Development of Antimicrobial agents for Gonorrhea in Japan

PMDA

Anti-gonorrhea agents in Japan

As of December 31, 2020

- 32 antimicrobial agents, 187 products are approved for Gonorrhea.
  - Cephalosporins, quinolones, penicillins, macrolides etc.
- Benefit/risk balance is confirmed in clinical trials for STD, UTI, PID etc.
  - Not special trials for Gonorrhea.
- Facing resistance to quinolones etc.
- Guideline for Clinical Evaluation of Antibacterial Drugs has been published in 2017, including gonorrhea infection.
  - https://www.pmda.go.jp/files/000234350.pdf
- New agents are being developed in Japan, currently at very early stage.

Gonococcal Urethritis in Guidance

https://www.pmda.go.jp/files/000234279.pdf

Inclusion Criteria	
Sex	Male
Symptoms	Patients with symptoms compatible with gonococcal urethritis
Microbiological test	Culture for Neisseria gonorrhoeae should be obtained from urethral secretion if available, or first-catch urine instead.
Exclusion Criteria	
	Patients with a negative culture for Neisseria gonorrhoeae performed from urethral secretion or first catch urine before treatment.

Gonococcal Urethritis in Guidance

https://www.pmda.go.jp/files/000234279.pdf

Evaluation	
Timing	5 to 9 days after the end of treatment
Microbiological [primary endpoint]	Based on presence of Neisseria gonorrhoeae, the patient should be evaluated as either “Eradicated” or “Failure” as follows: Eradicated; N. gonorrhoeae is not detected in culture. Failure; N. gonorrhoeae is detected in culture, or change of the antibacterial drug or additional treatment has been implemented.
Clinical	Patients with mixed infection of Chlamydia and Mycoplasma should be excluded from the evaluation. Based on clinical symptoms, patients should be evaluated as either “Cure” or “Failure” as follows: Cure; Symptoms attributable to urethritis are not observed Failure; Symptoms attributable to urethritis are observed, or change of the antibacterial drug or additional treatment has been implemented.

Gonococcal Cervicitis in Guidance

https://www.pmda.go.jp/files/000234279.pdf

Inclusion Criteria	
1) Patients who are female aged ≥ 16 years who have symptoms or findings of cervicitis. 2) Patients who have apparent clinical signs of sexually transmitted infections based on inflammatory findings and in whom presence of *N. gonorrhoeae* is confirmed by microbiological tests using cervical secretion or endocervical swab specimens.	
Exclusion Criteria	
1) Patients in whom presence of *N. gonorrhoeae* is not confirmed by culture before treatment. 2) Patients who concurrently have pelvic inflammatory disease such as uterine adnexitis or peritonitis.	
Evaluation	
Timing	1) End of Treatment (day of the end of treatment to 7 days after that) The efficacy and safety at the end of treatment should be evaluated. In addition, when treatment is discontinued or terminated within the specified period because of cure or resolution, the observation items applicable at this point should be assessed. 2) Test of Cure (1 to 3 weeks after the end of treatment, primary endpoint) At this point, whether the target disease is cured or not should be evaluated.

Gonococcal Cervicitis in Guidance

https://www.pmda.go.jp/files/000234279.pdf

Evaluation	
Clinical	**Success** • Signs and symptoms attributable to cervicitis have resolved or improved, and no longer require treatment with antibacterial drugs for the target disease. Patients who meet any of the following conditions. **Failure** • Signs or symptoms attributable to cervicitis have deteriorated. • Cases where the antibacterial drug was changed or additional treatment has been implemented for the target disease because the microbiological efficacy was evaluated as “Persists”, etc. **Indeterminate** • Cases where the microbiological efficacy is evaluated as “Indeterminate” and no other antibacterial drugs have been used for cervicitis since the end of treatment with the investigational antibacterial drug. • Cases where other antibacterial drugs have been used (systemically) for a disease other than the target disease before the end of treatment, even though symptoms and signs attributable to cervicitis had resolved or improved.

Gonococcal Cervicitis in Guidance

https://www.pmda.go.jp/files/000234279.pdf

Evaluation	
Microbial	Changes in *N. gonorrhoeae* should be evaluated as either “Eradicated” or “Persists” as follows: Eradicated; *N. gonorrhoeae* is not detected in culture. Persists; *N. gonorrhoeae* is detected in culture, or change of the antibacterial drug or additional treatment has been implemented.

Nationwide surveillance of the antimicrobial susceptibility of *N. gonorrhoeae* from male urethritis in Japan 2009-2010

Antibacterial agent	Minimum inhibitory concentrations (MICs) (μg/ml)														
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256	MIC_{50}	MIC_{90}
Penicillin G	1	12	9	8	25	19	4	3	1		1			1	4
Ampicillin		12	8	6	24	24	3	1	3	1		1		1	4
Amoxicillin -clavulanic acid			19	7	31	26								1	2
Cefpodoxime	34	5	5	7	21	10	1							0.25	2
Cefdinir	42	1	4	28	8									≤0.06	0.5
Cefixime	46	13	23	1										≤0.06	0.25
Cefditoren	29	22	25	7										0.125	0.25
Ceftriaxone	76	7												≤0.06	≤0.06
Cefodizime	52	24	7											≤0.06	0.125
Flomoxef		5	14	11	9	38	6							2	2
Aztreonam	3	17	11	10	3	4	23	12						1	8
Spectinomycin							9	65	9					8	16
Ciprofloxacin	18					3	10	19	27	6				8	16
Levofloxacin	18					10	24	30	1					4	8
Tosufloxacin	18				1	9	38	7	10					4	16
Sitafloxacin	30	16	37											0.125	0.25
Minocycline	5	14	16	36	7		1	1	3					0.5	1
Azithromycin	10	44	26	1		2								0.125	0.25

Journal of Infectious Disease and Chemotherapy, 19(4), 571, 2013 https://doi.org/10.1007/s10156-013-0637-2

Nationwide surveillance of the antimicrobial susceptibility of *N. gonorrhoeae* from male urethritis in Japan, 2012-2013

Table 1
Antimicrobial MIC distribution for 103 *N. gonorrhoeae* strains.

Antibacterial agent	MIC (μg/ml)														
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256	MIC_{50}	MIC_{90}
Penicillin G		6	24	17	33	20	2			1				1	2
Ampicillin		8	14	11	29	33	7				1			1	2
Amoxicillin			21	8	20	52	1				1			2	2
Clavulanic acid-amoxicillin		1	21	10	25	46								1	2
Cefpodoxime	38	3	5	15	23	17	2							0.5	2
Cefdinir	41		2	25	35									0.5	1
Cefixime	42	8	42	11										0.25	0.5
Cefditoren	52	24	22	5										≤0.06	0.25
Ceftriaxone	92	11												≤0.06	0.125
Cefodizime	79	21	3											≤0.06	0.125
Flomoxef		3	20	8	22	41	9							1	2
Aztreonam	10	15	14	2	1	1	38	22						4	8
Meropenem	68	35												≤0.06	0.125
Spectinomycin								3	95	5				16	16
Ciprofloxacin	21			1		1	13	18	36	12	1			8	32
Levofloxacin	21			1	1	6	26	38	10					4	8
Tosufloxacin	21			3	4	31	14	19	11					2	16
Sitafloxacin	38	32	32	1										0.125	0.25
Minocycline	2	29	26	40	1			1	3	1				0.25	0.5
Azithromycin	15	44	39	3	2									0.125	0.25

Journal of Infectious Disease and Chemotherapy, 21(5), 340, 2015 https://doi.org/10.1016/j.jiac.2015.01.010

Antimicrobial Susceptibility of *N. gonorrhoeae*

	2009-2010		2012-2013	
	MIC50	MIC90	MIC50	MIC90
Penicillin G	1	4	1	2
Ampicillin	1	4	1	2
Amoxicillin-CLA	1	2	1	2
Cafpodoxime	0.25	2	0.5	2
Cefdinir	≦0.06	0.5	0.5	1
Cefixime	≦0.06	0,25	0.25	0.5
Cefditren	0.125	0.25	≦0.06	0.25
Ceftriaxone	≦0.06	≦0.06	≦0.06	0.125
Cefodizime	≦0.06	0.125	≦0.06	0.125
Flomoxef	2	2	1	2
Aztreonam	1	8	4	8
Spectinomycin	8	16	16	16
Ciprofloxacin	8	16	8	32
Levofloxcin	4	8	4	8
Tosufloxacin	4	16	2	16
Sitafloxacin	0.125	0.25	0.125	0.25
Minocycline	0.5	1	0.25	0.5
Azithromycin	0.125	0.25	0.125	0.25

Standard of Diagnostics/Treatment for Gonococcal Infection

- Diagnostics
  - Gram stain, Culture, PCR
- Treatment
  - Urethritis, Cervicitis
    - Ceftriaxone 1g QD, DIV, 1day
    - Spectinomycin 2g IM, 1day
  - Epididymitis, PID
    - Ceftriaxone 1g QD or BID, DIV, 1-7day
    - Spectinomycin 2g IM on Day 1 + 2g BID IM on Day4

Japanese Society of Sexually Transmitted Infections, 2016
JAID/JSC, 2018

Thank You