

## Report on “Radiation Disaster Recovery Studies”

Course Radiation Disaster Medicine Course

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### ○Regarding “Radiation Disaster Recovery Studies”

In March 2011, The Great East Japan Earthquake stroke Japan so badly, which was considered the worst natural disaster ever in history. It has triggered a tsunami, and subsequently, causing severe damages due to the explosion of the Fukushima Nuclear Power Plant. It took the country decades so far to completely sweep away the radioactive contamination. This nuclear disaster alerted the whole world and arose the awareness about the shortcoming of radiation protection, crisis management, and safety control for nuclear power, especially in the case of unpredictable factors such as a natural disaster. In fact, right after the strategic nuclear accident, massive efforts have been undertaken, not only the Japanese government, the Universities and Institutes, but also a huge number of global experts have conducted numerous researches and experiments together with Japanese people in order to promptly and adequately solve the aftermaths of this nuclear crisis.

Radiation disasters adversely affected various aspects of life, including human health, environment, and society. Exposure to ionizing radiation has been known to result in short-term health effects (e.g. acute radiation syndrome, including nausea, vomit, diarrhea, hemorrhage, and hair loss) and long-term health effects (e.g., leukemia, cancer, cardiovascular disease, birth abnormalities, and genetic defects). Besides, the public health was placed at risk not only because of the biological effects of ionizing radiation itself but also because of the serious mental illness due to the anxiety about their future, the stigma induced by inaccurate information, and the inappropriate risk communication. For a long while, studies on the health effects of radiation primarily concentrated on natural science while neglecting its effects on psychosocial aspects. The radiation dose delivered to the public from the Fukushima accident was reported to be low and causing minor effects on human health, however, various issues unrelated to radiation have emerged, for example, the evacuation and long-term displacement of the vulnerable population, and psychological and social issues (1-3). Affected residents in Fukushima may face various mental health issues, for example, posttraumatic

responses, psychological effects on family members, depression and suicide, and radiation stigma and self-stigma (4). The elderly have been amongst the most vulnerable population in the society, with substantial risks of general diseases and mental health illness, resulting in an increased risk of mortality, especially during the evacuation process or the life in the temporary house with inadequate living support and family assistance. Besides, various other social issues have also been observed, for instance, the public criticism, discrimination and adverse psychological effects in emergency and recovery workers, the discordance in families and communities, or the lifestyle-related problems (2).

To solve the complicated issues from Fukushima nuclear accident, as well as to prevent a similar crisis in the future, multidisciplinary approaches should be considered and implemented, for examples, the protection for emergency and recovery workers from radiation and medical hazards, protection for citizens from radiation exposure, decision making for large-scale evacuation, evacuation plan for hospitals and nursing facilities, and psychological responses during nuclear disasters. In terms of preparedness for radiation emergencies, a "decision framework" with scientific expertise is mandatory, with the participation of radiation protection, medical support, social sciences, and communication experts (5). Besides, the emerging issue of a "super-aging" Japanese society places the country into challenges with regards to economic issues, pension, health service, and long-term care systems, prompted the need for community-based support systems that accommodate and protect them from disasters (6, 7).

Nowadays, in line with the rapid growth of the economy, the high demand for power supply is noticeable. It is no doubt about the relatively considerable advantages of developing nuclear power supply such as sustainable energy, mitigation of carbon dioxide omission, or cost reduction. However, the priceless lesson learned from the Fukushima Nuclear accident must be widely rule-making for our whole world, especially for the incoming newly construction of nuclear power plants. Also, the valuable lessons about stigma and risk communication from this disaster have been applicable not only to radiation accidents but also to the other crisis, for instance, the ongoing global pandemic of coronavirus disease 2019 (COVID-19) (8).

During the time I participated in the Phoenix Leading Education Program, I gained the knowledge and skills in radiation disaster recovery studies through engaging in various lectures, seminars, forums, and coursework with an interdisciplinary perspective, including radiation disaster medicine, radioactive environmental protection, and radioactivity social recovery courses. My doctoral thesis focused on the elderly population living in nursing homes, the essentially vulnerable population in ordinary life and even become more fragile in the case of a disaster. The elderly people needing nursing care and inpatients people at hospitals were subjected to serious effects from evacuation and

relocation, with the mortality rate were reported to increase 3 times within 3 months after the evacuation in comparison with this rate before the accident (2). Especially, the major cause of death among these patients was pneumonia. Pneumonia is a major cause of mortality in Japan, mostly occurs in the elderly population. The elderly people are at high risk of Nursing- and Healthcare-associated Pneumonia (NHCAP) and aspiration pneumonia (9). Some pathogens that frequently isolated from NHCAP include Pneumococcus, *Staphylococcus aureus*, Gram-negative enteric bacteria, and *Haemophilis influenzae*, etc. However, in patients who had the risk factors for involvement by drug-resistant pathogens, some additional pathogens may be involved, for examples, *Pseudomonas aeruginosa*, *Methicillin-resistant S. aureus*, *Acinetobacter*, and ESBL-producing enteric bacteria. My study was carried out to survey the prevalence of drug-resistance gram-negative bacteria in the oral cavity of the elderly living in a nursing home, the risk factors for colonization and the molecular epidemiology of these pathogens. The results from my study suggested the importance of oral health care in the elderly and enhanced the roles of health care staff in infection control and prevention of the dissemination of resistant bacteria within the health care facility.

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○Title of Doctoral Thesis

Oral colonisation by antimicrobial-resistant Gram-negative bacteria among long-term care facility residents: prevalence, risk factors, and molecular epidemiology

(長期療養型施設入所者における口腔内薬剤耐性 グラム陰性菌の保有、リスク因子及び分子疫学の検討)

○Summary of Doctoral Thesis

**Background:** Residents of long-term care facilities (LTCFs) have been widely considered as reservoirs of antimicrobial-resistant bacteria (ARB), yet the oral colonization of those pathogens in this population, which potentially leads to aspiration pneumonia, remains unclear. This study aimed to investigate the prevalence, phenotypic characteristics, and molecular epidemiology of antimicrobial-resistant (AMR) Gram-negative bacteria in the oral cavity of LTCF residents, and to analyse the risk factors for such carriers.

**Methods:** Ninety-eight residents of an LTCF in Hiroshima City, aged between 55 and 101 years, were included in this study. Oropharyngeal swabs were collected and plated on screening media for ESBL-producing (CHROMagar™ ESBL) and carbapenem-resistant bacteria (CHROMagar™ mSuperCARBA). Isolates were identified and tested for antibiotic susceptibility using the Vitek-2 system and results were interpreted according to the Clinical Laboratory Standards Institute M100-S25. Biofilm formation was tested *in vitro*. Identification of epidemic clones was pre-determined by PCR; AMR genes, sequence types (ST), and whole-genome comparisons were conducted using whole-genome sequences (WGS). Demographic data and clinical characterisations were collected and risk factors analysed.

**Results and Discussion:** Fifty-four isolates from 37 patients (38%) were detected as ARB using screening agar plates and primarily belonged to three main genera: *Acinetobacter* spp. (35%), *Enterobacteriaceae* spp. (22%), and *Pseudomonas* spp. (19%). Among these 54 ARBs, 46 isolates from 32 patients (33%) were confirmed as having reduced susceptibility to one or more tested antimicrobial agents, 29 isolates from 23 patients (23%) were confirmed as cephalosporin-resistant ARB, and 13 isolates from 13 patients (13%) were confirmed as carbapenem-resistant ARB by Vitek-2.

All *Escherichia coli* isolates were resistant to various  $\beta$ -lactams and ciprofloxacin. WGS indicated these isolates belonged to ST131, serotype O25:H4, fimH30, and carried multiple plasmid-mediated AMR genes. In terms of  $\beta$ -lactam resistance genes, 3 *E. coli* isolates were found to carry blaCTX-M-

27, while 1 other *E. coli* isolate carried blaCTX-M-14 and blaTEM-1B. Besides, these isolates also carried mutations in DNA sequences of the chromosomal quinolone resistance-determining regions of *gyrA* and *parC*, resulting in fluoroquinolone resistance.

One *Pseudomonas aeruginosa* isolate showed exceptional resistance to all  $\beta$ -lactams including carbapenems, aminoglycosides, and a new quinolone, showing a multidrug-resistant *P. aeruginosa* (MDRP) phenotype and remarkable biofilm formation. WGS of this isolate indicated that it belongs to ST235 and carries type I integron with multiple resistance genes, metallo- $\beta$ -lactamase blaIMP-1, aminoglycoside-resistance genes aac(6')-Iae and aadA1, and sulfamethoxazole-resistance gene *sul1*. Genome sequences comparison showed this isolate had a close clonal origin with the epidemic ST235 MDRP prevalent in Hiroshima region since 2005.

One *Acinetobacter ursingii* isolate displayed extensive resistance to various  $\beta$ -lactams due to multiple acquired resistance genes. *A. ursingii* is an uncommon opportunistic pathogen; sporadic cases involving serious bloodstream infections, in patients that are either immunocompromised or immunocompetent, have been reported. Our *A. ursingii* isolate carried some AMR genes identified with the ones carried by the isolates reported from the Netherland, for example, blaCARB-2, aac(6')Ib-cr, mph(E), msr(E), *sul1*, and tet(39).

Six *A. baumannii* isolates presented identical molecular characteristics and revealed more biofilm production than the others, strongly suggesting their clonal lineage. WGS data revealed these isolates belonged to the same sequence type, ST130. Besides the detection of ARB carrying multiple AMR genes, the presence of isolates with low minimum inhibitory concentration (MIC) based on biochemical tests and no acquired AMR genes while still growing on screening media plates, and high biofilm-formation ability, was also a noteworthy finding. This inconsistency, in fact, reflects the difference in the AMR phenotype between a planktonic lifestyle of bacteria in MIC biochemical tests and biofilm lifestyle on agar plates, where bacteria are encased in an extracellular matrix that provides them tolerance and resistance mechanisms to combat antimicrobial challenges. The growth of bacteria in the presence of an antimicrobial agent, despite their low MICs by Vitek-2 or the lack of AMR genes, may suggest their growability inside the human body with the presence of that antimicrobial agent. From the viewpoint of hospital infection control, the mobile AMR genes or plasmids are significant concerns given their horizontal gene transfer from organism to organism within the health-care setting. However, from the viewpoint of clinical implications, both the AMR gene-carriers and biofilm-producers are important for their resistance phenotype inside the human body, either through the enzyme-mediated mechanism or the biofilm-based mechanism or through a combination of both. Strong biofilm-producing *A. baumannii* isolates from this LTCF should be

regarded as a potential risk even though it lacks AMR genes.

Two risk factors, strokes (cerebral infarction or cerebral haemorrhage) (OR 3.46, 95 % CI 1.38-8.70,  $p = 0.007$ ) and percutaneous endoscopic gastrostomy tubes (PEG tubes) (Fisher's exact test,  $p = 0.002$ ), indicated the existence of ARB in the oral cavity. Stroke was significantly associated with disability in the elderly, requiring substantial assistance from care-givers with regard to dressing, toileting, eating, and other daily activities. The greater the advanced disability patients have, the more assistance and interaction with care-workers and medical-device operators are required, consequently facilitating the propagation of such microorganisms. In patients who were fed with PEG tubes, pathogenic colonisation inside the oral cavity might be promoted by a reduction in mastication activity and salivary secretion.

**Conclusions:** Our study detected a high prevalence of AMR Gram-negative bacteria, ESBL-producing and carbapenem-resistant pathogens relevant to aspiration pneumonia, which carried the resistance genes on mobile elements such as plasmids or integrons or in the chromosome and/or are strong biofilm producers, in the oral cavity of LTCF residents. Professional oral care methods, such as brushing teeth, swabbing the mucosa, cleaning dentures, using mouthwash, having dental check-ups by professional dentists, improving the staff practices for oral care, and promoting oral hygiene, should be thoroughly considered and implemented. Health care workers involved in oral care should perceive the existence of such ARB and acquire the skills for infection control and prevention to diminish the dissemination of ARB or the mobile resistance elements in LTCFs. Last but not least, with the rapid ageing of the Japanese society, surveillance initiatives and regional and national projects for infection control should not put aside the significant role of LTCFs or nursing homes in the healthcare network.

○Other theses published in academic research journals

- Title of academic research journals (Impact Factor, Peer Review)

Antimicrobial Resistance and Infection Control; 2020, 9(1):45. (2-year Impact Factor: 3.594, Peer Review)

- Title of thesis

Oral colonisation by antimicrobial-resistant Gram-negative bacteria among long-term care facility residents: prevalence, risk factors, and molecular epidemiology

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