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Guideline

Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition

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To determine criteria for objective evaluation of the efficacy of antimicrobial agents for urogenital infections in Japan, researchers involved in urinary tract infections (UTIs) gathered to establish the first criteria, “Criteria for the clinical evaluation of drug efficacy in UTI”, in the 1970s, and then the criteria were revised until the third edition was reported. Meanwhile, guidelines such as those of the IDSA and FDA in the United States or the European guidelines providing the criteria for clinical evaluation of drug efficacy, etc., were established, and international harmonization along with globalization of the development of antimicrobial agents became necessary. To meet this trend and use the data accumulated in Japan interchangeably with these criteria, the committee on clinical evaluation for antimicrobial agents against UTI in Japanese Society of Chemotherapy discussed the criteria and established the “Criteria for the clinical evaluation of drug efficacy in UTI, 4th edition, interim proposal and supplement” in 1996.

Thereafter, international joint development, extrapolation of foreign data, and the introduction of bridging studies have taken place, and the need for further international harmonization has increased. However, because there were many differences between Western countries and Japan in the pathogenesis or diagnosis of UTIs and the concept of the assessments of clinical evaluations and clinical cures, many points relating to international harmonization had to be discussed. Therefore, a committee to review criteria for the clinical evaluation of drug efficacy in UTI of the Japanese Society of Chemotherapy was established again, and the above criteria, for the clinical evaluation of drug efficacy in UTI were extensively revised in November 2009 and were organized with the name changed to “Guidelines for the implementation of clinical trials for urogenital infections, 1st edition”.

Recently, because the FDA guidance in US for clinical trials of complicated UTI was reviewed and inconsistencies were present in the entry criteria such as bacterial counts in urine between the guidance and the 1st edition, which is mentioned above, a committee was established in the Japanese Society of Chemotherapy to revise the guidelines for the implementation of clinical trials for urogenital infections, and a complete revision of the 1st edition was discussed. The revised edition was completed through that process and has been published under the title “Japanese guideline for clinical research of antimicrobial agents on urogenital infections: second edition”.

1. Introduction

This guideline aims to objectively evaluate the efficacy of antimicrobial agents for the treatment of urinary tract infections (UTIs). The criteria presented in this guideline aim to absolutely ensure urogenital infections for clinical trials. Therefore, it should be noted that the criteria listed in this guideline are not for the diagnosis of or assessment of therapeutic effect on urogenital infections.

We have made efforts to allow use of the guideline in both general clinical studies and comparative studies and objective

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comparisons of individual study results. We have established the minimum necessary criteria in the guideline so that there is allowance to change items when considering individual cases or according to the practice of each institution.

2. General considerations

2.1. Target infections

Urological infections are classified as UTIs (cystitis, pyelonephritis) and genital infections (urethritis, prostatitis, epididymitis) according to the site of infection. These infections are non-specific inflammations caused by common bacteria and are not specific inflammations caused by fungi, Mycobacterium species, viruses, etc. UTIs include acute uncomplicated cystitis, acute uncomplicated pyelonephritis, and complicated UTI.

UTIs are classified as acute or chronic according to the clinical course, as uncomplicated and complicated by the underlying disease, and as cystitis and pyelonephritis by the site of infection. Generally, the disease name is based on a combination of the clinical course, underlying disease, and site of infection. Although uncomplicated UTIs are infections with no underlying disease that could affect urination, complicated UTIs of a limited sense are defined as infections with underlying disease that could affect urination, and complicated UTIs of wider sense are infections with underlying disease (diabetes, immunosuppression, etc.) that could induce, exacerbate, and prolong the UTI, in addition to infections in the limited sense and infections in men. Complicated UTIs were defined in the conventional Criteria for Evaluation of Clinical Efficacy of Antimicrobial Agents on UTI as infections with underlying disease in the urinary tract; namely, complicated UTIs in the limited sense. Considering the following facts, that: (1) complications such as diabetes can induce, exacerbate, and prolong UTIs, as can underlying diseases in the urinary tract; (2) UTIs are retrograde infections, such that men tend not to develop retrograde infection compared with women, in whom the urethra is 10 times shorter than that in men; and (3) even if a male patient is diagnosed as having no underlying diseases in the urinary tract, further examination finds that most male patients with UTI have underlying diseases, including impaired urine excretion, we have decided to use the definition of complicated UTIs in the wider sense in this guideline. It is preferable to exclude from the guideline patients with urinary diversion using intestinal segments or those with a catheter, other than a permanent catheter, because it is difficult to determine the response of such patients to antimicrobial agents.

Genital infections include urethritis, acute bacterial prostatitis, and acute epididymitis. Prostatitis is classified into four categories according to clinical condition by the NIH: category I, acute bacterial prostatitis; category II, chronic bacterial prostatitis; category III, chronic pelvic pain syndrome/chronic pain syndrome associated with prostatitis (A, inflammatory; B, noninflammatory); and category IV, asymptomatic prostatitis. We include only category I; namely, acute bacterial prostatitis, in this guideline because the disease is clearly associated with bacteria, antimicrobial agents are used for the treatment of the disease, and it is possible to evaluate the efficacy of antimicrobial drugs over a relatively short period. In general, however, such an antimicrobial agent that is effective in acute bacterial prostatitis is also effective in chronic bacterial prostatitis. Likewise, regarding epididymitis, we include only acute epididymitis in the guideline.

2.2. Entry criteria

Age/sex: Individual diseases are determined. When a minor is included in the study, a thorough explanation of the details of the study is given to both the participant and the participant's parents or guardians at the time of agreement to enter the study.

Clinical symptoms: This guideline evaluates the efficacy of antimicrobial agents against urogenital infections. It is preferable to exclude cases of colonization resulting from pathogenic microorganisms. Therefore, clinical symptoms caused by urogenital infections are defined, and it essential for the entry criteria that participants present these symptoms.

Pyuria: Individual diseases are determined. However, the following test methods may also be used. In addition, when new methods equal to, or better than, these methods are developed, these methods will likely be replaced.

- Microscopy of urinary sediment (For observation of pyuria alone, 500 $g \times 5$ min is good, but for observation of bacteria, 500 $g \times 5$ min is not sufficient, and it is preferable to extend the centrifugation time).
- Urinary test strip (the principal measurement is esterase activity).
- Counting chamber method that uses non-centrifuged urine (Kova Slide 10 Grid®, HYCOR Biomedical Inc., Garden Grove, CA).
- Use of flow cytometry with non-centrifuged urine and a fully automatic urine analysis system is assumed to be fundamental (equal to or better than Sysmex UF-50®, UF-100®, UF110i®, and UF-1000i® [SYSMEX Corp., Kobe, Japan], and other systems).

2.3. Exclusion criteria

The number of bacteria is determined as an exclusion criterion. If the viable bacteria count before administration is $<10^5$ colony-forming units (CFU)/mL in a case, the bacteria are judged to be non-significant and the case is excluded. However, in cases of urethritis and chlamydial epididymitis, if *Neisseria gonorrhoeae* or *Chlamydia trachomatis* is not detected before administration, the cases are excluded.

2.4. Targeted bacterial strains

Of the bacteria isolated from urogenital tract, only the bacterial strains that have pathogenicity to urogenital tract are evaluated the efficacy of drug. However, when the bacterial levels beyond those already counted exceed the above-mentioned exclusion criteria, "acceptance" or "rejection" is decided after examining the details. In addition, when the pathogen type is clearly understood, it is possible to target that pathogen type.

2.5. Dosage period

The standard duration of treatment is assumed to be from a single dose to 14 days, but this may differ according to the disease, and it is also determined according to the characteristics of the experimental drug.

2.6. Completion of therapy

Basically, the final day a dose is given is considered to be the end of treatment with the experimental drug. However, when the half-life of a drug has effective blood and urine levels that continue for a longer period, the day on which it is estimated that no effective level of the drug is left in the bloodstream is considered to be the end of treatment with that drug.