Provisional Translation

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Ranking of the Importance of Antimicrobials against Bacteria which affect Human Health through Food Commodities

The use of antimicrobials in feed additive and veterinary drugs in food producing animals is anticipated to lead to selection of antimicrobial-resistant bacteria. As a basic material to be used for risk assessment of foodborne antimicrobial-resistant bacteria, FSCJ introduced a ranking of antimicrobials according to their importance in treatment of human infection with antimicrobial-resistant bacteria through food commodities according to the "Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Producing Animals" (FSCJ, September 30, 2004) (herein after referred to as the 'Assessment Guideline')

The ranking was developed, based on the reference materials and documents submitted by the Ministry of Agriculture, Forestry and Fisheries of Japan, to be used in the consequence assessment which is specified in Article 2-3 of Chapter 2 of the Assessment Guideline. Factors to be considered in the consequence assessment are human infectious diseases possibly caused by antimicrobial-resistant bacteria identified as a "hazard" as well as the importance of human antibiotics in clinical treatment of human infections. For instance, the following items will be considered in the consequence assessment considers the followings: 1) the availability of human antibiotics for the treatment of human infection, which is caused by foodborne antimicrobial-resistant bacteria, selected by the use of veterinary antimicrobial; 2) the importance of the antimicrobials in human medical practices.

Therefore, FSCJ ranked human antimicrobials commonly used in Japan considering their relative importance in medical field. The ranking focuses on risk assessment on foodborne antimicrobial-resistant bacteria and should not be considered as an absolute scale of importance in human medical practices. In addition, FSCJ will conduct the risk assessment comprehensively using the rank of antimicrobials and relevant scientific information indicated by the Assessment Guideline.

1. Points to be considered for the ranking

FSCJ considered that it would be appropriate to establish a criteria for the degree of importance of human antibiotics. Accordingly, based on various treatment manuals developed by The

Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases, etc., FSCJ collected and analyzed the following information on human antimicrobials: the antimicrobial activity and biological characteristics of its target pathogens, pharmacokinetics in humans, the amount and frequency of the use, administration route and dosage, and microbiological information including mechanisms of emergence of antimicrobial resistance. The emergence of antimicrobial-resistant bacteria derived from food-producing animals is an issue of global concern, and therefore, FSCJ also collected relevant information from international organizations such as OIE and WHO in order to ensure international consistency.

In order to rank of human antimicrobials used in Japan based on the importance in human medicine, the following four points should be considered for each antimicrobial.

- The availability of alternative antimicrobials for human therapy on the occasion of emergence of antimicrobial-resistant bacteria.
- The antimicrobial activity and its spectrum of the antimicrobial against target pathogens of antimicrobial treatment for human diseases.
- The severity of human diseases caused by target pathogens of antimicrobial treatment
- The mechanism by which bacteria develop resistance to the antimicrobial.

FSCJ considered that a concise and explicit criteria for the ranking can be set by considering primarily on “the availability of alternative antimicrobials for human therapy at the emergence of antimicrobial-resistant bacteria” among the four points. The remaining three points should be also comprehensively considered in ranking human antimicrobials.

FSCJ, therefore, developed the following criteria applicable to the ranking of antimicrobials. Based on the criteria, antimicrobials (antimicrobial classes), used for bacteria which affect human health through food commodities, were ranked according to their importance in human therapy.

2. Criteria of the importance for ranking antimicrobials

I. Critically important

The antimicrobial is used as the sole medicine for treatment of a specific human disease, or few alternative antimicrobials are available.

II. Highly important

For treatment of human infectious diseases caused by the antimicrobial-resistant bacteria, alternative antimicrobials are available, but the number of the alternatives is extremely limited compared with that for antimicrobials ranked as III.

III. Important

For treatment of human infectious diseases caused by the antimicrobial-resistant bacteria, alternative antimicrobials are available sufficiently among the same or different classes of the antimicrobial.

3. Ranking of antimicrobials used for bacteria which affect human health through food commodities

Antimicrobials ranked as I

- Macrolides with 14 and 15 membered ring structures (except for erythromycin)
- Oxazolidinones
- Arbekacin of kanamycins
- Carbapenems
- Glycopeptide antibiotics
- Glycylcyclines
- Anti-TB drugs
- Third and fourth generation cephalosporins ※and oxacephems
- Colistin and polymixin B
- Fluoroquinolones
- Mupirocin
- Monobactams
- Lipopeptides
- New antimicrobials which possess antimicrobial activity against pathogenic bacteria causing serious infectious diseases

Antimicrobials ranked as II

- Antimicrobials which contain β-lactamase inhibiting agents
- Kanamycins of which the antimicrobial activity against antimicrobial-resistant bacteria has been improved (except for arbekacin), gentamicins, sisomicins and streptomycins
- Chloramphenicols
- Streptoglamins
- Spectinomycins
- Sulfamethoxazole/trimethoprim
- Second generation cephalosporins (except for oxacephems)
- Tetracyclines of which the duration of activity has been improved

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* Cephalosporin antibiotics were classified based on antimicrobial activity against common gram negative bacteria. Among these, the cephalosporins which show antimicrobial activity against *Pseudomonas aeruginosa* and gram positive bacteria were categorized as the fourth generation.

- Penicillins
- Penems
- Fosfomycin
- Lincomycins
- Erythromycin

Antimicrobials ranked as III

- Macrolides with a 16 membered ring structure
- Astromicins, fradiomycins, and wild type kanamycins
- Quinolones (except for fluoroquinolones)
- Sulfonamides
- First generation cephalosporins
- Wild type tetracyclines
- Nitroimidazoles
- Fusidic acid
- Polypeptide antibiotics (except for colistin and polymixin B)

4. Revision of the criteria and ranking of antimicrobials

FSCJ will collect further information on antimicrobial-resistant bacteria and antimicrobials including distribution of antimicrobial-resistant bacteria, the change in the level of resistance, and the development of new antimicrobials. Based on the latest information, the criteria and ranking will be revised when needed.

5. Major References

1) Mizushima Y., Today's Drug Therapy in 2004, Nankodo, (2004).
2) The Japanese Association for Infectious Diseases, Japanese Society of Chemotherapy, Guidelines for antimicrobial use, Kyowa Kikaku, (2004).
3) Japan Antibiotics Research Association, Yagisawa M, A table of new “antimicrobials”, Appendix of Medicament News No. 1806 issued on July 25 2004, Life Science, (2004).
4) Totsuka K., Hashimoto M., The Sanford Guide to Antimicrobial Therapy 2005 (35th Edition), Life Science Publishing, (2005).
5) Arakawa Y., Classification of aminoglycoside antibiotics, the material for the joint meeting of Veterinary Medicine (No. 36) and Feed / Fertilizer (No. 14) (WG regarding antimicrobial resistant microbes), (2005).
6) Ike Y., Classification of cephem antibiotic generations, the material for the joint meeting of Veterinary Medicine (No. 36) and Feed / Fertilizer (No. 14) (WG regarding antimicrobial resistant microbes), (2005).
7) Ike Y., Guide to Antimicrobial Therapy of Gunma University Hospital, Department of Bacteriology and Bacterial Infection Control, Gunma University Graduate School of

Medicine, (1996).
8) Yoshida I., Sugimori G., Higashiyama I., Kimura Y., Yamano Y., Surveillance of susceptibility of clinical isolates of various bacterial species to antibacterial agents - Antimicrobial activity against gram-negative bacteria isolated in 2000 -, Japanese Journal of Chemotherapy, Vol. 51, No. 4,(2003)
9) Joel G. Hardman, *et al*, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, McGraw-Hill, (2001).
10) Wolfgang K. Joklik, Hilda P. Willett *et al*, Zinsser Microbiology, 20th edition, Prentice-Hall International Inc, (1992).
11) Mingeot-Leclercq MP, *et al*., Aminoglycosides: activity and resistance, Antimicrob Agents Chemother, 43, 727-737, (1999).
12) Shaw K. J., *et al*, Molecular genetics of aminoglycoside resistance genes and familial relationships of the aminoglycoside-modifying enzymes, Microbiol Rev 57, 138-163, (1993).
13) Poole K., Resistance in *Pseudomonas aeruginosa*, Antimicrob Agents Chemother, 49, 479-87, (2005).
14) Chow J. W., Aminoglycoside resistance in enterococci, Clin Infect Dis, 31, 586-589, (2000).
15) Ida T., Okamoto R., Shimauchi C., Okubo T., Kuga A., Inoue M., Identification of aminoglycoside-modifying enzymes by susceptibility testing: epidemiology of methicillin-resistant *Staphylococcus aureus* in Japan, J Clin Microbiol, 39, 3115-3121, (2001).
16) Galimand M., Sabtcheva S., Courvalin P., Lambert T., Worldwide disseminated *armA* aminoglycoside resistance methylase gene is borne by composite transposon Tn1548, Antimicrob Agents Chemother, 49, 2949-2953, (2005).
17) Yamane K., Wachino J., Doi Y., Kurokawa H., Arakawa Y., Global spread of multiple aminoglycoside resistance genes, Emerg Infect Dis, 11, 951-953, (2005).
18) Yan J. J., Wu J. J., Ko W. C., Tsai S. H., Chuang C. L., Wu H. M., Lu Y. J., Li J. D., Plasmid-mediated 16S rRNA methylases conferring high-level aminoglycoside resistance in *Escherichia coli* and *Klebsiella pneumoniae* isolates from two Taiwanese hospitals, J Antimicrob Chemother, 54, 1007-1012, (2004).
19) Yamane K., Doi Y., Yokoyama K., Yagi T., Kurokawa H., Shibata N., Shibayama K., Kato H., Arakawa Y., Genetic environments of the rmtA gene in *Pseudomonas aeruginosa* clinical isolates, Antimicrob Agents Chemother, 48, 2069-2074, (2004).
20) Doi Y., Yokoyama K., Yamane K., Wachino J., Shibata N., Yagi T., Shibayama K., Kato H, Arakawa Y., Plasmid-mediated 16S rRNA methylase in *Serratia marcescens* conferring high-level resistance to aminoglycosides, Antimicrob Agents Chemother, 48, 491-496, (2004).
21) Galimand M., Courvalin P., Lambert T., Plasmid-mediated high-level resistance to aminoglycosides in Enterobacteriaceae due to 16S rRNA methylation, Antimicrob Agents Chemother, 47, 2565-2571, (2003).

22) Yokoyama K., Doi Y., Yamane K., Kurokawa H., Shibata N., Shibayama K., Yagi T., Kato H., Arakawa Y., Acquisition of 16S rRNA methylase gene in *Pseudomonas aeruginosa*, Lancet, 362, 1888-1893, (2003).
23) U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine, Guidance for industry # 152, (2003).
24) EAGAR, Importance Rating and Summary of Antibiotic Use in Humans in Australia Draft Veterinary Drugs Directorate Guidance for Industry Preparation of Veterinary New Drugs Submissions: Human Safety Requirements
25) Health Canada, Categorization of antimicrobial drugs besed on importance in human medicine, (2009).
26) WHO, Critically Important Antimicrobials for Human Medicine 3rd rivision, (2011).
27) Committee drafting practical guide for appropriate use of colistin, Practical guide for appropriate use of colistin, Japanese Journal of Chemotherapy, Vol. 60, No. 4, (2012)
28) Andre Bryskier (ed.). Antimicrobial Agents: Antibacterials and Antifungals. ASM Press, Washington, (2005).
29) Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard− Eleventh Edition. M02-A11, Vol. 32, No.1. Clinical and Laboratory Standards Institute, Wayne, PA, (2012).
30) Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty Second Informational Supplement. M100-S22, Vol.32, No.3. Clinical and Laboratory Standards Institute, Wayne, PA, (2012).