

Social Hygiene Clinic as a Sentinel for Monitoring of Anti-microbial Resistance - *the Story of Neisseria Gonorrhoeae*

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Neisseria gonorrhoeae

- *Neisseria gonorrhoeae* also known as gonococci / gonococcus
- First described by Albert Neisser in 1879 -> also a dermatologist
- Causing → gonorrhoea – one of the commonest of STI - 淋病 (流白濁)
- Gram -ve coffee bean shaped diplococcic bacteria

Gonorrhoea 淋病 (流白濁) in SHS

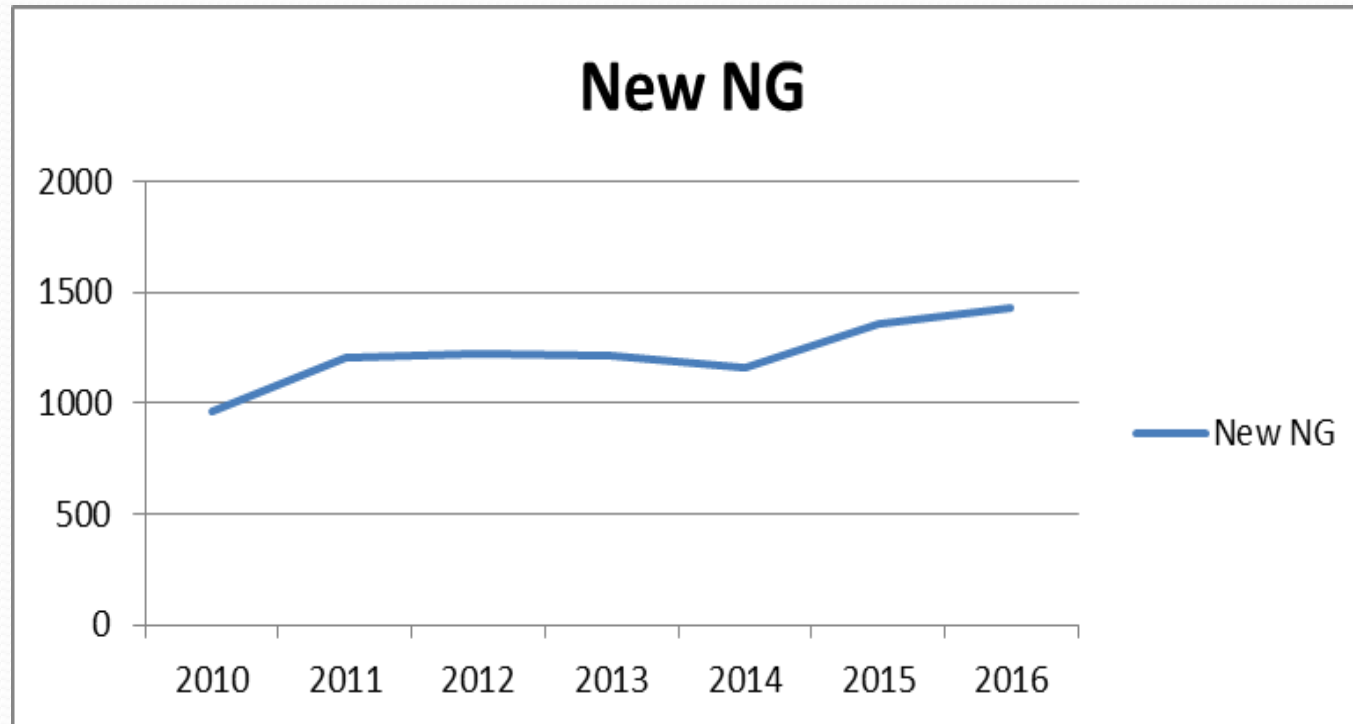
- In 2000, the annual number of new cases of gonorrhoea > 3,500.
- The number gradually declined since then.
- The number of new infections recorded in 2010 was 968

Gonorrhoea 淋病 (流白濁) in SHS

- increased to around 1,200 in 2011 and became static until 2014.
- It increased again to over 1,400 new cases in 2016.
- Gonorrhoea ranked third among all STIs managed in SHC.

Gonorrhoea 淋病 (流白濁) in SHS

- Figure 1 shows the trend of NG infection in SHC from 2010 to 2016 (unpublished data from SHS).



Historical perspective of *Neisseria gonorrhoeae* on antibiotic resistance

- Pre-antibiotics Era →
 - Herbs, urethral irrigation, metallic compounds → gold, silver, arsenicEvery methods that people could think of



- Sulfonamides* (1st antibiotics) --> ~ 1935 – later 1940s



15 years

- Penicillin* ~ WWII to mid 1970s



30 years

Historical perspective of *Neisseria gonorrhoeae* on antibiotic resistance

- Tetracyclines ~ mid 1970s to mid 1980s

-



- Quinolones (Especial fluoroquinolones) ~ mid 1980s to mid 1990s

-



- Oral 3rd G cephalosporins ~ mid to late 1990s to 2011

- Cefixime / Ceftibuten(Cedax)



20 years

Historical perspective of *Neisseria gonorrhoeae* on antibiotic resistance

- In 2011 – Cedax Resistant NG*

- Jan – 2.6% (2/77)
- Feb – 0% (0/94)
- Mar – 1% (1/100)
- Apr – 8.4% (8/95)
- May – 8% (9/112)
- Jun – 2.6% (2/76)
- July – 13.8% (13/94)
- Aug – 20% (26/130)
- Sept – 12% (10/83)

- * *Communicable Disease Watch Vol 8 (21) 2-15 Oct 2011 KM Ho, Janice YC Lo*

- *JYC Lo, KM Ho, et al. *Ceftibuten Resistance and treatment failure of Neisseria gonorrhoeae Infection. Antimicrobiol Agents Chemother 2008;52:3564-7*

Treatment guidelines for *Neisseria gonorrhoeae* infection

- WHO also recommended :
- criteria for selection of medicines for STIs treatment should be highly efficacious and at least has 95% cure rate*
- In other words, the treatment regimen should be changed when prevalence of antimicrobial resistance exceeds 5% for a specific antibiotic.
- **<http://www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/> .WHO Guidelines for the treatment of *Neisseria gonorrhoeae*.*

In Social Hygiene Clinic → NOW

- **Ceftriaxone** (rocephin)
250mg IMI stat x one dose

For Gonorrhoea Treatment

Around 10 – 20 years → needs to change
another antibiotics due to resistance

Ceftriaxone (Rocephin)
How long can we use???

High level Ceftriaxone Resistant NG

	Ho41 (2009)	F89 (2010)	A88o6 (2013)	GU140106 (2014)	FC428 (2015)
Place	Kyoto, Japan	Quimper, France	Sydney, Australia	Nagoya, Japan	Osaka, Japan
Sites	Pharynx FCSW	TOC after cefixime of urethral sample of MSM	Genital swab of female European traveller	Urethral swab, man received fellatio, condom-ve, FCSW	Urethral swab of man Sex Hx not mentioned
Mechanism	Novel Pen A mosaic gene	Novel Pen A mosaic +A501 alternation	Novel Pen A mosaic gene similar to Ho41	Novel Pen A mosaic gene similar to Ho41	Novel Pen A mosaic gene + Penicillinase producing NG
Tx given	Rocephin 1gm IV	Gentamicin 160mg IMI x 1 dose	Rocephin 500 mg IMI Azithromycin 1gm PO	Rocephin 1gm IV	Spectinomycin 2gm IMI
Fu Result	No post Rx specimen A/v	Negative culture	Negative culture	No Fu culture done but asymptomatic. FCSW -ve culture	Not mentioned
Sensitive to	Spectinomycin / rifampin / aminoglycosides ?carbapenum : ertapenem / meropenem / tazocin	Spectinomycin ?rifampicin ? Aminoglycosides ?carbapenum	Not mentioned	Not mentioned	Spectinomycin Azithromycin
MIC breakpoint	2-4mg/L	1-2mg/L	0.5mg/L	0.5mg/L	0.5mg/L

High level Ceftriaxone Resistant GC – Key messages

- Almost new strain every year
- All related to Pen A mosaic gene
- Seems High dose Rocephin 1gm IV still workable – at least clinically
- Spectinomycin is still working BUT out from market? / ? Working in pharyngeal GC
- **Oral Sex** / Received fellatio is **DANGER!!!!!!!!!!!!**

Beta-lactams Susceptibility Test – 2010 – 2014

: from CHP website

Year	Number tested	Penicillin				Ceftriaxone				Cefixime				Mosaic penA gene present
		S	%	R	%	S	%	R	%	S	%	R	%	
2010	947	0	0%	484	51.1%	947	100%	0	0%	946	99.9%	1	0.1%	7
2011	1225	0	0%	663	54.1%	1225	100%	0	0%	1223	99.8%	2	0.2%	66
2012	1149	0	0%	642	55.9%	1149	100%	0	0%	1135	98.8%	14	1.2%	179
2013	1134	0	0%	532	46.9%	1133	99.9%	1	0.1%	1126	99.3%	8	0.7%	121
2014	1048	0	0%	430	41.0%	1047	99.9%	1	0.1%	1046	99.8%	2	0.2%	83

Beta-Lactam susceptibility in 2015

: from CHP website

Month	Number tested	Penicillin				Ceftriaxone				Cefixime				Mosaic penA gene present
		S	%	R	%	S	%	R	%	S	%	R	%	
Jan	100	1	1.0%	39	39.0%	100	100%	0	0%	100	100%	0	0%	9
Feb	85	0	0%	35	41.2%	85	100%	0	0%	81	95.3%	4	4.7%	17
Mar	97	1	1.0%	50	51.5%	97	100%	0	0%	97	100%	0	0%	12
Apr	114	0	0%	56	49.1%	114	100%	0	0%	114	100%	0	0%	15
May	84	0	0%	46	54.8%	84	100%	0	0%	84	100%	0	0%	7
Jun	79	0	0%	38	48.1%	79	100%	0	0%	79	100%	0	0%	11
Jul	85	0	0%	52	61.2%	85	100%	0	0%	85	100%	0	0%	9
Aug	85	0	0%	49	57.6%	85	100%	0	0%	85	100%	0	0%	7
Sep	88	0	0%	57	64.8%	88	100%	0	0%	88	100%	0	0%	13
Oct	99	0	0%	55	55.6%	96	97.0%	3*	3.0%	96	97.0%	3*	3.0%	12
Nov	101	0	0%	57	56.4%	101	100%	0	0%	101	100%	0	0%	13
Dec	105	0	0%	61	58.1%	105	100%	0	0%	105	100%	0	0%	10
Cumulative total/ average %	1122	2	0.2%	595	53.0%	1119	99.7%	3	0.3%	1115	99.4%	7	0.6%	135

Beta-Lactam susceptibility in 2016

: from CHP website

Month	Number tested	Penicillin				Ceftriaxone				Cefixime				Mosaic penA gene present
		S	%	R	%	S	%	R	%	S	%	R	%	
Jan	80	0	0%	41	51.3%	80	100%	0	0%	80	100%	0	0%	8
Feb	88	0	0%	53	60.2%	88	100%	0	0%	88	100%	0	0%	10
Mar	94	0	0%	47	50.0%	94	100%	0	0%	94	100%	0	0%	15
Apr	93	0	0%	53	57.0%	93	100%	0	0%	93	100%	0	0%	15
May	65	0	0%	39	60.0%	65	100%	0	0%	65	100%	0	0%	6
Jun	105	1	1.0%	56	53.3%	105	100%	0	0%	105	100%	0	0%	9
Jul	102	0	0%	52	51.0%	102	100%	0	0%	102	100%	0	0%	13
Aug	99	0	0%	55	55.6%	99	100%	0	0%	99	100%	0	0%	17
Sep	90	0	0%	39	43.3%	90	100%	0	0%	90	100%	0	0%	11
Oct	134	0	0%	76	56.7%	134	100%	0	0%	134	100%	0	0%	28
Nov	122	0	0%	60	49.2%	122	100%	0	0%	122	100%	0	0%	19
Dec	107	0	0%	56	52.3%	107	100%	0	0%	107	100%	0	0%	18
Cumulative total/ average %	1179	1	0.1%	627	53.2%	1179	100%	0	0%	1179	100%	0	0%	169

Beta-Lactam susceptibility in 2017

: from CHP website

Month	Number tested	Penicillin				Ceftriaxone				Cefixime				Mosaic penA gene present
		S	%	R	%	S	%	R	%	S	%	R	%	
Jan	118	0	0%	67	56.8%	118	100%	0	0%	118	100%	0	0%	17
Feb	122	0	0%	71	58.2%	122	100%	0	0%	119	98%	3*	2%	26
Mar														
Apr														
May														
Jun														
Jul														
Aug														
Sep														
Oct														
Nov														
Dec														
Cumulative total/ average %	240	0	0.0%	138	57.5%	240	100%	0	0%	237	99%	3	1%	43

Gonorrhoea 淋病 (流白濁) in SHC

- In recent years, creeping up of minimal inhibitory concentration (MIC) to ceftriaxone in NG isolates has been observed in many parts of the World.

What is Social Hygiene Clinic doing to monitor the effectiveness and the resistance of ceftriaxone?

Measures to prevent NG resistance – SHC

- On site Diagnosis and on-site treatment
- Test of cure
- Questionnaire – investigating every ceftriaxone failure cases
- Anti-venereal disease office (AVDO) .
- Epidemiological treatment

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Measures to prevent NG resistance – SHC

- **On site Diagnosis and on-site treatment**

- In SHC, Gram stain for urethral / cervical smear → make immediate diagnosis of gonorrhoea and then single dose ceftriaxone could be given immediately.
- This clinic-based diagnosis and single dose, simple and immediate treatment can effectively reduce the opportunity of community spread of NG while waiting for confirmation of laboratory results.

Measures to prevent NG resistance – SHC

- **On site Diagnosis and on-site treatment**

- Nowadays, most of international authorities in US, UK, Europe are using NAAT such as PCR to dx NG
- Highly sensitive, Highly specific, may be more cost effective particular in large amount
- Not doing culture nowadays

Measures to prevent NG resistance – SHC

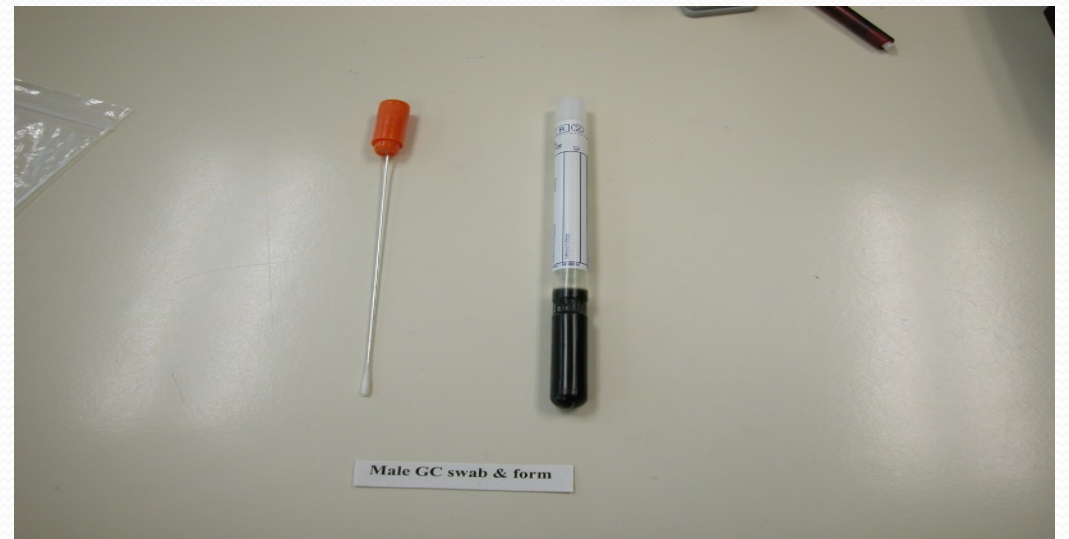
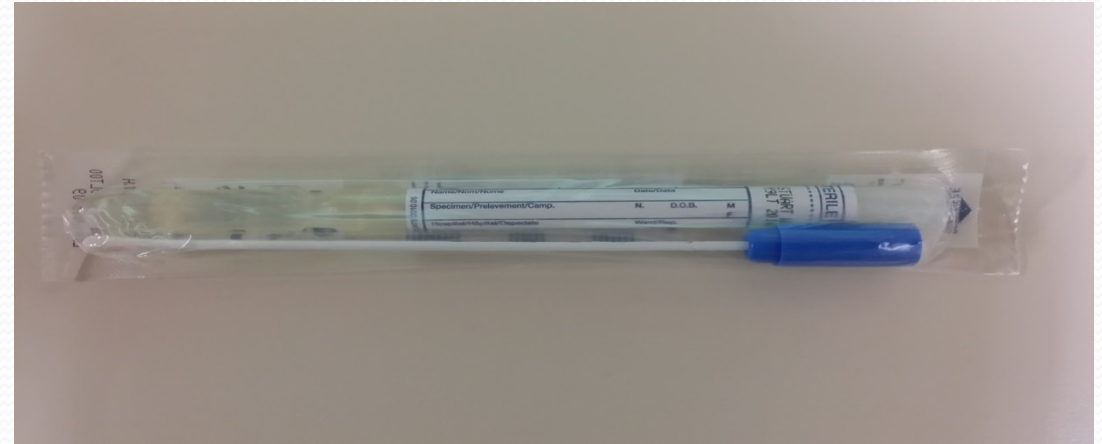
- On site Diagnosis and on-site treatment
 - In SHC, Dx of NG → Not only use PCR
 - We insist doing NG Culture

Neisseria gonorrhoeae – modified Thayer Martin Medium



- May cause false - ve culture if
- ordinary bacterial culture is used

- So Modified Thayer Martin Medium
- is used for *Neisseria gonorrhoeae*
- culture



Measures to prevent NG resistance – SHC

- **On site Diagnosis and on-site treatment**

- Reasons for insisting doing NG Culture → viable samples
- More comprehensive antibiotics sensitivity test for each patients
- Close monitoring MICs of , not only ceftriaxone but also other antibiotics such as azithromycin

Measures to prevent NG resistance – SHC

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Measures to prevent NG resistance – SHC

- **Test of cure**

- index patients x return one week x repeat Gram stain and culture of urethral smear
- ensure microbiological cure of NG

Measures to prevent NG resistance – SHC

- On site Diagnosis and on-site treatment
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- Epidemiological treatment

Measures to prevent NG resistance – SHC

- Questionnaire – investigating every ceftriaxone failure cases
 - If Gram stain shows positive diplococci at “test of cure”, further probing using a structured questionnaire is conducted and the culture results of the samples collected in the initial and test-of-cure visits will be traced to differentiate between re-infection and true resistance.

Gonorrhoea – Treatment Failure Report Form

Name: _____ Sex: _____
 ID No.: _____ Date of Birth: _____
 Clinic: _____ Age: _____

Please Fax to: 21109147 SHS HQ

Attn: Dr. KWAN Chi-keung

Sex Orientation: Homosexual (I/O/ both I&O) / Heterosexual / Bisexual

GC symptoms & signs / Results

1st Visit – Date 2nd Visit – Date 3rd Visit - Date

Genital

	Test of Cure		Test of Cure	
Dysuria <input type="checkbox"/>	Dysuria <input type="checkbox"/>	Dysuria <input type="checkbox"/>	Dysuria <input type="checkbox"/>	Dysuria <input type="checkbox"/>
Discharge <input type="checkbox"/>	Discharge <input type="checkbox"/>	Discharge <input type="checkbox"/>	Discharge <input type="checkbox"/>	Discharge <input type="checkbox"/>
Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>
Others, specify	Others, specify	Others, specify	Others, specify	Others, specify
Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve
Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve
NAAT <input type="checkbox"/> +ve / <input type="checkbox"/> -ve				

*for female please specify site e.g. cervix, vagina, urethra

Rectal

Proctalgia <input type="checkbox"/>	Proctalgia <input type="checkbox"/>	Proctalgia <input type="checkbox"/>
Discharge <input type="checkbox"/>	Discharge <input type="checkbox"/>	Discharge <input type="checkbox"/>
Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>
Others, specify	Others, specify	Others, specify
Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve
Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve
NAAT <input type="checkbox"/> +ve / <input type="checkbox"/> -ve		

Pharyngeal

Sore throat <input type="checkbox"/>	Sore throat <input type="checkbox"/>	Sore throat <input type="checkbox"/>
Exudate <input type="checkbox"/>	Exudate <input type="checkbox"/>	Exudate <input type="checkbox"/>
Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>	Asymptomatic <input type="checkbox"/>
Others, specify	Others, specify	Others, specify
Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Smear <input type="checkbox"/> +ve / <input type="checkbox"/> -ve
Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve	Culture <input type="checkbox"/> +ve / <input type="checkbox"/> -ve
NAAT <input type="checkbox"/> +ve / <input type="checkbox"/> -ve		

Sexual History

1st Visit – Date

Casual Sex

Partner
 Male / Female
 CSW:
 Date: _____
 Place: _____
 One night Stand:
 Date: _____
 Place: _____

2nd Visit – Date

Test of Cure

Partner (Same / New)
 Male / Female
 CSW:
 Date: _____
 Place: _____
 One night Stand:
 Date: _____
 Place: _____

3rd Visit - Date

Test of Cure

Partner (Same / New) Male / Female
 CSW:
 Date: _____
 Place: _____
 One night Stand:
 Date: _____
 Place: _____

Regular Sex

Partner
 Husband / Wife:
 Date: _____
 Boy / Girl Friend:
 Date: _____

Partner (Same / New)
 Husband / Wife:
 Date: _____
 Boy / Girl Friend:
 Date: _____

Partner (Same / New)
 Husband / Wife:
 Date: _____
 Boy / Girl Friend:
 Date: _____

Sexual Behaviour

<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Vaginal	<input type="checkbox"/> Yes / <input type="checkbox"/> No
<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Anal	<input type="checkbox"/> Yes / <input type="checkbox"/> No
<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Oral	<input type="checkbox"/> Yes / <input type="checkbox"/> No

<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Vaginal	<input type="checkbox"/> Yes / <input type="checkbox"/> No
<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Anal	<input type="checkbox"/> Yes / <input type="checkbox"/> No
<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Oral	<input type="checkbox"/> Yes / <input type="checkbox"/> No

<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Vaginal	<input type="checkbox"/> Yes / <input type="checkbox"/> No
<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Anal	<input type="checkbox"/> Yes / <input type="checkbox"/> No
<input type="checkbox"/> Penile –	Condom:
<input type="checkbox"/> Oral	<input type="checkbox"/> Yes / <input type="checkbox"/> No

Treatments

Rocephin 250mg IMI
 Spectinomycin 2-4gm IMI
 Azithromycin 2gm PO
 Others, specify: _____

Rocephin 250mg IMI
 Spectinomycin 2-4gm IMI
 Azithromycin 2gm PO
 Others, specify: _____

Rocephin 250mg IMI
 Spectinomycin 2-4gm IMI
 Azithromycin 2gm PO
 Others, specify: _____

Partner Treatments

(YES / No / Unknown)

Rocephin 250mg IMI
 Spectinomycin 2-4gm IMI
 Azithromycin 2gm PO
 Others specify: _____
 Unknown

Partner Treatments

(YES / No / Unknown)

Rocephin 250mg IMI
 Spectinomycin 2-4gm IMI
 Azithromycin 2gm PO
 Others specify: _____
 Unknown

Partner Treatments

(YES / No / Unknown)

Rocephin 250mg IMI
 Spectinomycin 2-4gm IMI
 Azithromycin 2gm PO
 Others specify: _____
 Unknown

NB: please specify date of treatment and where the treatment is delivered

Measures to prevent NG resistance – SHC

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- Anti-venereal disease office (AVDO) .
- Epidemiological treatment

Measures to prevent NG resistance – SHC

- **Anti-venereal disease office (AVDO)**

- Specific team of nursing staff
- is responsible for tracing index patients if they fail to attend for “test of cure” or default to follow-up.
- Partner notification and contact tracing are done once the index patients disclose voluntarily the information of their partners.

Measures to prevent NG resistance – SHC

- On site Diagnosis and on-site treatment
- Test of cure
- Questionnaire – investigating every ceftriaxone failure cases
- Anti-venereal disease office (AVDO)
- Epidemiological treatment

Measures to prevent NG resistance – SHC

● Epidemiological treatment

- In which the same treatment as the index patient will be given to their partners irrespective of the laboratory results of the latter.
- This measure can contribute to stop the spread of NG and reduce the chance of ping-pong transmission of STI.
- It can reduce the asymptomatic pools or carriers in the community particular important in female (as 1/3 are asymptomatic) and atypical site NG infection (throat or rectal → probably no symptoms)

Ceftriaxone Resistance - Patient

- M / 55 causal sex with friend in Mauca
- Penile – vaginal sex (condom+) / oral sex (condom-)
- Presented with yellowish Urethral Discharge x 3/7
- In SHC → Gram Stain → Gram negative diplococci +ve
 - → ceftriaxone 250mg IMI stat
 - (On site Diagnosis and on-site treatment)
- Counselling / contact tracing by AVDO (Anti-venereal disease office)
- Come back 1/52 later x Test of cure
 - TOC – Gram smear +ve (while pending 1st culture) / repeat 2nd culture
 - Claimed having sex with the friend again
 - Tx as Ping-Pong re-infection
 - → ceftriaxone 250mg IMI stat
 - (On site Diagnosis and on-site treatment)

Ceftriaxone Resistance - Patient

- Informed by PHLC (1st culture → ceftriaxone R)
- Call back patient (**AVDO Anti-venereal disease office**)
- Informed by PHLC (2nd culture → ceftriaxone R)
- 2nd **Test of cure** – Gram smear +ve , although asymptomatic (repeat 3rd culture)
 - Ceftriaxone 1gm IMI + Azithromycin 2mg PO stat given and **questionnaire** done x Ix (**On site Diagnosis and on-site treatment**)
- 3rd **Test of cure** – Gram smear –ve, asymptomatic, repeated 4th culture
 - Subsequently 3rd and 4th culture --> -ve (**On site Diagnosis and on-site treatment**)

Measures to prevent NG resistance – SHC

- On site Diagnosis and on-site treatment
- Test of cure
- Questionnaire – investigating every ceftriaxone failure cases
- Anti-venereal disease office (AVDO)
- Epidemiological treatment

Last but the least,

- Don't Forget our bubby – close collaborator to fight against NG resistance
- PHLC – Public Health Laboratory Centre, Department of Health

Acknowledgement

- Dr. KM HO Consultant Dermatologist I/C, Social Hygiene Services
- Dr. Teresa WANG , Senior Medical Officer, Microbiologist, PHLC



Thank you