have also been reported in the U.S. (*3*). The incubation period is 3-12 days (commonly 3-7 days), and the clinical features include fever, headache, muscle pain, joint pain, and rash. Although the symptoms are similar to those of dengue fever, chikungunya fever is characterized by more painful joint aches in the acute phase than dengue fever and possible long-term joint pain/arthritis.

Zika virus infection is an infectious disease caused by the Zika virus, which belongs to the genus *Flavivirus*, as does the dengue virus. In recent years, after outbreaks in French Polynesia in 2013 (*4*) and in Brazil in 2015, the disease became a pandemic in Central and South America in 2016 (*5*). In addition to mosquito bites, Zika virus can be transmitted through sex and blood transfusion. The incubation period of Zika virus infection is 2-7 days, and infected persons exhibit fever, headache, joint pain, muscle pain, bulbar conjunctival injection, and rash (*6*). There have been many individuals who have developed Guillain-Barré syndrome following Zika virus infections (*7*), which is considered a rare complication. Zika virus infection in pregnant women is associated with a high risk of fetal microcephaly (*8*), and this has become a social issue.

In the diagnosis of these mosquito-borne infectious diseases, the detection of viral genes by virus isolation from blood/urine or RT-PCR, of IgM antibodies or neutralizing antibodies with paired serum, or of significant increases in antibody titers are used as diagnostic methods. There are no effective antiviral drugs or vaccines for any infectious diseases. Therefore, it is important to take the following precautionary measures to protect one self against mosquitoes.

In order to eliminate skin exposure, wear long-sleeve shirts and long pants, and avoid sandals without socks. DEET is widely used as an effective ingredient in repellents; and in Japan, aerosols, wet sheets, and lotions or gels that contain up to 30% DEET are commercially available. Repellents can be appropriately used in accordance with required drugs or quasi-drugs following directions/dosages in accordance with age and precautions. Re-apply repellents often when sweating or getting wet by rain or stationary water. *Aedes aegypti* mosquitoes and *Aedes albopictus* mosquitoes, which

transmit dengue fever, Zika virus infection, *etc*., also inhabit cities and resorts overseas, and their numbers increase during the rainy season. These mosquitoes have a habit of actively sucking blood, particularly in the early morning/daytime/evening (especially before and after sunset); and thus, mosquito protection needs to be performed mainly during these periods. In Japan, *Aedes albopictus* mosquitoes transmit disease and suck blood from the morning through the evening (highly active in the early morning/daytime/evening, before and after sunset). Although *Aedes albopictus* mosquitoes suck blood indoors and outdoors, blood-sucking is more common outdoors.

Viral hemorrhagic fever and severe fever with thrombocytopenia syndrome

In Japan, viral hemorrhagic fever, which is transmitted by contact with blood/body fluids, is designated as a category I infectious disease, and the treatment is supposed to be provided by four institutions that are designated for specific infectious diseases and 54 institutions that are designated for type 1 specific infectious diseases across the country.

Viral hemorrhagic fever is designated as a category I infectious disease, and this category includes five diseases in Japan: Ebola virus disease (Ebola hemorrhagic fever), Marburg virus disease, Crimean-Congo hemorrhagic fever, Lassa fever, and South American hemorrhagic fever. In particular, Ebola virus disease has repeatedly caused outbreaks in Africa, and the 2014 outbreak in West Africa infected 28,652 people and caused 11,325 deaths (the mortality rate: 39.5%), which is the largest outbreak to date (*9*). Since then, Ebola virus disease has repeatedly increased in prevalence in the Democratic Republic of the Congo; and most recently, an outbreak has been reported in May 2018.

Although the life cycles of pathogens that cause viral hemorrhagic fever have not been fully elucidated for some diseases; for example, the natural host of Lassa virus is considered to be *Mastomys*, whereas that of Ebola virus is considered to be bats. Ebola virus disease has been known to occur not only in humans, but also in gorillas and chimpanzees. Thus, the disease can be transmitted by the consumption of bats, gorillas, and chimpanzees infected with Ebola virus. It can also be transmitted by direct contact with the body fluids of humans with Ebola virus disease (including dead bodies), and human-to-human transmission was the main route of transmission in the Western African epidemic. Therefore, healthcare workers who frequently come into direct contact with the blood and vomit of patients with Ebola virus disease are at high risk of infection and should wear appropriate personal protective equipment (PPE) during the medical care of patients with Ebola virus disease. After an incubation period of less than three weeks, viral hemorrhagic fever develops with nonspecific symptoms, such as fever, headache, and joint pain. Gastrointestinal symptoms such as nausea/diarrhea start to occur three days after onset, and impaired consciousness and shock occur seven days after onset, in a typical course (*9*). Bleeding symptoms such as blood in the stool and petechiae occur in approximately 20% of patients. Blood tests show decreased white blood cell counts, decreased platelet counts, increased AST/ALT, prolonged PT/APTT, renal dysfunction, and electrolyte abnormalities (hyponatremia and hypokalemia). Since viral hemorrhagic fever is transmitted by direct contact with blood/body fluids, preventing direct contact with body fluids is the main measure for infection prevention. However, "preventing direct contact with body fluids" measures are the exact idea of standard preventive measures, and special measures for infection prevention are never needed. Nevertheless, since becoming infected is directly linked to life or death for healthcare workers, strict infection prevention measures are needed in addition to ordinary standard preventive measures. In Japan, there are no rules regarding PPE use against viral hemorrhagic fever; and thus, specific rules need to be made in accordance with the actual situation, such as the arrangement and space of the rooms at each institution. The standard protective equipment that is used in the care for patients with viral hemorrhagic fever (including suspected patients) at our hospital is shown in Figure 1. Double gowns, double gloves, an N95 mask, goggles, a face shield, boots, and shoe covers are worn. The center for disease control has prepared guidelines for PPE that should be used in the examination of patients with Ebola virus disease (including suspected patients), and these guidelines are expected to be used as the PPE reference at each institution (*10*). PPE may be contaminated when it is taken off, and one should properly put on and take off PPE. Therefore, continued training to ensure the proper application and removal of PPE is essential.

In Japan, specifically in western Japan, patients with severe fever with thrombocytopenia syndrome (SFTS) have been also reported. SFTS is viral hemorrhagic fever in the broad sense, and a case of transmission by direct contact with body fluids in a healthcare worker is reported (*11*). Although there are no regular measures for infection prevention in the care for patients with SFTS, Disease Control and Prevention Center, Center Hospital of the National Center for Global Health and Medicine prepared "The 2019 revision of the guidance for the care for patients with severe fever with thrombocytopenia syndrome (SFTS)" (*http://dcc.ncgm.go.jp/information/pdf/SFTS_2019.pdf*), in which an example of measures for infection prevention is introduced.

Avian Influenza and Middle East Respiratory Syndrome (MERS)

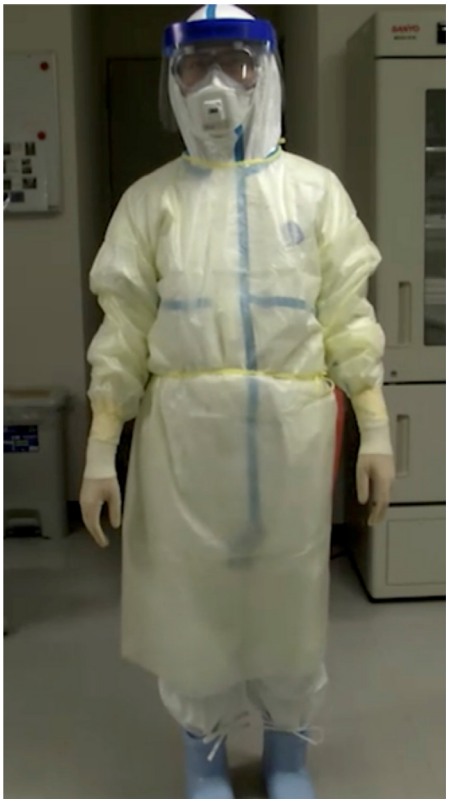

Figure 1. The standard protective equipment in the care for patients with viral hemorrhagic fever (including suspected patients) at Center Hospital of the National Center for Global Health and Medicine.

Avian influenza and MERS are designated as category II infectious diseases, and treatment can be conducted in 346 institutions across Japan that are designated for type 2 specific infectious diseases. The clinical features of both diseases include fever, respiratory symptoms, such as cough and breathing difficulty, and general symptoms, such as headache, joint pain, and muscle pain. The mortality rates are very high (40-50% (avian influenza), 35% (MERS)); as the name suggests, birds are reservoirs for avian influenza, whereas bats and dromedary camels are reservoirs for MERS. Although both diseases are transmitted through droplets, H5N1 avian influenza is prevalent in Southeast Asia and Egypt and H7N9 avian influenza is prevalent in China and are both rarely transmitted through human-to-human contact. However, MERS is commonly transmitted through human-to-human contact and easily spreads within hospitals (*12*). Healthcare workers were found to be at high risk of infection during the outbreak in South Korea. Therefore, appropriate infection prevention measures are required for patient care.

For infection prevention, when a suspected or confirmed patient requires admission, the patient should be placed in a well-ventilated private room or a negative-pressure room, as recommended by the World Health Organization (*13*). Healthcare workers rigidly enforce standard preventive measures (hand hygiene, wearing PPE that avoids contact with patient blood/body fluids/discharge) and take contact and droplet precautions (medical mask, goggles or face shield, gown, and gloves). When performing a procedure that generates aerosol, such as endotracheal intubation, BAL, and manual ventilation, airborne precautions are recommended. The CDC recommends wearing an N95 mask regardless of the presence/absence of aerosol generation (*14*).

Conclusions

As seen from the above stated measures for prevention of the transmission of emerging and re-emerging infectious diseases, ultimately, standard preventive measures are the most important. Even if, by chance, a patient with Ebola virus disease unexpectedly visits your hospital, the risk of infection can be minimized if standard preventive measures are properly taken. Because it may be impossible to know when a patient with an emerging or re-emerging infectious disease visits your hospital, regular standard preventive measure enforcement is crucial.

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Cardiovascular disease and 1,5-anhydro-d-glucitol

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Abstract: The serum 1,5-anhydro-d-glucitol (1,5-AG) level rapidly decreases concomitantly with urinary glucose excretion in hyperglycemia. 1,5-AG is a sensitive clinical marker of short-term glycemic control, postprandial hyperglycemia and glucose fluctuation. Increasing evidence about the relationship between cardiovascular disease (CVD) and glucose fluctuations have been published. In this review, we summarize the possibilities and limitations of 1,5-AG as a marker of CVD. Research showed that 1,5-AG level is associated with prevalence of CVD and is also a predictive value for cardiovascular (CV) events. Especially in a high risk population, the predictive value of 1,5-AG for CV events becomes more effective. Besides, 1,5-AG is an effective glycometabolic marker that complements HbA1c in terms of glucose fluctuation. Appropriate use of 1,5-AG might lead to improved prognosis for patients or decrease medical financial burden of the population through early detection of glucose disorder and quality glucose control.

***Keywords*:** Cardiovascular disease, 1,5-anhydro-d-glucitol, biomarker, prognosis

Introduction

Type 2 diabetes mellitus (DM) extremely impairs the prognosis of patients with cardiovascular disease (CVD) (*1*). Currently, because of the well-established relationships between micro-vascular disease and hemoglobin A1c (HbA1c), the American Diabetes Association (ADA) recommends the evaluation of HbA1c as a criterion for diagnosing DM (*2*). The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) have shown that long-term favorable glycemic control improves the complications of DM (*3,4*). However, in patients with advanced DM, HbA1c guided intensive glucose control does not always reduce macro-vascular complications, and in some cases increases the risk of death (*5-7*). To improve the patient's prognosis, early diagnosis and early intervention for glycemic abnormalities are essential (*4*). Increasing evidence has reported that postprandial hyperglycemia and glucose level fluctuation impairs mortality rate and promotes CVD progression (*8-14*). Feasible and sensitive clinical markers to detect glucose fluctuations are needed.

1,5-anhydro-d-glucitol (1,5-AG)

1,5-AG is a monosaccharide originating primarily from dietary sources that is found in constant concentrations in the blood in normal glycemic status (*15*). 1,5-AG is a naturally occurring 1-deoxy form of glucose (Figure 1) and was discovered in a milkwort plant, Polygala senega in 1888. Further investigation was repeated and became commercially available in Japan from 1991 (Table 1). Approximately 500 to 1,000 mg 1,5-AG exists in the human body mainly in its free form (*15*). 1,5-AG is adjusted by urinary excretion in the kidneys. Most 1,5-AG, which is filtered in glomerulus is reabsorbed at a specific fructose-mannose active transporter in the renal tubule (*15,16*) (Figure 2A). The reabsorption is competitively inhibited by glucose. Therefore, the serum 1,5-AG level rapidly decreases when the serum glucose level exceeds the threshold of urine glucose excretion (160-180 mg/dL) and is an important and feasible clinical marker of short-term glycemic status (Figure 2B) (*17,18*). Therefore, low 1,5-AG is associated with postprandial hyperglycemia or poor glycemic control status. Yamanouchi reported distribution of 1,5-AG levels in Japanese healthy subjects (Male: 26.6 ± 7.2 μg/mL, Female: 21.5 ± 6.0 μg/mL, Total: 24.6 ± 7.2 μg/mL) (*19*). There is no significant statistical difference between lower limits of healthy males and females (Male: 14.2 μg/mL, Female: 13.5 μg/mL). Therefore, as the normal lower limit of 1,5-AG levels, a cut-off value of 14.0 μg/mL calculated by all healthy subjects is recommended (*19*). The mean 1,5-AG value of patients with DM was 7.3 ± 7.1 μg/mL and was significantly lower than that of healthy subjects (Figure 3) (*19*).

Unlike HbA1c, although the 1,5-AG value is not affected by red blood cell life span, several clinical conditions should be considered in interpretation of

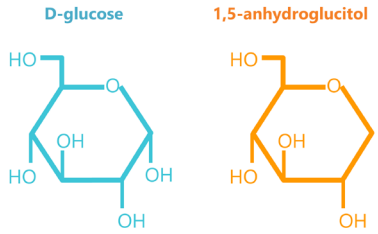
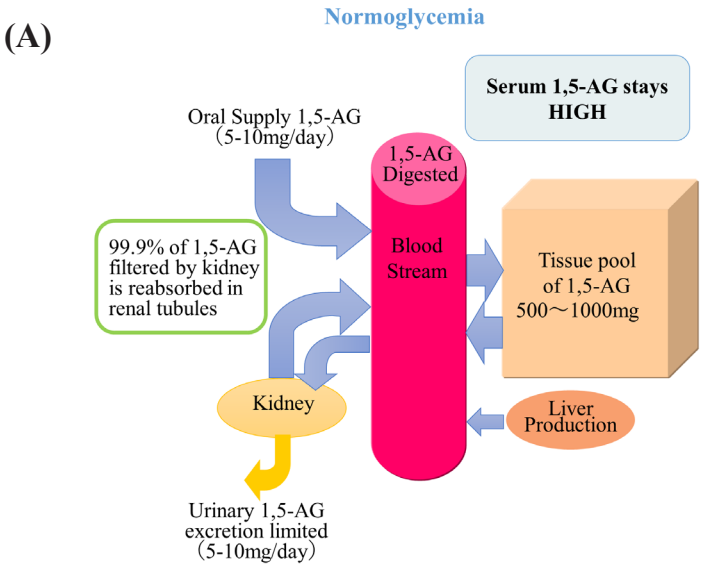


Figure 1. Molecular structures of D-glucose and 1,5-Anhydro-d-glucitol (1,5-AG).

Table 1. History of 1,5-Anhydro-d-glucitol

Year	Items
1888	1,5-AG discovered in a milkwort plant, Polygala senega
1975	Low levels discovered in patients with diabetes by Pitkänen (Finland)
1981	Studied the relationship between diabetes and 1,5-AG levels in Japan
1987	Developed kits measuring 1,5-AG by Nippon Kayaku
2003	Commercially available in Japan from 1991
2011	US FDA approval (Bland name is GLYCOMARK) CE Marked



- Like glucose, 1,5-AG is filtered out of the bloodstream and transported back into the bloodstream.
- Primary source of 1,5-AG is food, though up to 10% is synthesized in liver.
- 1,5-AG does not metabolized much in body.
- Under normal glucose condition, 1,5-AG levels in blood are stable, with balance between ingestion and excretion supported by large body pool of 1,5-AG. Thus, 1,5-AG levels in blood are not affected by meal.
- When glucose levels exceed the renal threshold (hyperglycemia excursions), glucose is excreted in the urine (glycosuria).
- Due to the similarities in molecules, large amount of 1,5-AG is also excreted during glycosuria.
- 1,5-AG serum levels fall rapidly, representing hyperglycemia during the prior 1-2 weeks.
- The greater the duration, magnitude and frequent hyperglycemia, the lower 1,5-AG levels.

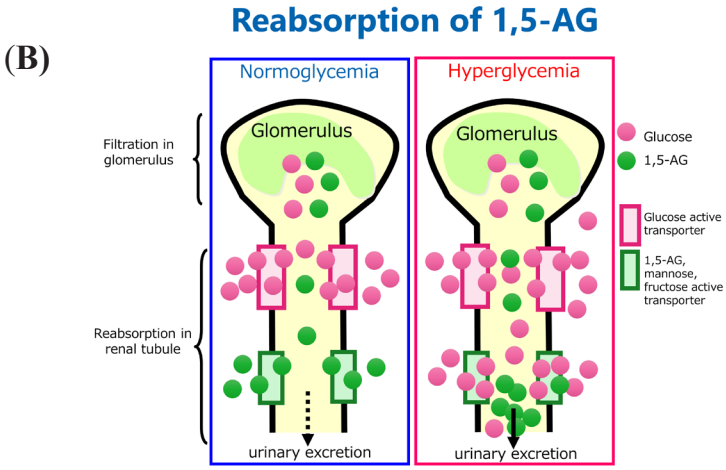


Figure 2. Metabolism of 1,5-Anhydro-d-glucitol (1,5-AG). (A) *In vivo* kinetics of 1,5-AG; **(B)** Filtration and reabsorption of 1,5-AG in the kidney. Normoglycemia: Nearly 99.9% of filtered 1,5-AG at the glomerulus is reabsorbed in the renal tubule. Hyperglycemia (over 160-180 mg/dL): Competitive tubular reabsorption of glucose and 1,5-AG.

1,5-AG values (Table 2). Recently the use of sodium–glucose cotransporter 2 inhibitor (SGLT2i) has been rapidly increasing. Although SGLT2i improves glycemic control, serum 1,5-AG decreases. The reabsorption of 1,5-AG occurs predominantly *via* a SGLT4 and the effect of SGLT2i for 1,5-AG reabsorption is indirect (*20*). The amount of glycosuria caused by SGLT2i is about 60-80 g/day. Serum 1,5-AG level will be reduced to 0-1 μg/mL in a week, when a large amount of glycosuria (above 50 g/day) appears. If SGLT2i therapy causes substantial glycosuria, the serum 1,5-AG level will generally decrease to near 1 μg/mL in a week after administration. If serum 1,5-AG levels increase during administration, it could show decreasing effectiveness of SGLT2i.

Postprandial hyperglycemia and glucose fluctuation

It is well known that postprandial hyperglycemia is associated with cardiovascular (CV) events (*14*). Recently, there has been increasing evidence that fluctuations in glucose levels leads to endothelial dysfunction and increases the risk of CV events and the progression of

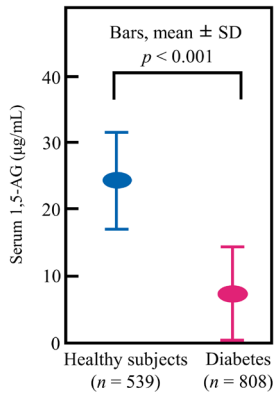


Figure 3. Serum 1,5-AG levels of healthy subjects and patients with diabetes mellitus. (Modified from Yamanouchi T, et al. Journal of the Japan Diabetes Society. 1990; 33:41-47. (*Ref. 19*))

Table 2. Clinical factors affecting 1,5-Anhydro-d-glucitol

Increased	Decreased
Chinese herbal drugs containing Polygalae Radix	Females Newborns
Some enteral nutrition products	Renal failure Glomerulonephritis Pregnancy Total parenteral nutrition Acarbose Sodium–glucose cotransporter 2 inhibitor (SGLT2i)

atherosclerosis (*21,22*). Glucose fluctuations have a bad effect on coronary plaque vulnerability and progression in patients with CAD (*10-13*). These findings may explain the increased CV mortality rate during intensive glycemic therapy. Most evidence about glucose fluctuation and CV events or coronary plaques are based on continuous glucose monitoring (CGM) and oral glucose tolerance tests (OGTT) (*10-14*). 1,5-AG can be used to differentiate patients with glucose fluctuation despite having a similar HbA1c (*23*).

As a reduced 1,5-AG value strongly correlates with glucose excursions, it is also associated with postprandial hyperglycemia (*17,18*). Furthermore, 1,5-AG values have been correlated with the mean amplitude of glycemic excursions (MAGE) and other parameters of CGM (*23,24*). Therefore, 1,5-AG has potential to be a marker for CVD and a predictor of CV events.

Relationship with CVD and events

Prevalence of coronary artery disease, carotid artery disease and acute ischemic stroke/transient ischemic attack

Several previous reports demonstrated that 1,5-AG is associated with prevalence of coronary artery disease (CAD) and carotid artery disease (*25-28*). Patients with CAD showed significantly lower 1,5-AG values than those without CAD (*25,28*). Fujiwara presented that serum 1,5-AG was significantly lower in patients with CAD (16.6 ± 8.50 *vs*. 21.1 ± 7.97 μg/mL, $p < 0.001$) (*28*). Ikeda showed that patients with CAD presented significantly lower 1,5-AG and higher HbA1c values than patients without CAD (11.6 *vs*. 17.6 μg/mL, $p < 0.001$, and 6.0% *vs*. 5.7%, $p < 0.001$, respectively) (*25*). In addition, 1,5-AG values have a correlation with severity of CAD assessed by SYNTAX score ($\rho = -0.27$, $p < 0.001$) (*25*). Even in patents without DM, serum 1,5-AG values can be a help to detect the prevalence of CAD, and the correlation is superior to HbA1c (*26,28*). Watanabe evaluated carotid arteries of 72 patients without DM and CVD by high-resolution ultrasonography. They reported that a higher pulsatility index of carotid arteries is associated with lower 1,5-AG values, but intima media thickness was not correlated with 1,5-AG values (*27*). They suggested that 1,5-AG is associated with stiffness but not with morphological changes of carotid arteries (*27*). Shiga demonstrated that a low serum 1,5-AG value (1,5-AG < 14 μg/mL) is a marker for acute ischemic stroke or transient ischemic attacks in patients with well-controlled DM (HbA1c < 7%) (*29*).

Prediction of cardiovascular events

There is a certain consensus that 1,5-AG can be used to predict cardiovascular events in patients with DM. The evidence was reported that a lower serum 1,5-AG value is associated with cardiovascular events, mainly from Japan (*30-35*) (Table 3).

Watanabe showed that the measurement of serum 1,5-AG is useful to detect high risk men for CVD, regardless of the presence or absence of diabetes (*34*). This report is a relatively long-term (11 years) population-based cohort study. The usefulness of 1,5-AG was limited. Selvin demonstrated the data from Atherosclerosis Risk in a Communities (ARIC) study. Compared with persons with 1,5-AG ≥ 6.0 μg/mL and no history of DM, persons with DM and 1,5-AG < 6.0 μg/mL showed an increased risk of cardiovascular events (*35*). However, the predictive value of CVD or CV events was inadequate in the population without diagnosis of DM (*35*). The study subjects of these two cohort studies were low risk for CVD or a healthy population (*34,35*). In such a low risk population, the effectiveness of 1,5-AG for prediction of CV events might not have been fully evaluated. On the other hand, in high risk populations, the predictive value of 1,5-AG for CV events is excellent. Low serum 1,5-AG values are significantly associated with cardiac mortality or adverse clinical events in patients with CAD (*31-33*). Fujiwara evaluated 141 patients after percutaneous coronary intervention (PCI) with follow-up coronary angiography (CAG). Median 1,5-AG values were significantly lower in patients with coronary revascularization (13.4 *vs*. 18.7 μg/mL, $p < 0.01$, $p =$

Table 3. Publication of 1,5-Anhydro-d-glucitol for prediction of cardiovascular events

First author (*ref.*)	Year	Patients Number	Location	Main Finding
Ikeda N (*30*)	2016	889	Japan	Low 1,5-AG value predicts cardiac and cerebrovascular events even in non-DM patients without CAD. Cut off value of 1,5-AG is 10μg/mL.
Takahashi S (*32*)	2016	200	Japan	Low 1,5-AG value is associated with adverse clinical events in patients with HbA1c < 7.0% after first time elective percutaneous coronary intervention
Selvin E (*35*)	2016	11,106	USA	Compared with persons with 1,5-AG ≥ 6.0μg/mL and no history of DM, persons with DM and 1,5-AG < 6.0μg/mL showed increased risk of cardiovascular events. Participants in the Atherosclerosis Risk in Communities (ARIC) study without CVD at baseline
Ouchi S (*33*)	2017	388	Japan	Low 1,5-AG value predicted long-term cardiac mortality in patients with acute coronary syndrome and HbA1c < 7.0%.
Shiga Y (*29*)	2017	1,246	Japan	Low serum 1,5-AG value is a marker for acute ischemic stroke or transient ischemic attacks in patients with well-controlled DM.
Watanabe M (*34*)	2011	2,095	Japan	The measurement of serum 1,5-AG value is useful to detect high risk men for CVD, regardless of the presence or absence of diabetes.
Fujiwara T (*31*)	2016	141	Japan	Lower 1,5-AG is a risk factor for adverse clinical events after percutaneous coronary intervention.

CAD, coronary artery disease; CVD, cardiovascular disease.

0.005) (*31*). Takahashi showed that a low 1,5-AG value was associated with adverse clinical events after first time elective PCI even in patients with well-controlled DM (HbA1c < 7.0%) (*32*). Ouchi presented that low 1,5-AG levels predict long-term cardiac mortality in patients with acute coronary syndrome with HbA1c levels < 7.0%. The 1,5-AG value of the cardiac death group was significantly lower than that of the survivor group (12.3 ± 5.3 *vs*. 19.2 ± 7.7 μg/mL, $p < 0.01$) (*33*). Ikeda reported that in a high risk population, a low 1,5-AG value predicts major cardiac and cerebrovascular events (MACCE) even in non-DM patients without CAD. The study subjects were the patients who needed their first CAG. Therefore, these patients were potentially high risk even if CAG did not reveal CAD. The low 1,5-AG group (1,5-AG < 10.0 mg/mL) showed significantly higher risk of not only MACCE but also all causes of death (*30*).

Conclusions

1,5-AG level is associated with prevalence of CV disease and has also predictive value for CV events. Especially in a high risk population, the predictive value for CV events of 1,5-AG becomes more effective. Measurement of serum 1,5-AG values is useful for not only evaluation of individual glucose control but also population risk assessment from a public health perspective. 1,5-AG is an effective glycometabolic marker that complements HbA1c in terms of glucose fluctuation. Appropriate use of 1,5-AG might lead to improved prognosis for patients or decreased medical financial burden of the population through early detection of glucose disorders and quality glucose control.

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Tenofovir nephrotoxicity among Asians living with HIV: review of the literature

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Abstract: Tenofovir disoproxil fumarate (TDF), prodrug of tenofovir (TFV), is one of the most widely used nucleotide reverse transcriptase inhibitors (NRTIs) for the treatment of HIV infection in resource-rich and resource-limited settings with proven efficacy and safety, and also for the treatment of hepatitis B infections. However, TDF can cause renal proximal tubular dysfunction and also reduces estimated glomerular filtration rate (eGFR) more than other NRTIs. To date, TDF-associated renal dysfunction is generally regarded as mild and tolerable. However, it is notable that low body weight is one of the risk factors for TFV nephrotoxicity and that Asians are generally of smaller body stature and can be susceptible to such nephrotoxicity, as shown in several cohort studies. Until tenofovir alafenamide (TAF), another prodrug of TFV with minimal renal toxicity, becomes widely accessible for people living with HIV and replaces TDF, it is warranted that physicians who prescribe TDF have a good understanding of TFV nephrotoxicity. This paper reviews recent literature on TFV nephrotoxicity among people living with HIV especially focusing on Asians who might be susceptible to TFV nephrotoxicity due to their lower body weight and discusses implications for clinical care and future directions.

***Keywords*:** Tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, nephrotoxicity, HIV infection, Asians

Introduction

The advent and evolution of antiretroviral therapy (ART) substantially improved the prognosis of people living with HIV (PLHIV) (*1*). As life expectancy of PLHIV increases and patients age, the importance of the management of non-communicable diseases (NCDs) has increased (*1,2*). Both chronic kidney disease (CKD) and end-stage renal disease (ESRD) are important NCDs that affect morbidity and mortality (*3,4*). Maintaining renal function is particularly important among PLHIV, as HIV infection is currently not curable and patients need lifelong ART. Tenofovir disoproxil fumarate (TDF), prodrug of tenofovir (TFV), is one of the most widely used nucleotide reverse transcriptase inhibitors (NRTIs) for the treatment of HIV infection in resource-rich and resource-limited settings (*5,6*) with proven efficacy and safety (*7-9*), and also for the treatment of hepatitis B infections (*5,6*).

However, TDF can cause renal proximal tubular dysfunction (*10-13*) and also reduces estimated glomerular filtration rate (eGFR) more than other NRTIs (*14-16*). To date, TDF-associated renal dysfunction is generally regarded as mild and tolerable (*17,18*), and one meta-analysis published in 2010 recommended that TDF use should not be restricted even when regular monitoring of renal function and serum phosphate levels is impractical (*17*). But it is notable that low body weight is one of the risk factors for TFV nephrotoxicity and that Asians are generally of smaller body stature and have a lower median body weight than Whites and Blacks (*19,20*), who mostly comprise the cohorts of studies published to date.

This report reviews recent literature on TFV nephrotoxicity among PLHIV especially focusing on Asians who might be susceptible to TFV nephrotoxicity due to their smaller body stature and discusses implications for clinical care and future directions. Although tenofovir alafenamide (TAF), a new prodrug of TFV, which is safer for kidney than TDF, has been licenced and is available in some resource rich countries (*21*), the main focus of this review will be on TDF-associated nephrotoxicity, since TDF has been and will be used by the vast majority of PLHIV especially in low and middle income countries including many Asian countries.

Tenofovir nephrotoxicity: its mechanism and history

Compared with abacavir (ABC) or other NRTIs, TDF is highly potent with a high genetic barrier (*22*). TDF was first licensed for use in 2001 (*23*), and soon after, a series of cases which developed tubulopathy such as Fanconi syndrome or acute tubular necrosis, or

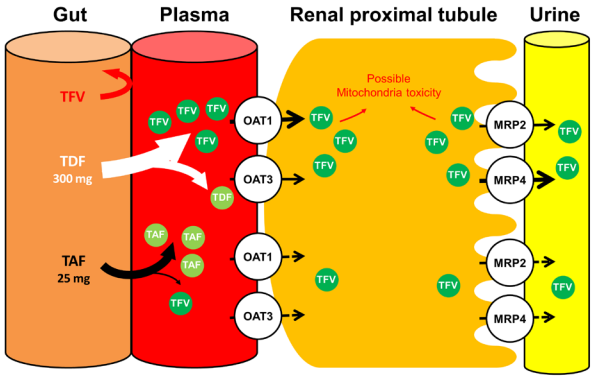

Figure 1. Excretion of tenofovir at the proximal tubular cells of the kidney and mechanism of tenofovir nephrotoxicity. Tenofovir (TFV), which is a metabolite from tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), is excreted through glomerular filtration and enters kidney tubular cells through the basolateral membrane and is transported mainly by organic anion transporter (OAT) 1 and, to a lesser extent, OAT 3 (*60*). TFV is excreted into the urine at the apical membrane by 2 transporters on the luminal membrane; multidrug resistance protein (MRP) 4 and MRP 2 (*61,62*). TFV cannot be absorbed from the gut. TDF is rapidly metabolized to TFV in the plasma, whereas TAF is stable in the plasma and largely metabolized to TFV within target cells, resulting in lower plasma TFV levels (*21,63*). Accumulation of TFV within proximal tubular cells leads to mitochondrial injury and tissue hypoxia, but with TAF, likelihood of tubular injury is less (*25-27,63*). TAF itself is not a substrate for OAT-1 or OAT-3.

acute renal failure have been reported (*10-13*). TFV, a metabolite of TDF, is excreted through glomerular filtration and *via* active tubular secretion at the proximal tubules of the kidney (*24*). TDF-associated tubulopathy is considered to be a result of accumulation of TFV, which causes mitochondria toxicity in tubular cells through inhibition of mitochondrial DNA polymerase-γ (*25-27*) (Figure 1). Renal biopsy of cases, which presented with TFV tubulopathy showed mitochondrial enlargement, depletion, and dysmorphic changes in proximal tubular cells (*28*). The use of TDF is also associated with increased bone turnover and bone demineralization, and although the mechanism is not fully understood, renal phosphate loss due to proximal tubulopathy is considered to be a primary cause (*29,30*).

A post-marketing report for Australia, Europe and US in 2007 showed that cases, which developed tubulopathy or acute renal failure were rare; among 10,343 patients, acute and chronic renal failure was reported in 0.3% and Fanconi syndrome in < 0.1%. Also other renal events, such as nephrogenic diabetes insipidus, nephritis, and proteinuria were reported in ≤ 0.1% of patients (*8*). In tenofovir-induced nephrotoxicity, tubulopathy is considered to precede the decline in GFR (*31,32*). In 2010, a meta-analysis, which analyzed 17 randomized trials and cohort studies on renal safety of TDF in PLHIV (*17*) was published and it concluded that, although TDF use was associated with a statistically significant loss of renal function (mean difference compared with control subjects in calculated creatinine clearance, 3.92 mL/min, 95% CI: 2.13-5.70 mL/min), the clinical magnitude of this effect was modest and they do not support the need to restrict TDF use in jurisdictions where regular monitoring of renal function and serum phosphate levels is impractical. However, it is notable that only one study from Asia (*33*) was included in this meta-analysis and that this study from Japan showed largest decrement in eGFR in TDF users compared to other NRTI users among 17 studies (mean difference: -17 mL/min (95% CI: -31.35, -2.65)) (*17*).

Low body weight as one of the risk factors for TFV nephrotoxicity

Many risk factors for TFV nephrotoxicity have been identified; including HIV specific factors, such as concomitant use of didanosine or ritonavir-boosted protease inhibitors (PI/r), advanced HIV infection, and classic risk factors for renal dysfunction, such as older age, impaired baseline renal function, diabetes mellitus, hypertension, coinfection with hepatitis C virus, and concurrent use of nephrotoxic medication (*8,34*). Low body weight is one of the risk factors for TFV nephrotoxicity; the animal model study reported that tenofovir tubulopathy occurs dose-dependently (*35*) and also a post-marketing report showed association between low body weight and renal dysfunction (*8*). Patients with low body weight are potentially at higher risk for larger drug exposure and, thus, more severe toxicity (*19,20,36*). However, most evidence on tenofovir nephrotoxicity has been from Europe and US, where body stature is generally larger than that of Asians. For example, whereas the mean body weight for the Japanese male 30-39 years old is 71 kg (*37*), that for US male 30-39 is 90.2kg (*38*); the mean body weight for American males is approximately 20kg heavier than that of the Japanese male. It is notable that the body weight of PLHIV is even lighter; median 60 kg in West India (*39*), median 56.5 kg in Thailand (19), and mean 55 kg for Vietnam (*40*).

Tenofovir nephrotoxicity for Asians living with HIV infection

The reported degree of TDF-associated renal function decrement in Asians is not negligible. Among treatment-experienced 405 Thai patients with median baseline body weight of 56.5 kg who initiated TDF, 19.3% experienced a 25% decrement in GFR with an incidence rate of 16.2 per 100 person-years (*19*). Also among 495 treatment-naïve Japanese patients with median weight of 63kg who initiated TDF-containing ART, 19.6% developed ≥ 25% decrement in eGFR (*36*).

Among the 792 treatment-naïve Japanese patients with a median weight of 63kg who either initiated

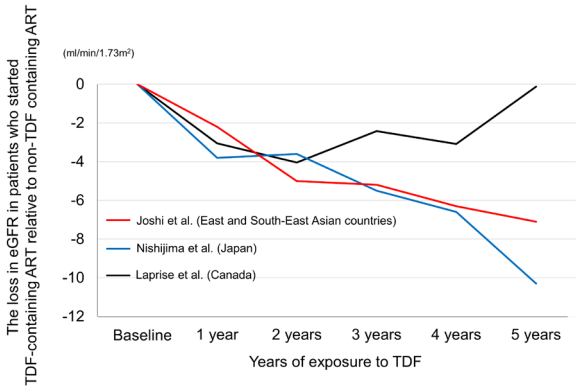

Figure 2. The loss in eGFR in patients who started TDF-containing ART relative to non-TDF containing ART: results from two Asian studies and one study from Canada. Whereas two studies from Asia (Joshi *et al*. and Nishijima *et al*.) showed that the loss in eGFR among the patients who started TDF containing ART relative to those who started non-TDF containing ART continued to increase over time, the study from Canada (Laprise *et al*.) showed that most of the loss in eGFR was acquired during the first year of exposure and stabilized after that (*15,20,41*). eGFR, estimated glomerular filtration rate; ART, antiretroviral therapy; TDF, tenofovir disoproxil fumarate.

TDF- or ABC-containing ART, those who initiated TDF-containing ART were twice as likely to develop > 10 mL/min/1.73 m^2 decrement in eGFR and ≥ 25% decrement in eGFR than those who initiated ABC-containing ART (*20*). Among patients with body weight of < 70 kg, the effect of TDF use on the risk of > 10 mL/min/1.73m^2 decrement in eGFR was more evident (adjusted OR: 2.5, 95% CI: 1.55-4.00, $p < 0.001$) than that among the entire study population (adjusted OR: 2.1, 95% CI: 1.45-3.14, $p < 0.001$) (*20*).

Although evidence is still limited to draw any firm conclusions, it is interesting that two observational studies from Asia showed that the loss in eGFR among the patients who started TDF-containing ART relative to that in those who started non-TDF-containing ART continued to increase over time (*20,41*), whereas one cohort study from Canada did not show such finding and concluded that most of the loss in eGFR was acquired during the first year of exposure and stabilized after that (*15*) (Figure 2). In the Japanese cohort study, the loss in eGFR in the TDF group relative to the ABC group continuously increased over time, and reached -10.3 mL/min/1.73 m^2 at 5 years of TDF exposure (*20*) (Figure 2). Another multi-country observational study from East and South-East Asia reported that among 2547 patients with median body weight of 56 kg (703 on TDF-containing ART, 1844 on non-TDF-containing ART), the loss in eGFR in the TDF group relative to the non-TDF group increased over time and reached -7.1 mL/min/1.73 m^2 at 5 years of TDF exposure (*41*). It is notable that whereas in the Japanese study 85% of the study patients were on PI/r, one of the risk factors for TFV nephrotoxicity, it was only 18.7% for the multi-country study and it still showed the increasing loss in eGFR in the TDF group compared to the non-TDF group (*41*). On the other hand, a single-center study from Montreal, Canada reported that among 1043 patients mostly comprised of Whites, there was no trend between the years of exposure and the loss in eGFR in the TDF group relative to non-TDF group (*15*). Body weight for this study was not available.

Utility of renal tubular markers for prediction of tenofovir nephrotoxicity

Because tenofovir tubulopathy precedes actual decrement in GFR, renal tubular markers are considered to be more sensitive than creatinine based eGFR (*31,42*). Among the renal tubular markers, urinary β2 microglobulin (β2M) has been most studied (*31,42-46*). β2M has been shown to be a sensitive marker for TFV nephrotoxicity (*31*), and can predict TDF-related GFR decrement in PLHIV who initiate TDF containing antiretroviral therapy (*42*). Whether new tubular markers, such as kidney injury molecule 1 (KIM-1), liver type fatty acid binding protein (L-FABP), and neutrophil gelatinase-associated lipocalin (NGAL) are useful in diagnosing or predicting TDF-related GFR decrement remains to be elucidated.

Many antiretroviral agents increase serum creatinine by inhibiting excretion of creatinine at the renal tubule, which can complicate interpretation of eGFR decrement shortly after initiation of TDF containing ART (Figure 3). Dolutegravir, an integrase inhibitor, which is a component of preferred ART regimen in many treatment guidelines including the WHO guidelines (*5,47,48*), is one such agent (*49*). Measurement of urinary tubular markers, such as β2M, might help distinguishing causes of eGFR decrement, which is due to inhibition of creatinine by antiretroviral agents or due to TFV nephrotoxicity, although evidence is limited.

Tenofovir alafenamide

Tenofovir alafenamide (TAF), a new prodrug of TFV is stable within plasma and metabolized to TFV mostly within target cells, enabling a small amount of dosing (25mg), which results in low plasma TFV levels and is thus safer to the kidney (*50*) (Figure 1). High efficacy and tolerability, especially minimal renal toxicity, of TAF have been shown in phase 3 trials and other studies including those which examined treatment-naïve patients, treatment-experienced patients, and patients with renal impairment (*51-54*). The phase 3 study, which randomly compared the efficacy and tolerability of elvitegravir/cobicistat/emtricitabine/TAF and elvitegravir/cobicistat/emtricitabine/TDF among treatment-naïve patients showed that a median change from baseline in creatinine clearance was significantly lower with TAF (-1.6 mL/min) than TDF (-7.7 mL/min)

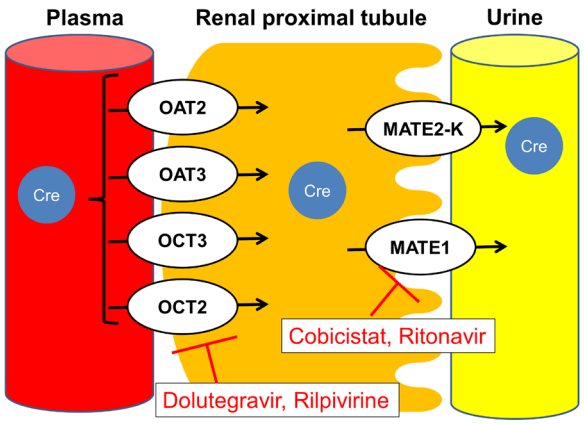

Figure 3. Mechanism for serum creatinine elevation by several antiretroviral drugs and pharmacoenhancers. Creatinine is transported through tubular cells on the basolateral side by organic anion transporters (OAT) 2 and 3, and organic cation transporters (OCT) 2 and 3. Creatinine is secreted *via* multidrug and toxin extrusion transporter 1 (MATE1) and MATE2-K on the apical side. Ritonavir and cobicistat inhibit MATE1 and inhibit creatinine efflux to urine. Dolutegravir and rilpivirine inhibit OCT2 and inhibit creatinine entry into the tubular cell (*21,49,64,65*).

at week 144 (*55*). Furthermore, a recent pooled analysis of 26 trials showed the renal safety of TAF over TDF by examining a total of 12,519 person-years of exposure to TAF; there were no cases of proximal renal tubulopathy or Fanconi syndrome, and significantly fewer discontinuations due to renal adverse events in the TAF group than the TDF group (*51*). A sub-analysis of phase 3 clinical trials, which investigated efficacy and safety of elvitegravir/cobicistat/emcticitabine/TAF extracted the data of Asians and showed comparable efficacy and safety data between Asians and non-Asians *(56)*. TAF is included as one of the components of the preferred ART regimens in the treatment guidelines in many high income countries (*5,48,57,58*).

Tenofovir nephrotoxicity in the future

TDF has been one of the most widely used NRTIs for the treatment of HIV infection with proven efficacy and safety (*7-9*) and will remain as the main NRTI especially in resource-limited settings (*5,6*). It will take time for TAF, another prodrug of TFV with minimal renal toxicity, to be widely accessible for people living with HIV to replace TDF. In the meantime, it is warranted that physicians who prescribe TDF have a good understanding of TFV nephrotoxicity.

Prior to initiating TDF, it is suggested that renal function is monitored with use of at least serum creatinine and a urine dipstick test, and they should be regularly monitored. Risk factors for renal dysfunction or chronic kidney diseases, such as diabetes mellitus, hypertension, hepatitis B or C infection, should be also screened. If eGFR is < 50 mL/min/1.73m^2 or there is persistent proteinuria, TDF should be switched to TAF or if TAF is not available, the dose of TDF should be adjusted or TDF should be switched to abacavir or zidovudine, if available. Measurement of renal tubular markers, such as β2M, is useful to diagnose TDF-associated tubulopathy (*59*).

To date, TFV nephrotoxicity is generally regarded as mild and tolerable (*17,18*); severe tubulopathy such as Fanconi syndrome or acute tubular necrosis is rare (*8*), and a TDF-related eGFR decrement is generally modest (*17*). However, it is notable that low body weight is one of the risk factors for TFV nephrotoxicity and that Asians are generally of smaller body stature and can be susceptible to such nephrotoxicity, as shown in several cohort studies (*19,20,41*).

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Treatment for intractable asthma: bronchial thermoplasty

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Abstract: Bronchial Thermoplasty (BT) is an epoch-making treatment that reduces bronchial smooth muscle by using a bronchoscope to reach the basket catheter to the bronchus and directing high-frequency current directly into the bronchi. In GINA Guidelines 2019, BT is considered to be additional treatment at Step V (the most severe), and the evidence level is B. The Japanese guidelines (JGL) also added BT as a treatment for Step 4, but it is reserved because there are still unclear points regarding long-term efficacy and safety. In Japan, as of April 1, 2019, 672 treatments were performed at 123 institutions nationwide. The average age of patients was 54.1 years, but 84 cases were over 70 years old. The average value of %FEV1 was 78.2%, but there were 94 cases less than 60%. There were 32 cases that underwent BT treatment at our institution. Of them, 12 cases with progress up to one year later could be observed. The average age was 56.1 years old, and each of 6 men and women had a %FEV1 of 70.5%. One year later, AQLQ and %FEV1 improved, and the number of exacerbations decreased, but exhaled NO values increased. %FEV1 improvement might be due to poorer lung function (70.5% *vs*. 77.8%) and more BT activation (average 1.28 times AIR2) compared to the AIR2 trial. In terms of improvement in %FEV1, patients with moderate obstructive disorder from 50 to 80% responded well after BT treatment. In the near future, various new antibody preparations such as IL-4 / 13 antibody and anti-TSLP antibody are expected to be promoted. Therefore, we first consider whether these antibody preparations can be applied to patients with refractory asthma. We consider that BT is indicated only when there is no indication or no expected effect of antibody preparations. In other words, BT treatment is the last resort of intractable asthma, and it is the duty of medical professionals involved in BT treatment to be able to advocate when it is best to give BT to such patients.

***Keywords*:** Bronchial thermoplasty, intractable asthma, refractory asthma, bronchial asthma, efficacy, safety

Introduction

Bronchial asthma is a disease characterized by clinical symptoms such as chronic airway inflammation and variability in airway stenosis (wheezing, dyspnea) and cough (*1*). The current standard treatment, combination of inhaled corticosteroids (ICS) and long acting β2 agonists (LABA), is used to suppress airway inflammation and dilate the airways. Although many patients can be controlled by this treatment method, there are still patients whose symptoms persist, and it is difficult to treat as so-called "refractory asthma".

Whatever the cause of bronchial asthma, the end result is airway remodeling such as subepithelial fibrosis, smooth muscle thickening, and submucosal gland hyperplasia resulting in irreversible airway stenosis and increased airway hyperresponsiveness, it has contributed to intractable asthma. Unfortunately, ICS and LABA are ineffective against airway remodeling once it occurs. In contrast, bronchial thermoplasty has been developed for the purpose of physically suppressing airway contraction.

Bronchial Thermoplasty (BT)

BT is an epoch-making treatment that reduces bronchial smooth muscle by using a bronchoscope to reach the basket catheter to the bronchus and directing high-frequency current directly into the bronchi (*2,3*). Although it was listed in Japan since April 2015, there are no clinical trials in Japan, and there is little knowledge about BT.

As a mechanism of action, in basic experiments using animals, BT reduces bronchial smooth muscle mass and suppresses airway hyperresponsiveness (*4*). In experiments using a tracheal ring, tracheal contraction due to acetylcholine disappears when heat treatment is performed at 60°C or higher for 10 seconds (*5*). Recently, a decrease in airway smooth muscle capacity and nerve-related tissue due to BT has been correlated with clinical effects, and in particular, a decrease in nerve-related tissue due to BT is closely related to suppression of exacerbations (*6*). Significant reduction of nerve fibers in the submucosa and airway smooth muscle was reported (*7*). Based on the above, BT is thought to act directly on

airway smooth muscle and surrounding nerve-related tissues to suppress airway contraction.

In GINA Guidelines 2019, BT is considered to be additional treatment at Step V (the most severe), and the evidence level is B. The Japanese guidelines (JGL) also added BT as a treatment for Step 4, but it is reserved because there are still unclear points regarding long-term efficacy and safety (*8*).

BT insurance coverage in Japan is for patients with severe asthma over 18 years of age who cannot control asthma symptoms with high-dose ICS and LABA and are candidates for bronchoscopic procedures. In fact, in addition to high doses of ICS and LABA, even using other drugs (long acting anti-cholinergic agents, theophylline preparations, biologic agents, *etc*.), asthmatic patients who cannot control asthma symptoms and required steroid burst several times a year are targeted patients. In theory, all asthma patients regardless of disease types can be indicated.

BT is basically not contraindicated in patients who can safely undergo bronchoscopy. However, because of the use of high-frequency current, users of implantable medical devices such as pacemakers and ICDs, patients with unstable asthma symptoms, patients with respiratory infections such as bronchiectasis, and blood coagulation disorders are contraindicated. For BT, long-term usefulness and safety exceeding 5 years have not been established. In addition, there is no example of BT used a second time in Europe and the United States, so it is currently a one-time treatment for life.

Evidence for BT

The most extensive AIR2 study is explained (*9*). The subjects were bronchial asthma patients aged 18 to 65 years who had been using ICS (beclomethasone equivalent 1000 μg/day or more) and LABA (salmeterol equivalent 100 μg/day or more) for 4 weeks or more (but oral steroids were 10 mg/day PSL equivalent days or less). Inclusion criterion were the following. The AQLQ score, which is an index of QOL, is 6.25 or less, the %Forced expiratory volume in 1 second (%FEV1) before administration of bronchodilators is 60% or more, airway hypersensitivity has been demonstrated in the methacholine inhalation test, and asthma symptoms at least 2 days during the 4-week observation period. It was also necessary to be a non-smoker (no smoking during the last year, less than 10 pack-years). However, patients with chronic sinus disease or emphysema, and patients who were hospitalized for more than 3 asthma attacks or lower respiratory tract infections in the previous year were excluded. In a randomized, double blind study, 190 were assigned to the BT group and 98 to the Sham group (with bronchial catheters inserted but not energized). The average age of patients in the BT group/ Sham group was 40.7 years/40.6 years old, and the %FEV1 was 77.8%/79.7%, which were relatively good. The primary endpoint was the degree of improvement in AQLQ. As a result, the rate of clear improvement in AQLQ (+0.5 or higher) was 80.9% in the BT group, 63.2% in the Sham group, and clear exacerbation (-0.5 or higher) were 2.9% in the BT group and 7.4% in the Sham group, with statistically significant differences between the two groups. In addition, the number of serious asthma exacerbations and emergency visits, which were secondary endpoints, were clearly lower in the BT group. However, there was no difference between the two groups in Peak flow rate (PEF) values and FEV1. Adverse reactions included exacerbation of asthma, wheezing, dyspnea, chest pain, lower respiratory tract infection, atelectasis, and blood clots, but no serious events were observed.

The above is the result for 1 year after BT treatment, but after that, the results for 5 years after BT treatment were reported (*10*). Both the serious exacerbation of asthma and a decrease in the number of emergency visits observed in the AIR2 study after 1 year of BT treatment were confirmed even after 5 years of BT treatment. The %FEV1 did not change before and after inhalation of bronchodilators. Recently, a 3 years post-marketing survey (PAS2) in the US was reported (*11*), as in AIR2, over 1 to 3 years after BT, severe asthma exacerbations, emergency visits, and number of hospitalizations were clearly decreased in the group.

Current status of BT in Japan

As of April 1, 2019, 672 treatments were performed at 123 institutions nationwide. The average age of the patients was 54.1 years, but 84 cases were over 70 years old. The average value of %FEV1 was 78.2%, but there were 94 cases less than 60%. As anesthesia methods, local anesthesia was often performed at 91 institutions (76%) (information provided by Boston Scientific Japan). In the real world, older and more severe cases are treated with BT. We have 32 BT treatments. Here are our champion cases and problem cases.

Case 1 is a 62-year-old male with a morbidity of 18 years and a history of smoking of 20 pack-years. Although oral steroids are not commonly used, oral administration of steroids is required 5-8 times a year, and severe asthma corresponding to JGL Step 4 and GINA Step V. The drugs used were Symbicort® 8 inhalations/day, tiotropium 5 μg/day, theophylline 400 mg/day, montelukast 10 mg/day, and omalizumab was canceled due to ineffectiveness. When this patient was treated with BT, unlike the AIR2 study, improvement in respiratory function and decrease in exhaled NO (FeNO) levels were observed (Figure 1). Figure 2 and Figure 3 show marked improvement of respiratory function and impedance. Complications, wheezing, chest pain and chest discomfort were observed immediately after BT treatment, and chest radiographs showed transient atelectasis and infiltrative shadows consistent with the

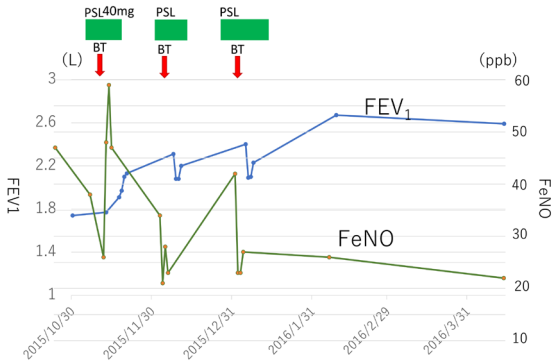

Figure 1. Changes of FEV1 and FeNO in Case 1. FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; BT, Bronchial Thermoplasty.

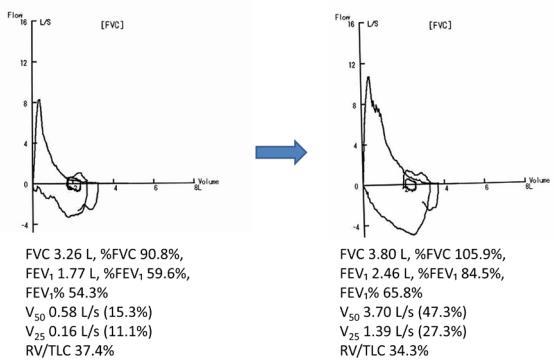

Figure 2. Flow-volume curve after 1 year in Case 1. BT, Bronchial Thermoplasty.

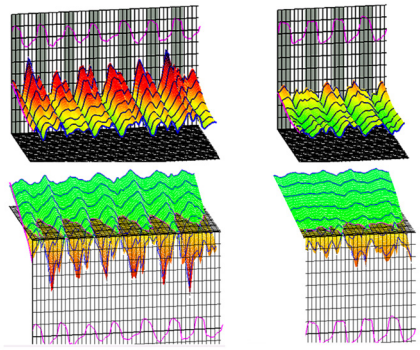

Figure 3. Change of respiratory impedance before (left side) and after (right side) BT in Case 1. BT, Bronchial Thermoplasty.

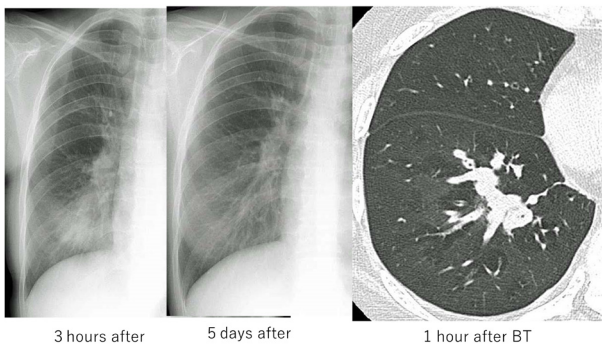

Figure 4. Radiological changes after 1st BT. BT, Bronchial Thermoplasty; HRCT, high-resolution computed tomography.

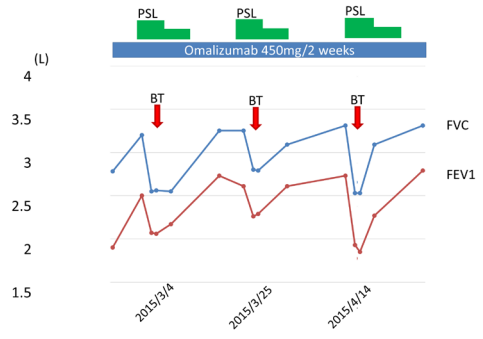

Figure 5. Changes of FVC and FEV1 after BT in the Case 2. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; BT, Bronchial Thermoplasty.

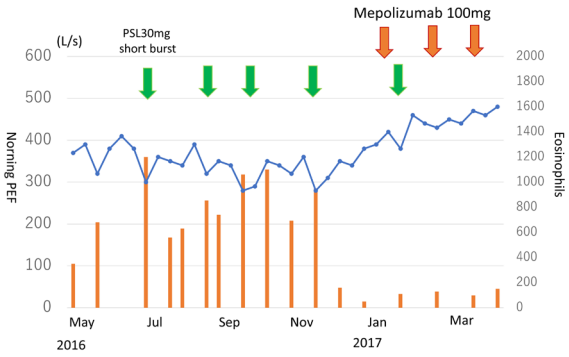

Figure 6. Clinical course 1 to 2 years after BT in the Case 2. BT, Bronchial Thermoplasty.

BT site. These phenomena are common in all cases and appear immediately after BT treatment and disappear 5-7 days later. Chest high-resolution computed tomography (HRCT) shows marked thickening of the bronchial wall involving the surrounding bronchial tissue and severe narrowing of the bronchial lumen (Figure 4). It is speculated that extensive thermal damage has spread to and around the bronchi due to BT treatment.

Case 2 is a 33-year-old, non-smoker woman who suffered for 21 years. Previously she was steroid dependent but it was possible to discontinue steroids after administration of omalizumab. The number of exacerbations of asthma within the past year has been 3, and severe asthma corresponding to JGL Step 4 and GINA Step V. The drugs used were Relvar 200® inhalations/day, theophylline 400mg/day, montelukast 10mg/day, omalizumab 450mg/2 weeks. After BT treatment, the morning PEF value increased from 350 to 500 L/S, and the %FEV1 also improved markedly from 65.5% to 80.1% (Figure 5). However, after 2 months of BT treatment, the PEF value and FEV1 decreased gradually, and a steroid burst was required once a month (Figure 6).

At the same time, the number of eosinophils in the blood increased, and chest CT showed infiltrative shadows. Therefore, when mepolizumab was introduced because it was considered as eosinophilic pneumonia, improvement of asthma symptoms, disappearance of chest infiltration shadows, and improvement of respiratory function were observed (Figure 6). In this case, omalizumab was originally introduced but it was insufficiently controlled, so there was a history so that BT treatment was introduced. Eosinophilia was not clear before BT introduction. However, although the respiratory function was once improved by the introduction of BT, the basic immunological abnormality was not controlled, and it is considered that the asthma symptoms worsened due to the exacerbation of eosinophilic inflammation.

Table 1, Figure 7 and Figure 8 show the results of 12 cases in which BT was performed at our hospital and the progress up to one year later could be observed (*12*). The average age was 56.1 years old, and each of 6 men and women had a %FEV1 of 70.5%. One year later, AQLQ and %FEV1 improved, and the number of exacerbations decreased, but exhaled NO value increased. %FEV1 improvement might be due to poorer lung function (70.5% *vs*. 77.8%) and more BT activations (average 1.28 times of AIR2) compred to the AIR2 trial. In terms of improvement in %FEV1, patients with moderate obstructive disorder from 50 to 80% responded well after BT treatment (Figure 7). In addition, the absence of a decrease in exhaled NO level is proof that it has no effect on eosinophilic inflammation of the airway in the background. We reported dilation of the bronchial lumen and decreased bronchial wall thickness was evident after BT using three-dimensional airway analysis (*13*). Recently, Ishii *et al*. have reported chest HRCT at inspiratory and expiratory levels before and after BT treatment, and reported that the expiratory lung volume decreases after BT treatment (Figure 9) (*14*). Langton *et al*. also reported increase of the luminal airway volume and decrease of residual volume after BT (*15,16*). It can be said that measurement of expiratory lung volume can be a tool for estimating the usefulness of BT treatment. Langston *et al*. also reported that BT improved gas trapping and speculated this improvement may relate to changes in the mechanical properties of small airways that are not measured with spirometry (*17*).

Table 1. Outcomes of BT in National Center for Global Health and Medicine (n = 12)

Items	Before	1M after BT	12M after BT
AQLQ	4.9 + 1.1	5.7 + 1.4*	5.8 + 1.3*
ACQ-5	1.5 + 0.9	0.9 + 1.0*	0.9 + 0.9*
ACT	19.0 + 4.2		20.5 + 4.4
%FEV1	70.5 + 21.7	82.2 + 20.6*	82.3 + 21.8**
FeNO	50.2 + 70.8	51.3 + 61.0	68.8 + 80.4*
Exacerbation	5.8 + 5.3		2.0 + 2.8*

*: $P < 0.05$; **: $P < 0.01$.

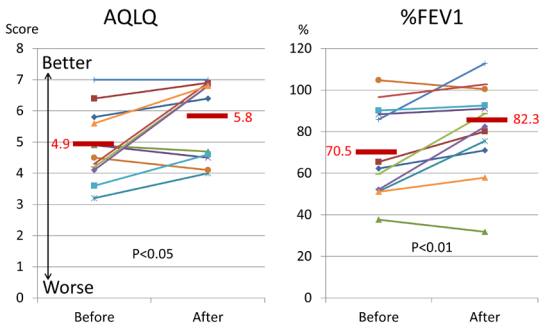

Figure 7. Change of AQLQ and %FEV1 12mo after BT. FEV1, forced expiratory volume in 1 second; BT, Bronchial Thermoplasty.

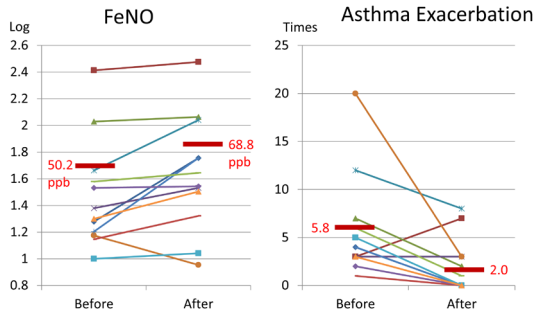

Figure 8. Change of FeNO and asthma exacerbation 12 months after BT. FeNO, fractional exhaled nitric oxide; BT, Bronchial Thermoplasty.

Concerning severe adverse effects, we experienced a case of *Aspergillus* and *Nocardia* infections after BT (*18*). There were two cases of pulmonary cysts/pneumothorax (*19*), and other cases of hemoptysis as serious adverse reactions associated with the BT treatment we performed. Regarding hemoptysis, there are reports in the literature that mediastinal hemorrhage and hemothorax occurred several days after BT treatment, and the cause was pseudo bronchial aneurysm, which was improved by bronchial embolization (*20*). In the aforementioned AIR2 test, there was a case of hemoptysis and bronchial artery embolization. The association between hemoptysis and BT has not been proven, but BT treatment can cause rare but severe bleeding.

Future task of BT

Recently, antibody therapies targeting IL-5 (mepolizumab, benralizumab) have appeared and new tools have been added to treat asthma. The problem here is which should be prioritized, the antibody formulations or BT treatment. At present, it is reasonable to start with antibody preparations first for patients with appropriate indications. This is because BT treatment is highly invasive for patients and cannot control airway inflammation behind asthma. The introduction of BT treatment is appropriate for cases in which various antibody preparations are still insufficiently controlled. Recently, we have experienced a case in which the

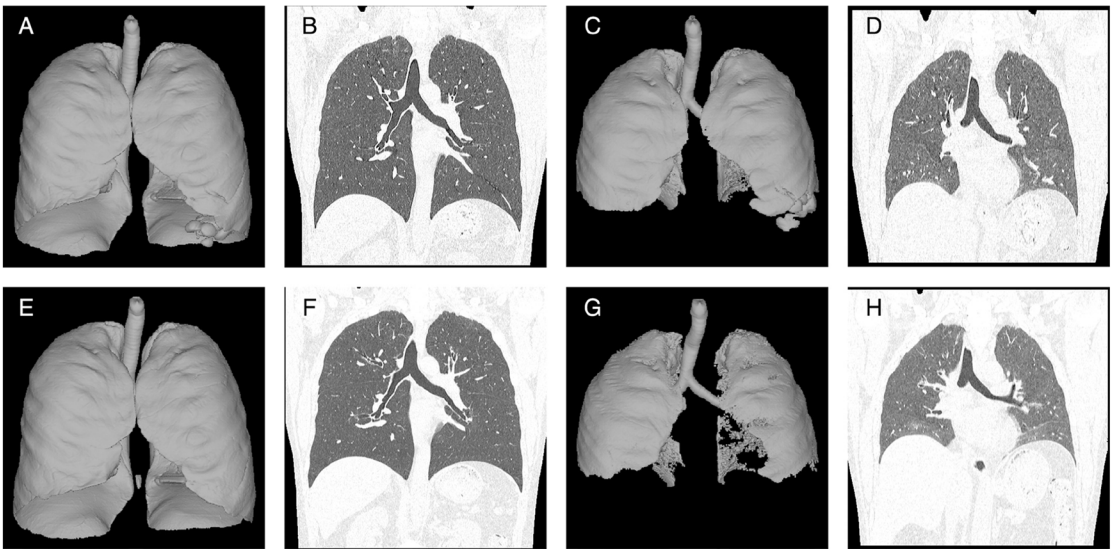

Figure 9. Lung capacity by virtual place in the inspiration and expiration. Upper row: Before BT; Lower row: After BT. BT, Bronchial Thermoplasty.

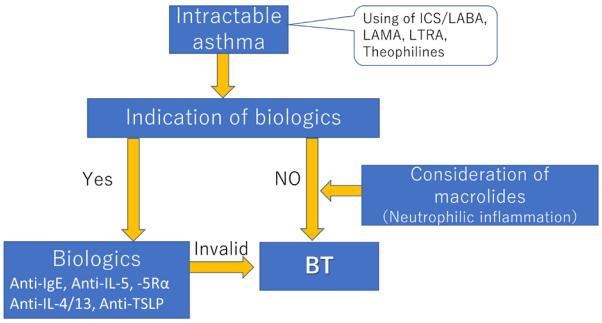

Figure 10. Flow chart in the decision making of BT. BT, Bronchial Thermoplasty.

amount of goblet cells in the bronchial mucosa decreased and the amount of sputum decreased after BT treatment (*21*). BT treatment may be effective even in cases with much sputum and possible involvement of neutrophilic inflammation.

In the near future, various new antibody preparations such as IL-4/13 antibody and anti-TSLP antibody are expected to be promoted. Therefore, we first consider whether these antibody preparations can be applied to patients with refractory asthma. We consider that BT is a good indication only when there is no indication or no expected effect of antibody preparations. In other words, BT treatment is the last resort of intractable asthma. Figure 10 shows a flowchart of antibody formulation and BT treatment, which we consider at this time. However, it should be emphasized that this flowchart only describes the principle, since BT treatment may be prioritized due to the individual circumstances of each patient.

The biggest problem in conducting BT treatment is that its effectiveness cannot be predicted in advance. Since BT is a highly invasive treatment, if any factor that can predict effectiveness can be identified in advance, unnecessary treatment should be avoided. Since BT is a one-time treatment at present, we believe that it is the duty of medical professionals involved in BT treatment to be able to advocate when it is best to give BT to such patients.

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Intestinal-type histology is associated with better prognosis in patients undergoing liver resection for gastric/esophagogastric-junction liver metastasis

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Abstract: The indication for resection of gastric/esophagogastric-junction liver metastasis (GELM) has yet to be established. This study aimed to investigate prognostic factors in patients undergoing GELM resection. From 2001 to 2015, 31 consecutive patients underwent resection for GELM; and factors for poor prognosis were evaluated. Of the 31 patients, 23 (74.2%) developed multiple liver metastases. The histology of gastric cancer was intestinal-type adenocarcinoma in 21 patients (67.7%). Median overall survival (OS) was 3.2 years. The 1-, 3-, and 5-year OS rates were 92.8%, 56.2%, and 42.2%, respectively. The 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 58.5%, 31.3%, and 31.3%, respectively. Multivariate analysis indicated that intestinal-type adenocarcinoma was associated with a significantly lower risk of OS (hazard ratio [HR], 0.26; p =0.022) and RFS (HR, 0.25; p = 0.008). In multiple logistic regression analysis, intestinal-type adenocarcinoma (odds ratio, 0.14; p = 0.012) reduced incidence of extra-hepatic recurrence after GELM resection. In conclusion, GELM resection in patients with intestinal-type histology is preferable because intestinal-type adenocarcinoma is associated with better prognosis and a lower incidence of extra-hepatic recurrence than diffuse/other-type adenocarcinoma.

Keywords: Gastric liver metastasis, gastric/esophagogastric-junction liver metastasis, the intestinal-type adenocarcinoma, liver resection

Introduction

The prognosis of gastric cancer has improved over the last two decades, but it remains the third highest cause of cancer-related death worldwide (1-3). Surgical resection of the stomach is the mainstay of management for resectable gastric cancer, but cumulative recurrence rates still remain high; 79% within 2 years of operation (*1*). Liver is one of the major organs that develop gastric cancer metastases, with an incidence of 4-34% (*2*).

Although chemotherapy is regarded as the standard treatment for gastric/esophagogastric-junction liver metastases (GELMs), several retrospective studies have reported favorable prognosis for liver resection concerning GELM (*3-7*). These studies demonstrated the following risk factors for poor prognosis: number and maximum size of liver metastases; R1/R2 resection; synchronous metastases; primary tumor stage pT4; and the presence of other distal metastases. However, the study periods were mainly limited before the year 2000. The appropriate indication criteria for GELM resection are still debatable because effective chemotherapies for gastric cancer were introduced in the early 2000s. Additionally, factors for poor prognosis regarding liver resection for GELM are not well established, as compared with those for colorectal liver metastases.

The aim of this study was to investigate prognostic factors for GELM by evaluating patients who underwent liver resection for GELM.

Materials and Methods

Indication for liver resection for GELMs

Liver resection was indicated for three or fewer GELMs without metastases at other sites, based on previous reports (*6*). In patients with four or more GELMs, preoperative chemotherapy was performed. In cases where no extra-hepatic gastric metastases occurred after chemotherapy, liver resection was indicated. Simultaneous resection of the stomach and GELM was performed for synchronous GELMs, when they

were easily removed using limited non-anatomic liver resection. The final surgical procedures were planned to resect all GELMs to secure negative histologic margins.

Definition of histology

Histopathological classification of gastric cancer was classified into three groups, intestinal type, diffuse type, and other type, based on the criteria of Japanese Classification of Gastric Cancer third edition. Intestinal-type adenocarcinoma was defined as a tumor with glandular architecture, resembling colonic carcinoma, whereas diffuse-type adenocarcinoma was defined as a tumor composed of solitary or small clusters of cells, and lacking glandular structures. Gastric cancer with uncommon variant was classified as other type (*8*).

Patients

Between January 2001 and December 2015, 31 consecutive patients underwent liver resection for GELM at the University of Tokyo Hospital. The clinical records of these patients were retrospectively reviewed from a prospectively maintained database. Patient characteristics are summarized in Table 1. All operations were performed after obtaining informed consent from each patient, and all aspects of the procedures were conducted according to the principles expressed in the Declaration of Helsinki. In the preparation of this study, all efforts have been made to protect patient privacy and anonymity. The study was approved by the institutional review board at the University of Tokyo (2158-5).

Preoperative evaluation

The surgical procedure was planned with reference to tumor location, size, and the results of the volumetric analysis. All patients underwent ultrasonography, plain and contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI) for the staging of GELM; they underwent chest X-ray, chest CT, gastroscopy, and, if necessary, positron emission tomography-CT for the surveillance of extra-hepatic metastases. Intraoperative tumor surveillance was performed using visual inspection, manual palpation, and intraoperative ultrasonography, and the final surgical procedures were planned to resect all GELMs and secure negative histologic margins.

Surgical procedures

Liver resection was indicated under criteria based on preoperative liver function parameters, such as the presence/absence of uncontrolled ascites, serum bilirubin level, and indocyanine green retention rate at 15 min (*9,10*). Non-anatomical limited resection was principally performed to preserve as much liver parenchyma as possible. A major anatomical hepatectomy was performed when liver metastases were adherent to or invading major hepatic vessels and/or were identified in the hemi-liver. After retrieving surgical specimens,

Table 1. Patient characteristics

Variables	Value
Number of patients	31
Patient factor	
Age, years [range]	73 [47-84]
Sex, *n* (%)	
Male	27 (87.1)
Female	4 (12.9)
ASA score, *n* (%)	
1	13 (41.9)
2	18 (58.1)
3	0 (0.0)
BMI, kg/m^2 [range]	21.6 [14.6-30.7]
AFP, U/mL [range]	9.0 [1.0-32.5×10^5]
CEA, ng/mL [range]	9.0 [1.0-5370]
CA19-9, U/mL [range]	100 [69-100]
Primary lesion factors	
Location, *n* (%)	
Esophagogastric junction	4 (12.9)
Upper	5 (16.1)
Middle	11 (35.5)
Lower	11 (35.5)
Maximum size, cm [range]	4.0 [0.4-19]
Histology, *n* (%)	
Diffuse/other-type adenocarcinoma	10 (32.3)
Intestinal-type adenocarcinoma	21 (77.7)
T classification, *n* (%)	
T1	9 (29.0)
T2	3 (9.7)
T3	12 (38.7)
T4	7 (22.6)
N classification, *n* (%)	
N0	15 (48.4)
N1	3 (9.7)
N2	9 (29.0)
N3	4 (12.9)
Liver metastasis factor	
Timing of liver metastases, *n* (%)	
Synchronous	13 (41.9)
Metachronous	18 (58.1)
Tumor number, *n* (%)	
1	23 (74.2)
2-3	5 (16.1)
≥ 4	3 (9.7)
Maximum tumor size, cm [range]	3.1 [0.8-22]
Tumor distribution, *n* (%)	
Unilobular	23 (74.2)
Bilobular	8 (25.8)
Preoperative chemotherapy, *n* (%)	13 (41.9)
Regimen of preoperative chemotherapy, *n* (%)	
S-1 and CDDP	6 (19.4)
CPT-11 and CDDP	2 (6.5)
CPT-11 and MMC	1 (3.2)
S-1 and CDDP and Tmab	2 (6.5)
S-1 and Oxaliplatin	1 (3.2)
CDDP and 5-FU	1 (3.2)
wPTX and Tmab	1 (3.2)

Abbreviations: ASA, American society of anesthesiologists; BMI, body mass index; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; S-1, Tegafur gimestat otastat potassium; CDDP, Cisplatin; CPT-11, Irinotecan; MMC, Mitomycin C; Tmab, Trastuzumab; 5-FU, 5-Fluorouracil; wPTX, weekly Paclitaxel.

the distance between tumors and the cut surface were measured, and the shortest distance from multiple tumors was defined as a surgical margin. When one of the surgical margins was positive, the tumor was defined as having a positive surgical margin. Major hepatectomy was defined as the resection of ≥ 3 contiguous segments, according to Couinaud's classification (*11*).

Statistical analysis

Categorical variables are expressed as numbers (%). Continuous variables are expressed as the median and range. The TNM classification and stage were determined according to the International Union Against Cancer (version 7), when gastrectomy or synchronous gastric and liver resection were performed.

Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Overall survival (OS) was calculated from the day of liver resection in patients undergoing upfront resection, or the initiation of neoadjuvant chemotherapy in patients undergoing neoadjuvant chemotherapy. Loss to follow-up and death without recurrence were censored for the recurrence-free survival (RFS) analysis.

Factors with a p value < 0.05 using the Cox proportional-hazards model were considered as potential risk factors and were further analyzed using a multivariate Cox model. Factors with a p value < 0.05 using logistic regression in univariate analysis were considered as potential predictors and were further analyzed in a multiple logistic regression analysis. Hazard ratios (HR), odds ratio (OR), and 95% confidence interval (CI) were calculated for each factor. The cutoff level for estimated blood loss in our study was set at 1,000 mL, based on previous reports (12). Tumor markers were categorized by institutional upper limits: carcinoembryonic antigen (≥ 5 *vs*. < 5), carbohydrate antigen 19-9 (≥ 37 *vs*. < 37), and α-fetoprotein (≥ 9 *vs*. < 9). Other continuous variables were categorized using the median value. A *p* value < 0.05 was considered to indicate statistical significance.

Statistical analysis was performed using JMP software (version 11.0.6; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The median maximum GELM size was 3.1 (range, 0.8-22.0) cm. Histological outcomes of gastric cancer were intestinal type in 21 patients (67.7%) and diffuse type/other type in 10 patients (32.3%). Liver resection for synchronous and metachronous metastases were performed in 13 (41.9%) patients and 18 (58.1%) patients, respectively. Before liver resection for GELM, 45.2% of patients (*n* = 14) underwent chemotherapy with regimens that mainly included S-1 and/or cisplatin, including three patients (9.7%) who were treated with neoadjuvant chemotherapy.

Intraoperative, postoperative outcomes

Intraoperative and postoperative outcomes are summarized in Table 2. Major hepatectomy was performed in six patients (19.3%). The morbidity rate was 12.9% (*n* = 4) including no Clavien-Dindo III-V complications. Resection rates of R0, R1, and R2 were 71.0 % (*n* = 22), 22.5% (*n* = 7), and 6.5% (*n*

Table 2. Intraoperative and postoperative outcomes

Variables	Value
Number of patients	31
Intraoperative outcomes	
Operative time, min [range]	358 [146-724]
Estimated blood loss, mL [range]	690 [20-3270]
Blood transfusion, *n* (%)	10 (32.3)
Major hepatectomy, *n* (%)	6 (19.3)
Postoperative outcomes	
Morbidity rate	16.1%
Clavien-Dindo classification, *n* (%)	
≥ IIIA	0 (0.0)
I-II	4 (12.9)*
Length of hospital stay, days [range]	14 [5-49]
R1 and R2 resection, *n* (%)	9 (29.0)
Postoperative chemotherapy, *n* (%)	15 (48.4)

*Cholangitis in two patients (6.5%), congestive heart failure in one patient (3.2%), and ileus in one patient (3.2%).

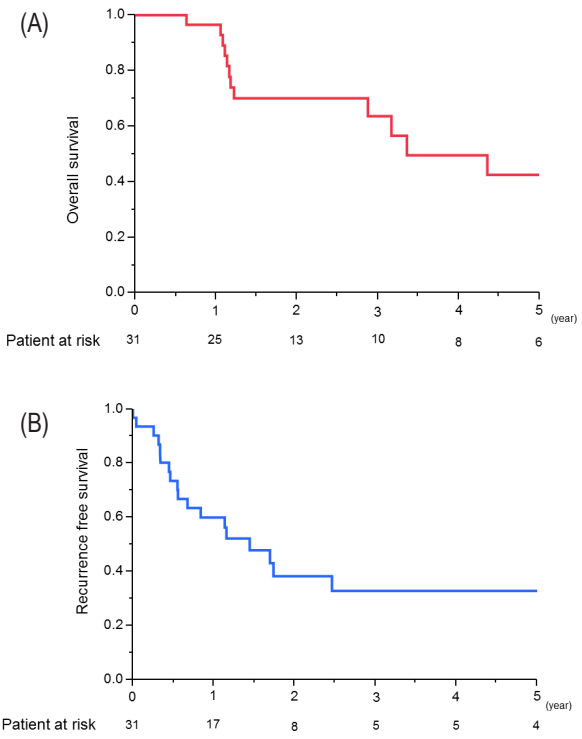

Figure 1. (A) Overall survival in patients with gastric/esophagogastric-junction liver metastasis. (B) Recurrence-free survival in patients with gastric/esophagogastric-junction liver metastasis.

= 2), respectively. Postoperative chemotherapy was prescribed in 15 patients (48.4%). All histopathological findings of GELM were consistent with those of a primary tumor.

Overall survival and recurrence-free survival

The median follow-up period was 3.3 (range, 0.3-8.4) years. The 1-, 3-, and 5-year OS rates were 92.8%, 56.2%, and 42.2%, respectively. The median OS was 3.2 years (Figure 1A). The 1-, 3-, and 5-year RFS rates were 58.5%, 31.3%, and 31.3%, respectively. The median RFS was 1.4 years (Figure 1B). Recurrence after liver resection for GELM occurred in 18 (58.1%) patients; this included the liver in eight (25.8%), the lung in two (6.5%), the bone in two (6.5%), the lymph nodes in one (3.2%), and the peritoneum in one (3.2%), including multiple site recurrence in four (22.2%).

Table 3. Univariate and multivariate analysis of overall survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Patient factors						
Sex,						
Male / Female	1.11	0.20-20.6	0.918			
Age						
≥ 70 years / ≤ 69 years	1.21	0.36-3.86	0.756			
BMI						
≥ 25.0 kg/m^2 / ≤ 24.9 kg/m^2	1.23	0.55-2.75	0.684			
ASA						
≥ 2 / ≤ 1	0.60	0.21-1.45	0.183			
AFP						
≥ 9.0 IU/mL / ≤ 8.9 IU/mL	0.41	0.06-1.80	0.251			
CEA						
≥ 5.0 IU/mL / ≤ 4.9 IU/mL	0.88	0.19-2.75	0.787			
CA19-9						
≥ 37.0 IU/mL / ≤ 36.9 IU/mL	0.91	0.19-3.40	0.902			
Preoperative chemotherapy	0.91	0.31-2.48	0.924			
Primary cancer-related factors						
Tumor location						
EGJ, Upper / Middle, Lower	1.78	0.55-4.84	0.314			
Maximum primary tumor size						
≥ 5 cm / ≤ 4.9 cm	1.72	0.59-5.52	0.312			
T classification						
≥ 3 / ≤ 2	1.17	0.73-2.94	0.240			
N classification						
≥ 1 / ≤ 0	1.35	0.50-3.94	0.552			
Histological type						
Intestinal / Diffuse and other	0.26	0.08-0.85	**0.027**	0.24	0.07-0.81	0.022
Liver metastases-related factors						
Timing of liver metastases						
Metachronous / Synchronous	0.68	0.63-4.94	0.284			
Tumor number						
Multiple / Single	1.06	0.33-2.86	0.914			
Tumor distribution						
Bilobular / Unilobular	1.34	0.42-3.68	0.586			
Maximum tumor size						
≥ 5 cm / ≤ 4.9 cm	0.66	0.15-2.09	0.518			
Operative procedures						
Synchronous hepatectomy	1.65	0.54-4.62	0.354			
Major hepatectomy	3.43	1.09-44.7	**0.044**			
Operating time						
≥ 360 min / ≤ 359 min	1.57	0.57-4.45	0.371			
Estimated blood loss						
≥ 1000 mL / ≤ 999 mL	1.26	0.44-3.46	0.648			
Resection						
≥ R1 / R0	4.86	1.32-17.9	**0.018**	5.31	1.40-20.5	0.015
Postoperative factors						
Clavien-Dindo classification						
≥ I / ≤ 0	0.81	0.59-2.00	0.786			
Duration of hospital stay						
≥ 14 days / ≤ 13 days	1.34	0.48-3.85	0.567			
Postoperative chemotherapy	1.12	0.41-3.09	0.815			

Abbreviations: BMI, body mass index; ASA, American society of anesthesiologists; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; EGJ, esophagogastric junction; Por, undifferentiated adenocarcinoma; HR, hazard ratios; CI, confidence intervals.

Risk factors for OS and RFS

Intestinal-type adenocarcinoma, major hepatectomy, and R1/R2 resection were found to be significantly associated with OS (Table 3). Of these factors, intestinal-type adenocarcinoma was associated with a significantly lower risk of OS (HR, 0.24; 95% CI, 0.07-0.81; p = 0.022). In contrast, R1/R2 resection (HR, 5.31; 95% CI, 1.40-20.5; p = 0.015) was an independent risk factor for OS. Primary gastric location (esophagogastric junction and upper stomach) and intestinal-type adenocarcinoma were found to be significantly associated with RFS (Table 4). Of the two factors, intestinal-type adenocarcinoma was associated

Table 4. Univariate and multivariate analysis of recurrence-free survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Patient factors						
Sex						
Male / Female	1.08	0.32-6.72	0.938			
Age						
≥ 70 years / ≤ 69 years	1.02	0.41-2.59	0.949			
BMI						
≥ 25.0 kg/m^2 / ≤ 24.9 kg/m^2	0.73	0.38-1.30	0.307			
ASA						
≥ 2 / ≤ 1	0.91	0.28-2.20	0.460			
AFP						
≥ 9.0 IU/mL / ≤ 8.9 IU/mL	1.68	0.54-5.09	0.356			
CEA						
≥ 5.0 IU/mL / ≤ 4.9 IU/mL	4.88	0.53-4.85	0.447			
CA19-9						
≥ 37.0 IU/mL / ≤ 36.9 IU/mL	2.65	0.89-8.16	0.077			
Preoperative chemotherapy	0.89	0.44-2.99	0.821			
Primary cancer-related factors						
Tumor location						
EGJ, Upper/ Middle, Lower	3.03	1.08-8.12	**0.039**			
Maximum primary tumor size						
≥ 5 cm / ≤ 4.9 cm	1.93	0.71-4.86	0.183			
T classification						
≥ 3 / ≤ 2	1.28	0.51-3.45	0.596			
N classification						
≥ 1 / ≤ 0	1.03	0.41-2.62	0.934			
Histological type						
Intestinal /Diffuse and other	0.25	0.10-0.68	**0.006**	0.34	0.09-0.72	**0.008**
Liver metastases-related factors						
Timing of liver metastases						
Metachronous / Synchronous	0.88	0.24-2.25	0.786			
Tumor number						
Multiple / Single	1.61	0.59-4.02	0.329			
Tumor distribution						
Bilobular / Unilobular	1.24	0.43-3.16	0.661			
Maximum tumor size						
≥ 5 cm / ≤ 4.9 cm	1.93	0.71-4.86	0.183			
Portal vein thrombosis	2.18	0.60-6.30	0.210			
Operative procedures						
Synchronous hepatectomy	0.73	0.17-1.83	0.650			
Major hepatectomy	3.16	0.77-9.98	0.093			
Operating time						
≥ 360 min / ≤ 359 min	1.23	0.48-3.17	0.654			
Estimated blood loss						
≥ 1000 mL / ≤ 999 mL	1.05	0.64-2.71	0.922			
Blood transfusion	0.92	0.32-2.39	0.881			
Resection						
≥ R1 / R0	1.82	0.62-4.82	0.256			
Postoperative factors						
Clavien-Dindo classification						
≥ I / ≤ 0	1.16	0.56-2.14	0.646			
Duration of hospital stay						
≥ 14 days / ≤ 13 days	0.86	0.31-2.26	0.776			
Postoperative chemotherapy	0.79	0.29-1.98	0.631			

Abbreviations: BMI, body mass index; ASA, American society of anesthesiologists; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; EGJ, esophagogastric junction; Por, undifferentiated adenocarcinoma; HR, hazard ratios; CI, confidence intervals.

with a lower risk of RFS (HR,0.34; 95% CI, 0.09-0.72; $p = 0.008$).

Factors predicting extra-hepatic recurrence

Intestinal-type adenocarcinoma and a maximum tumor size ≥ 5 cm were found to be significantly associated with extra-hepatic recurrence after liver resection for GELM (Table 5). Subsequent multiple logistic regression analysis revealed that intestinal-type adenocarcinoma (OR, 0.13; 95% CI, 0.02-0.66; $p = 0.012$) was associated with a lower incidence of extra-hepatic recurrence. Extra-hepatic recurrence rates after liver resection were significantly lower in patients

Table 5. Univariate and multivariate analysis of extra-hepatic recurrence

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Patient factors						
Sex						
Male / Female	0.56	0.02-5.13	0.630			
Age						
≥ 70 years / ≤ 69 years	0.57	0.11-2.52	0.463			
BMI						
≥ 25.0 kg/m^2 / ≤ 24.9 kg/m^2	0.82	0.16-3.26	0.363			
ASA						
≥ 2 / ≤ 1	1.03	0.52-2.82	0.623			
AFP						
≥ 9.0 IU/mL / ≤ 8.9 IU/mL	3.00	0.46-26.7	0.256			
CEA						
≥ 5.0 IU/mL / ≤ 4.9 IU/mL	0.53	0.09-2.64	0.449			
CA19-9						
≥ 37.0 IU/mL / ≤ 36.9 IU/mL	1.50	0.31-7.66	0.610			
Preoperative chemotherapy	2.66	0.57-15.0	0.213			
Primary cancer-related factors						
Tumor location						
EGJ, Upper/ Middle, Lower	0.30	0.05-1.48	0.140			
Maximum primary tumor size						
≥ 5 cm / ≤ 4.9 cm	1.67	0.26-2.46	0.253			
T classification						
≥ 3 / ≤ 2	1.54	0.33-7.11	0.568			
N classification						
≥ 1 / ≤ 0	0.47	0.09-2.06	0.318			
Histological type						
Intestinal /Diffuse and other	0.14	0.02-0.67	**0.006**	0.13	0.02-0.66	**0.012**
Liver metastases-related factors						
Timing of liver metastases						
Metachronous / Synchronous	3.03	0.69-14.5	0.141			
Tumor number						
Multiple / Single	1.07	0.20-6.27	0.943			
Tumor distribution						
Bilobular / Unilobular	2.30	0.42-18.1	0.345			
Maximum tumor size						
≥ 5 cm / ≤ 4.9 cm	1.08	1.02-5.06	**0.049**			
Operative procedures						
Synchronous hepatectomy						
Major hepatectomy	1.77	0.27-11.4	0.531			
Operating time						
≥ 360 min / ≤ 359 min	1.08	0.20-4.14	0.919			
Estimated blood loss						
≥ 1000 mL / ≤ 999 mL	1.23	0.13-4.07	0.803			
Blood transfusion	1.55	0.32-8.91	0.589			
Resection						
≥ R1 / R0	2.67	0.54-14.0	0.221			
Postoperative factors						
Clavien-Dindo classification						
≥ I / ≤ 0	0.72	0.20-3.08	0.654			
Duration of hospital stay						
≥14 days / ≤13 days	1.94	0.43-9.61	0.387			
Postoperative chemotherapy	2.40	0.55-11.1	0.241			

Abbreviations: BMI, body mass index; ASA, American society of anesthesiologists; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; EGJ, esophagogastric junction; Por, undifferentiated adenocarcinoma; OR, odds ratio; CI, confidence intervals.

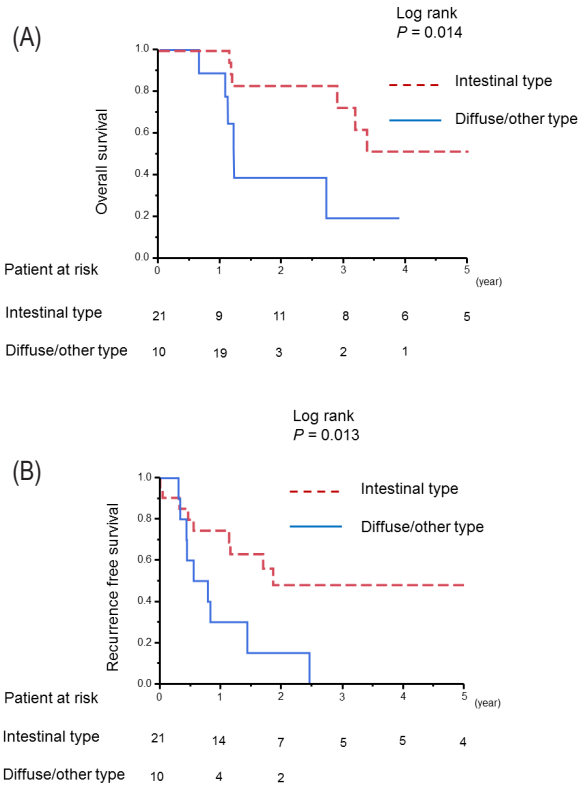

Figure 2. (A) Overall survival in patients with intestinal-type adenocarcinoma and with diffuse-type adenocarcinoma/other type in GELM. (B) Recurrence-free survival in patients with intestinal-type adenocarcinoma and with diffuse-type adenocarcinoma/other type in GELM. GELM, gastric/esophagogastric-junction liver metastasis.

with intestinal-type adenocarcinoma than in those with diffuse-type adenocarcinoma/other type (23.8% [5/21] *vs*. 60.0% [6/10]; $p = 0.002$).

OS and RFS in patients with intestinal-type adenocarcinoma

OS ($p = 0.014$) and RFS ($p = 0.013$) differed significantly between patients with intestinal-type adenocarcinoma and patients with diffuse-type adenocarcinoma/other type (Figure 2). The 1-, 3-, and 5-year OS rates in patients with intestinal-type adenocarcinoma were 100.0%, 72.9%, and 52.0%, respectively, whereas diffuse-type adenocarcinoma/other type were 88.8%, 19.4%, and 19.4%, respectively. The 1-, 3-, and 5-year RFS rates in patients with intestinal-type adenocarcinoma were 74.5%, 48.0%, and 48.0%, respectively, while those in patients with diffuse-type adenocarcinoma/other type were 30.0%, 0.0%, and 0.0%, respectively. Recurrence after liver resection occurred in nine of 10 (90%) patients with diffuse-type adenocarcinoma/other type, including in the liver in three, in the lymph nodes in one, in the peritoneum in one, in the bone in one, and in multiple sites in three.

Summary of outcomes for GELM resection in previous study

Table 6 shows Indication, long-term outcomes, and prognostic factors of patients undergoing GELM resection in previous studies that included > 30 patients in recent years.

Discussion

Our study demonstrated that the 5-year OS and RFS rates in selected patients who underwent liver resection for GELM were 42.2% and 31.3%, respectively. Intestinal-type adenocarcinoma was associated with a lower risk for both OS and RFS, and with a lower incidence for extra-liver recurrence after liver resection for GELM.

The 5-year OS and RFS rates in our study are similar to those reported in previous studies. The OS and RFS rates reportedly ranged from 9.3% to 42.1% and from 8.6% to 27.7%, respectively (*3-7,12-18*). The median OS time was 38.0 months for selected patients in our study, which was also comparable to previous studies, where it ranged from 11 to 36 months (*3,6,15,16,18,19*). In contrast, according to a recent phase III clinical trial for GELM (*20*), the median OS was 9.5-14.1 months without liver resection. However, to address appropriate selection criteria for GELM resection, factors for poor prognosis concerning GELM resection and predictors for extra-hepatic recurrence after liver resection should be investigated; this is because gastric cancer develops peritoneal dissemination and lymph node metastases more frequently than colorectal cancer (*21*). In the present study, intestinal-type adenocarcinoma reduced a risk for OS and RFS. Additionally, intestinal-type adenocarcinoma was associated with a lower incidence of extra-hepatic recurrence. This finding is reasonable because diffuse-type histology is associated with infiltrative growth and peritoneal dissemination (*22*). Actually, the peritoneal dissemination rate is reported to be higher in patients with diffuse-type adenocarcinoma than those with intestinal-type adenocarcinoma (31% *vs*. 6%) (*23*). In our study, extra-hepatic recurrence rates after liver resection were significantly higher in patients with diffuse-type adenocarcinoma/other type than in those with intestinal-type adenocarcinoma (60% [6/10] *vs*. 23.8% [5/21]; $p = 0.002$). Accordingly, GELM resection is preferable for patients with intestinal-type adenocarcinoma. It would be reasonable to limit solitary GELM and/or to use a mandatory neoadjuvant chemotherapy strategy for non-intestinal-type histology, instead of upfront liver resection, although the effect of perioperative chemotherapy for GELM remains unclear. Additionally, the use of a strong adjuvant chemotherapy regimen can be recommended for GELM with diffuse-type adenocarcinoma/other type.

According to previous studies that included > 30

Table 6. Surgical indication, long-term outcomes, and prognostic factors reported in the previous and present studies

Author	Year	*n*	Surgical indication	Median OS (month)	5-year RFS rate (%)	5-year OS rate (%)	Prognostic factors for poor survival
Shildberg *et al*.	2012	31	Without other distal metastasis	NS	NS	13	Multiple liver metastases R1/R2 resection Synchronous
Takemura *et al*.	2012	64	Three or fewer GELMs (More liver metastases at the surgeon's discretion) Only R0 resection	34	27	37	≥ 5 cm in size pT4 of primary tumor
Wang *et al*.	2012	30	Without other distal metastasis preoperatively Synchronous GELMs Only R0 resection	11	NS	16.7	Peritoneal dissemination Multiple distal metastases
Kinoshita *et al*.	2014	256†	Three or fewer GELMs (More liver metastases at the surgeon's discretion) Only R0 resection	31	30.1	31.1	pT4 of primary tumor ≥ 5 cm in size ≥ 3 GELMs
Tiberio *et al*.	2014	53†	Without other distal metastasis	34	NS	31.5	≥ 6 cm in size D2 dissection
Wang *et al*.	2014	39	Without other distal metastasis	14	7.7	10.3	Lymph node metastasis Multiple distal metastases
Guner *et al*.	2015	68†	Not stated in detail (case by case)	24	26.0	30.0	≥ 3 cm in size
Liu *et al*.	2015	35	Without other distal metastasis	33	NS	14.3	Lymphovascular invasion Multiple liver metastasis
Oki *et al*.	2015	94†	Without other distal metastasis	34	27.7	42.3	≥ 3 cm in size Multiple GELMs ≥ N2 of primary tumor
Present study	2018	31	Three or fewer GELMs Controllable after chemotherapy Only R0 resection	38	31.3	42.2	Diffuse/other type R1/R2 resection

Abbreviations: OS, overall survivals; RFS, recurrence-free survivals; GELM, gastric/esophagogastric-junction liver metastasis; NS, not stated. †, Multicenter cohort study.

patients in the past 5 years, multiple liver metastases, R1/R2 resection, synchronous metastases, maximum size of liver metastases, pT4 of primary tumor, and other distant metastases were reported to be risk factors for OS (*3,5,6,16,18,19*). Unlike the previously reported covariates, the diffuse-type adenocarcinoma in our study is one of the prognostic factors for OS and RFS, and it is a predictor of extra-liver metastasis development. This is most likely because the previous series included advanced-stage patients with GELM and other organ metastases, and patients with four or more GELMs. These factors tempered the influence of the diffuse/other-type adenocarcinoma of primary gastric cancer in the analysis. In contrast, our indication criteria are more restrictive than the previous series, namely three or fewer GELMs without any distant metastases; in addition, the diffuse-type carcinoma was found to be a factor for poor prognosis.

The present study had several limitations. Its retrospective nature and the small number of patients enrolled may weaken the reliability of the statistical analyses. Genomic expressions including α-fetoprotein and human epidermal growth factor receptor-related 2 (HER2) were not evaluated in the study. Further investigations with a large number of patients in a well-designed multicenter study are needed to evaluate appropriate patient selection criteria for GELM resection.

In conclusion, intestinal-type adenocarcinoma was associated with a lower risk for OS and RFS; it was also associated with a lower incidence of extra-hepatic recurrence, under the GELM resection criteria involving three or fewer tumors without distant metastases. Therefore, GELM resection is preferable for patients with intestinal-type histology. A strict indication such as solitary GELM and/or the use of mandatory neoadjuvant chemotherapy, and the use of a strong adjuvant chemotherapy regimen, can be recommended for GELM with diffuse-type adenocarcinoma/other type.

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How can we strengthen pathology services in Cambodia?

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Abstract: Rapid economic growth and a changing disease burden have increased the demand for pathology services in Cambodia. This paper describes the status of pathological services and international support for pathology professionals in Cambodia, and discusses future needs for strengthening pathology services. In 2016, there were only four pathologists and 18 pathology technologists in Cambodia. A postgraduate course in pathology was created in 2015, and five residents became certified in 2018. Besides multinational support with lectures and practice for pathologists, the Japanese team provides on-the-job training for pathology technologists to improve slide preparation for diagnosis. A clinicopathological conference was introduced to strengthen the communication among pathologists, pathology technologists, and gynecologists. Although there is a long way to go to reach high quality pathological services, coordination among international partners needs to continue, as does the balance between human resource development for pathology professionals, to provide a higher level of care to local citizens.

***Keywords*:** Pathologist, pathology technologist, human resource development, cervical cancer

Introduction

Today, the prevalence of major non-communicable diseases (NCDs) in Cambodia has been increasing. Among the increased disease burden of NCDs in Cambodia, cervical cancer was the leading cause of female cancers, which was estimated at 767 among the entire population, 16 million in 2014 (*1*), exceeding the maternal mortality rate in 2015, which stood at 590 (*2*). With an urgent need for action, cervical cancer was elevated to a disease to be given priority, focusing on prevention, screening, and treatment services (*3*).

To respond to the cervical cancer problem, in 2015 the Cambodian Society of Gynecology and Obstetrics started a joint project on cervical cancer with the Japan Society of Gynecology and Obstetrics. Following the World Health Organization (WHO) recommendation of a comprehensive approach (*4*), a primary cervical cancer screening with testing for the high-risk human papillomavirus, followed by a secondary screening with a colposcopy and early treatment for positive cases, were successfully introduced (*5*). WHO announced in 2018 a global call to action towards the elimination of cervical cancer, and called for all stakeholders to unite behind this common goal. However, the major obstacle in scaling up a cervical cancer screening program in Cambodia was identified as the extremely limited capacity of its pathological services. When any screening program is scaled up in a country, there will inevitably be a large increase in the detection rate of the target cancer. The national capacity for pathological diagnosis and the treatment of cancer therefore need to be considered in parallel.

This paper aims to describe the status of pathological services and international support for pathology professionals since 2017 in Cambodia, and to discuss future needs for strengthening pathology services.

The situation of pathology services in Cambodia

In 2016, for the population of 16 million Cambodians, there were only four pathologists and 18 pathology technologists available. After five residents completed a postgraduate course discussed below, the number of pathologists increased to nine in 2018. Thereafter, some certified pathologists went abroad to get further training, therefore, eight pathologists actually work in Cambodia at the present time (Table 1).

Considering pathology laboratories in the public sector, there are three national hospitals with pathology

Table 1. Pathological services in national hospitals in Phnom Penh, Cambodia

Items	Calmette Hospital	Kossamak Hospital	KSFH	NMCHC
Number of medical staff				
Pathologists*	2	1	3	1
Pathology technicians	5	3	6	2
Staining methods				
Papanicolaou	+	+	+	+
Hematoxylin eosin		+	+	
Hematoxylin phloxine saffron	+			
Giemsa	+	+	+	
Grocott	+			
Periodic acid Schiff	+	+	+	
Masson trichrome	+			
Ziehl Neelsen	+	+		
Iron stain	+			
Alcian Blue	+			

*There is another pathologist working in national university. Abbreviation: KSFH, Khmer Soviet Friendship Hospital; NMCHC, National Mother and Child Health Center.

services, and one national hospital with cytology services. Three national hospitals deal with approximately 4,000 histology specimens annually, and only one of them is capable of performing immunohistochemistry. However, as there are several private laboratories in which specialists provide pathology services as a dual practice, it is difficult to precisely estimate the actual number of pathology services provided in Cambodia.

The University of Health Sciences (UHS), established in 1946, has been the first and only national medical school that has a department of anatomical pathology. Responding to the increased demand for pathological services, a postgraduate course in Pathology was created at UHS in 2015, and six doctors entered. However, it was difficult to accomplish the curriculum because of insufficient numbers of Cambodian lecturers and institutes for clinical practice. Although overseas training is part of the curriculum, UHS faced the difficulty of identifying appropriate institutions to receive Cambodian postgraduate students. The Technical School for Medical Care under UHS served as the leading institute for laboratory technologists. Since there are no pathology classes in the pre-service educational curriculum, current pathological technologists learned the techniques on-site in the hospital pathology department.

Intervention by international supporters

Pathologists

Lectures and overseas training for the post-graduate course were covered by volunteer pathologists from France, Germany, Japan, Singapore, and Australia. In addition, overseas training was supported by the German and Japanese team. As a result, the first batch of five residents became certified and the number of pathologists in Cambodia rose to nine in 2018. The second batch of postgraduate courses in Pathology will be opened in 2020 contributing the specialists' education to serve to ensure the quantity and quality of the pathologists.

The German and European groups of pathologists introduced the iPath network (*6*) of telemedicine pathology consultation, and a weekly Skype teaching session. The Japanese team has supported regular clinicopathological conferences between pathologists and gynecologists since 2018 to strengthen communication between pathologists and clinicians. In 2017 the Japanese team also invited the existing four Cambodian pathologists to share Japan's education system and the functions of the professional society. From individual and fragmented support to more complementary and integrated ones, meetings to communicate with UHS and its supporters started in 2017 among a small community of pathologists in Cambodia.

Pathology technologists

Although basic pathology equipment and supplies were available, slides were often difficult to read due to inadequate preparation. Therefore, step-by-step training has been offered to technologists for improving the quality of slide preparation by a team of Japanese pathology technologists since 2017. In the beginning, four Cambodian technologists were invited for technical training in Japan, and their skills improved enough to prepare good-quality slides in Japan, where laboratories have no resource constraints on reagents and consumables. As a next step, the technical support mainly focused on two activities: developing Standard Operating Procedures (SOP) for adapting the Cambodians' process of embedding, sectioning, and staining; and developing a self-evaluation form to evaluate slides for quality improvement.

Future perspective responding to the demands of pathology services

Table 2. The number of pathology professionals in Asian, African, and high-income countries

Country	Population (*8*)	GDP per Capita (*8*)	Population per pathologist	Pathologists	Pathology Technologists
Asia					
Cambodia	16,486,542	4,018	2,060,818	8	18
Lao PDR*	7,169,455	7,038	796,606	9	7
Vietnam (*9*)	96,462,106	6,790	263,558	366	NA
Malaysia (*10*)	31,949,777	29,551	85,886	372	NA
Africa (*11*)					
Chad	15,946,876	1,945	7,973,438	2	2
Malawi	18,628,747	1,205	2,069,861	9	2
Senegal	16,296,364	3,458	2,328,052	7	NA
Zambia	17,801,030	4,033	2,966,838	6	6
Zimbabwe	14,645,648	2,434	2,929,130	5	1
High-income countries					
Japan (*12*)	126,860,301	42,067	49,965	2,539	NA
United States (*13*)	329,064,917	59,928	25,630	12,839	NA
United Kingdom (*14*)	67,530,172	44,920	46,766	1,444	NA

Data source: References (*8-14*). *personal communication

Human resources capacity building of pathology professionals with focus not only for pathologists but also pathology technicians

According to the calculation of required human resources for pathological services presented by Sayed *et al*. (*7*), the minimum pathology and laboratory medicine staffing needs are one general pathologist, six pathology technologists, and one pathology assistant for every 50,000-200,000 people, for typical surgical procedure levels: basic trauma surgery, general surgery, emergency obstetrics and gynecology, and surgery by some specialists. With a population of approximately 16 million in Cambodia, 71 more pathologists and 460 more technologists are needed to meet the recommended level.

Table 2 shows the number of pathology professionals in Asian, African, and high-income countries (*8-14*). There is a huge gap between low- and middle- income countries and high-income countries. In Southeast Asian countries, Cambodia and Lao People's Democratic Republic have scarce human resources, similar to African countries. Notably all pathological laboratories are only in the capital city.

Although there is a long way to go to develop human resources to achieve qualified pathological services for surgical diagnosis in Cambodia, the pathology technologist workforce should be prioritized. With improved transportation, if pathology technologists are able to make slides in rural areas, it is possible for pathologists to make a diagnosis in the national hospitals. Furthermore, as it is predicted that telepathology technology could be installed in low- and middle-income countries, if all the specimens were of high quality suitable for telepathology, pathologists could make a diagnosis wherever they are (*15*). Since the post-graduate pathology course has only recently started, qualified pathology technologists are urgently needed for pathology services in Cambodia.

Coordination with international donors and national stakeholders

In a country with scarce human resources like Cambodia, a short-term visitor program is suggested as a common beneficial model, although it has the negative aspects of non-sustainability, intermittency, and dependency on local communities (*11*). Coordination and collaboration among technical supporters would be imperative for identifying how to effectively fill the gap and build a consensus for moving the country toward sustainability. Setting up a communication mechanism among international supporters with national stakeholders would be applicable for other resource-limited countries as well.

Golden triangle for sustainable quality management

Good communication and collaboration among clinicians, technicians, and pathologists would be imperative and could be called the golden triangle to improve the quality of pathology services in Cambodia. Cervical cancer could be an entry point for capacity building of pathology professionals. When the multidisciplinary and multinational supporters communicate thoroughly, we can identify appropriate resources and opportunities to effectively fulfill the gap of pathology services in Cambodia.

No matter how many pathology technicians are trained, it is still important to evaluate the quality of the specimens. Although SOP and the “evaluation sheet” have been introduced in each department to maintain the quality of slides, these schemes must be revised continuously as the quality management cycle in Cambodia.

Strengthening infrastructure

Inadequate infrastructure such as the supply chain of reagents and maintenance of the equipment is often the major problem in laboratories in low-and-middle income countries, but often neglected. While the number of pathological examinations is increasing, an unstable supply of reagents, which does not meet the demand will result in a deteriorated quality of specimens, and clinicians. Human resources for the maintenance of medical equipment and devices can also be essential to keep laboratories functioning because they often use second-hand equipment for pathological examinations, which sometimes need to be repaired. Therefore, in order to achieve an accurate pathological diagnosis, strengthening infrastructure is an essential issue, and needs to be solved among Cambodians in the long run.

In conclusion, rapid economic growth and a changing disease burden has increased the demand for pathology services, with more clinicians expected for improving quality of pathology services in Cambodia. Although there is a long way to go to achieve quality pathological services for surgical diagnosis in Cambodia, coordination among international partners is essential, as is empowerment of the golden triangle among pathologists, technicians and clinicians. In addition, continuous quality management plays an important role to deliver sustainable high-quality pathological services to provide a higher level of care to local citizens.

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COMMUNICATION

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Definition of perforator flap: what does a "perforator" perforate?

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Abstract: Perforator flap concept plays an important role in reconstructive surgery, because it allows less invasive and more complex reconstruction by preserving major vessels and muscles with intramuscular vessel dissection. Originally "perforator" represents vessel perforating the muscle, then vessel perforating the deep fascia regardless of muscle perforation. With technical progress in reconstructive microsurgery, the previous definition becomes inappropriate for least invasive flaps, only requiring intra-adiposal vessel dissection, such as superficial circumflex iliac artery perforator flap. Based on our experience of various least invasive flap reconstructive surgeries, a new concept for perforator flap has been developed. The new definition of perforator is a vessel perforating an envelope of a targeted tissue to be transferred; the superficial fascia for skin, the periosteum for bone, the perineurium for nerve, and the deep fascia for muscle. According to the new definition, all flaps can be precisely classified based on the corresponding "perforator".

***Keywords*:** Perforator, supermicrosurgery, reconstruction, microsurgery, flap, surgery

Introduction

With clinical application of reconstructive microsurgery, various tissues can be transferred for covering defects and for reconstructing various functions. Among various reconstructions, soft tissue (skin and fat) reconstruction is the most common (*1-3*). Myocutaneous (MC) flap, consisting of the vascular pedicle, the muscle, the deep fascia, the fat, and the skin, was commonly used to reconstruct a soft tissue defect in the beginning era of reconstructive microsurgery. However, MC flap sacrifices major vessel and the muscle. With advancement of anatomical study on microvasculature of soft tissue, fasciocutaneous (FC) flap and perforator flap were developed as less invasive reconstructive methods. FC flap consists of a vascular pedicle, the deep fascia and the overlying soft tissue, whereas perforator flap consists of a pedicle and soft tissue.

Perforator flap

With clinical application of reconstructive microsurgery, various tissues can be transferred as perforator flaps such as deep inferior epigastric artery perforator (DIEP) flap, anterolateral thigh (ALT) perforator flap, and thoracodorsal artery perforator flap (*3-5*). Since perforator flap preserves muscle function, it has become a choice of soft tissue reconstructive methods for most experienced microsurgeons. DIEP flap has been reported as the first perforator flap, which contains a muscle perforator running through the rectus abdominis muscle. Based on the first case of perforator flap using the DIEP flap, perforator was defined as a skin flap without the deep fascia or the muscle based on a muscle perforator requiring intramuscular pedicle vessel dissection (*2,3,5*). The definition seemed feasible at that time, because intramuscular dissection is technically more demanding, and preservation of the muscle function allows less invasive reconstruction.

With popularization of ALT perforator flap, the definition of perforator flap has been changed to include septocutaneous perforator as a vascular pedicle of perforator flap (*3,4,6*). ALT flap has anatomical variations in vascular pedicle; some ALT flap is based on a muscle perforator, and others on a septocutaneous perforator, which runs between the muscles. Dissection of septocutaneous perforator is easier than that of muscle perforator, because intramuscular dissection is not required. Though, clinical usefulness of ALT flap based on a septocutaneous perforator is the same as one based on a muscle perforator. Therefore, the definition of perforator flap was changed to a skin flap based on a vessel perforating the deep fascia (muscle perforator or septocutaneous perforator), and a major advantage of perforator flap was characterized as less invasively elevated flap with preservation of muscle function (*3,4*).

Emergence of new various perforator flaps

As microvascular anatomy was further elucidated,

Table 1. The new definition of perforator and corresponding perforated envelope

Target tissue	Perforator	Envelope
skin	perforator to the skin (skin perforator)	superficial fascia
nerve	perforator to the nerve (nerve perforator)	perineurium
lymph node	perforator to the node (node perforator)	lymph node capsule
fascia	perforator to the fascia (fascia perforator)	peri-fascial areolar tissue
muscle	perforator to the muscle (muscle perforator)	deep fascia
tendon	perforator to the tendon (tendon perforator)	paratenon
bone	perforator to the bone (bone perforator)	periosteum

various flaps were reported as perforator flaps, such as chimeric perforator flap with muscle, and true perforator flap without dissection of pedicle perforating the deep fascia (*7-10*). Chimeric flap consists of multiple vascular pedicle branch-based various tissues such as skin, fat, fascia, muscle, nerve, and bone, allowing three-dimensional complex reconstruction. For example, chimeric ALT flap, one of the most popular chimeric flaps, consists of a skin paddle and the vastus lateralis muscle based on separate pedicle branches from one larger pedicle. True perforator flap is elevated above the deep fascia, which does not include muscle or septocutaneous perforator. These new perforator flaps have advantages of less invasiveness and clinical usability similar to conventional perforator flaps, but do not meet the definition of perforator flap. A new definition is warranted for emerging useful flaps with advantages of less invasive tailor-made reconstruction.

The new definition of perforator flap

The most important characteristics of "perforator flap" are that it consists of selectively elevated target tissues and allows three-dimensionally insets of various tissue reconstruction (*6,7,10*). Dissection course or technique is not essential to define "perforator flap". Since all the tissue to be transferred as flaps have envelope surrounding the tissue, it seems optimal to define a "perforator" as a vessel perforating an envelope of a target tissue to be transferred. Envelopes of various tissues can be classified as follows; the superficial fascia for the skin, the deep fascia for the muscle, the periosteum for the bone, the paratenon for the tendon, and the perineurium for the nerve (Table 1). When a target tissue (flap) is elevated with the intention to selectively include a "perforator" perforating the corresponding envelope of the target tissue, it can be classified as "perforator flap" regardless of dissection technique or course.

Using the new definition, all flaps can be easily classified and understood correctly. Superficial circumflex iliac artery (SCIA) perforator (SCIP) flap is becoming one of the most popular flaps recently, and has two patterns of vascular pedicle; the superficial branch and the deep branch of the SCIA. The superficial branch of the SCIA runs in the fat tissue above the deep fascia, and the deep branch runs through the sartorius muscle and the deep fascia to the skin and various tissues. When a skin flap is raised based on the deep branch of the SCIA, it can also be defined as a perforator flap according to the old definition, whereas a skin flap based on the superficial branch of the SCIA cannot be defined as a perforator flap according to the old definition (*7,10*). The new definition can classify skin flaps based both on the superficial and deep branch of the SCIAs regardless of their pedicle courses. Chimeric flaps or various flaps using tissues other than the skin can also be classified according to the new definition.

Conclusion

By defining "perforator" as a vessel perforating an envelope of a target tissue to be transferred, all emerging useful flaps such as super-thin flap and chimeric flap can be classified appropriately. The new definition allows better understanding of these flaps, which is important for microsurgeons to perform less invasive sophisticated reconstructions.

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Brief Reports definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references. Brief Reports should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results and Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate.

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Policy Forum articles discuss research and policy issues in areas related to global health and medicine, such as public health, medical care, and social science that may address governmental issues at district, national, and international levels of discourse. Policy Forum articles should not exceed 3,000 words in length (excluding references), have no more than 30 references, and have up to 5 figures and/or tables.

Communications are short, timely pieces that spotlight new research findings or policy issues of interest to the field of global health and medical practice that are of immediate importance. Depending on their content, Communications will be published as "Perspectives," "Comments," or "Correspondence". Communications should not exceed 2,000 words in length (excluding references), have no more than 20 references, and have up to 2 figures and/or tables.

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Editorials are short, invited opinion pieces that discuss an issue of immediate importance to the fields of global health, medical practice, and basic science oriented for clinical application. Editorials should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

Letters are articles that provide readers with an opportunity to respond to an article published in *Global Health & Medicine* within the previous two months or to raise issues of general interest to our readers. Letters should provide new information or insights. If appropriate, letters are sent to the authors of the article in question for a response. Letters should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

News articles should report the latest events in health sciences and medical research from around the world. News should not exceed 800 words in length (excluding references), have no more than 5 references, and have one figure or table.

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Manuscripts should be written in clear, grammatically correct English and submitted as a Microsoft Word file in a single-column format. Manuscripts must be paginated and typed in 12-point Times New Roman font with 24-point line spacing. Please do not embed figures in the text. Technical terms should be defined. Abbreviations should be used as little as possible and should be explained at first mention unless the term is a well-known abbreviation (*e.g.* DNA). Single words should not be abbreviated. Please include page numbers in your submitted file. We also encourage use of line numbers.

The submission to *Global Health & Medicine* should include:

1. Cover letter
2. Main manuscript
3. Figures
4. Supplementary Data, if appropriate

The main manuscripts should be assembled in the following order:

1. Title page
2. Abstract
3. Main Text
4. Acknowledgments
5. References
6. Tables
7. Figure Legend
8. List of Supplementary Data, if appropriate

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Please provide all figures as separate files in an acceptable format (TIFF or JPEG). Supplementary Data should also be submitted as a single separate file in Microsoft Word format.

An abstract is necessary for all types of articles. An Original Article should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate. A Brief Report contains the same sections as an Original Article, but the Results and Discussion sections should be combined. For manuscripts that are Reviews, Policy Forum articles, Communications, Editorials, Letters, or News, subheadings should be used for increased clarity.

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Title page: The title page must include 1) the title of the paper (Please note the title should be short, informative, and contain the major key words); 2) full name(s) and affiliation(s) of the author(s), 3) abbreviated names of the author(s), 4) full name, mailing address, telephone/fax numbers, and e-mail address of the corresponding author; and 5) conflicts of interest (if you have an actual or potential conflict of interest to disclose, it must be included as a footnote on the title page of the manuscript; if no conflict of interest exists for each author, please state “There is no conflict of interest to disclose”).

Abstract: The abstract should briefly state the purpose of the study, methods, main findings, and conclusions. For articles that are Original Articles, Brief Reports, Reviews, or Policy Forum articles, a one-paragraph abstract consisting of no more than 250 words must be included in the manuscript. For Communications, Editorials, Letters, and News, a one-paragraph brief summary of the main

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content in 150 words or less should be included in the manuscript. Abbreviations must be kept to a minimum and non-standard abbreviations should be explained in brackets at first mention. References should be avoided in the abstract. Three to six key words or phrases that do not occur in the title should be included on the Abstract page.

Introduction: The introduction should provide sufficient background information to make the article intelligible to readers in other disciplines and sufficient context clarifying the significance of the experimental findings.

Materials and Methods: The description should be brief but with sufficient detail to enable others to reproduce the experiments. Procedures that have been published previously should not be described in detail but appropriate references should simply be cited. Only new and significant modifications of previously published procedures require complete description. Names of products and manufacturers with their locations (city and state/country) should be given and sources of animals and cell lines should always be indicated. All clinical investigations must have been conducted in accordance with Declaration of Helsinki principles. All human and animal studies must have been approved by the appropriate institutional review board(s) and a specific declaration of approval must be made within this section.

Results: The description of the experimental results should be succinct but in sufficient detail to allow the experiments to be analyzed and interpreted by an independent reader. If necessary, subheadings may be used for an orderly presentation. Two levels of subheadings may be used if warranted, please distinguish them clearly. All Figures and Tables should be cited in order, including those in the Supplementary Data.

Discussion: The data should be interpreted concisely without repeating material already presented in the Results section. Speculation is permissible, but it must be well-founded, and discussion of the wider implications of the findings is encouraged. Conclusions derived from the study should be included in this section.

Acknowledgments: All funding sources should be credited in the Acknowledgments section. In addition, people who contributed to the work but who do not meet the criteria for authors should be listed along with their contributions.

References: References should be numbered in the order in which they appear in the text. Two references are cited separated by a comma, with no space, for example (*1*,*2*). Three or more consecutive references are given as a range with an en rule, for example (*1*-*3*). Citing of unpublished results, personal communications, conference abstracts, and theses in the reference list is not recommended but these sources may be mentioned in the text. In the reference list, cite the names of all authors when there are fifteen or fewer authors; if there are sixteen or more authors, list the first three followed by *et al*. Names of journals should be abbreviated in the style used in PubMed. Authors are responsible for the accuracy of the references.

Examples are given below:

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Example 2 (Sample journal reference with more than 15 authors):
Darby S, Hill D, Auvinen A, *et al*. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005; 330:223.

Example 3 (Sample book reference):
Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: Post-traumatic Stress Disorder, Diagnosis, Management and Treatment (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

Example 4 (Sample web page reference):
World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. *http://www.who.int/whr/2008/whr08_en.pdf* (accessed March 20, 2019).

Tables: All tables should be prepared in Microsoft Word and should be arranged at the end of the manuscript after the References section. Please note that tables should not be in image format. All tables should have a concise title and should be numbered consecutively with Arabic numerals. Every vertical column should have a heading, consisting of a title with the unit of measure in parentheses. If necessary, additional information should be given below the table.

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name within the legend.

Figure Preparation: All figures should be clear and cited in numerical order in the text. Figures must fit in a one- or two-column format on the journal page: 8.3 cm (3.3 in.) wide for a single column, 17.3 cm (6.8 in.) wide for a double column; maximum height: 24.0 cm (9.5 in.). Please make sure that the symbols and numbers appearing in the figures are clear. Please make sure that artwork files are in an acceptable format (TIFF or JPEG) at minimum resolution (600 dpi for illustrations, graphs, and annotated artwork, and 300 dpi for micrographs and photographs). Please provide all figures as separate files. Please note that low-resolution images are one of the leading causes of article resubmission and scheduling delays.

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(*As of October 2019*)

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