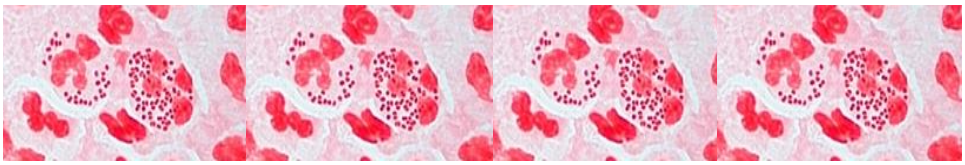

Treating Gonorrhoea in the Absence of Cephalosporins

Practical Considerations and Future Options

2017 Australian Sexual Health Conference - 9th November 2017

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NSW GOVERNMENT Health Western Sydney Local Health District | WSSHC WESTERN SYDNEY SEXUAL HEALTH CENTRE | THE UNIVERSITY OF SYDNEY

Cephalosporin Allergy

- Cephalosporins widely used for treatment and surgical prophylaxis
- Historically, cephalosporins avoided in penicillin allergic patients based on a '10% cross-reactivity' rule
- Rule now thought to have a poor evidence base
  - Early cephalosporins contained small amounts of penicillin (confounder)
  - Allergic reactions to cephalosporins may be primary reactions (c.f. cross-reactions)
  - Many early studies had small numbers
- In the modern AMR era, use of 'questionable' antibiotics may result in sub-optimal therapy
- Ceftriaxone is a critical drug for STI management (Ng, Hd, Tp, Kg)

 Cormier *et al.*, Paediatr Child Health 2007;**12**:387-388; Kelkar & Li, NEJM 2001;**345**:804-809

Cephalosporin Allergy

Type of reaction	Frequency (%)	References
Dermatologic	1.0-2.8	Norrby, Sanders *et al.*, Arndt & Jick, Platt
Positive direct anti-globulin test	1.0-2.0	Sanders *et al.*, Platt, Meyers
Anaphylaxis	0.0001-0.1	Gadde *et al.*, Sogn *et al.*, Apter *et al.*
Fever	0.5-0.9	Sanders *et al.*, Meyers
Eosinophilia	2.7-8.2	Sanders *et al.*, Platt

- Cross-reactivity between cephalosporins and penicillins depends on the generation of the cephalosporin – higher incidence with 1st/2nd generation cephalosporins (Atanaskovic-Merkovic *et al.*, Pichichero)

Norrby, Drugs 1997;**34** (Suppl 2):105-120; Sanders *et al.*, Ann Intern Med 1985;**103**:70-78; Arndt & Jick, JAMA 1976:**235**:918-923; Platt, J Antimicrob Chemother 1982;**10** (Suppl C):135-140; Meyers, Am J Med 1985;**79**:96-103; Gadde *et al.*, JAMA 1993;**270**:2456-2463; Sogn *et al.* Arch Intern Med 1992;**152**:1025-1032; Apter *et al.*,Am J Med 2006;119:354:e11-e19; Atanaskovic-Markovic et al., Pediatr Allergy Immunol;2005:16;341-347; Pichichero, Pediatrics 2005;**115**:1048-1057

Penicillin and Cephalosporin Cross-Reactions

- Ability to generate an immune response depends on the chemical structure of the cephalosporin side chain (Pichichero)

TABLE 6. Chemical Structures of 7-Position Side Chains of Penicillins and Cephalosporins

Similar Structure/Possible Cross-Reactivity With Group			Dissimilar Structures/Unlikely Cross-Reactivity	
Related	Related	Related	Not Related	Not Related
Penicillin G	Amoxicillin	Cefotaxime	Cefsulodin	Cefotiam
Cephaloridine	Ampicillin	Ceftizoxime	Cefazolin	Ceftazidime
Cephalothin	Cefaclor	Ceftriaxone	Cefonicid	Cefamandole
Cefoxitin	Cephalexin	Cefpodoxime	Cefotetan	Cephapirin
	Cephradine	Cefpirome	Cefuroxime	Cefixime
	Cefprozil	Cefepime	Cefoperazone	Cefmetazole
	Cefatrizine	Cefetamet	Cefdinir	Ceftibuten
	Cefadroxil	Cefteram		Moxalactam

0.5-6.5% higher chance of allergy in penicillin-allergic patients

Amoxycillin/Ampicillin and Cephalosporin Cross-Reactions

TABLE 6. Chemical Structures of 7-Position Side Chains of Penicillins and Cephalosporins

Similar Structure/Possible Cross-Reactivity With Group			Dissimilar Structures/Unlikely Cross-Reactivity	
Related	Related	Related	Not Related	Not Related
Penicillin G	Amoxicillin	Cefotaxime	Cefsulodin	Cefotiam
Cephaloridine	Ampicillin	Ceftizoxime	Cefazolin	Ceftazidime
Cephalothin	Cefaclor	Ceftriaxone	Cefonicid	Cefamandole
Cefoxitin	Cephalexin	Cefpodoxime	Cefotetan	Cephapirin
	Cephradine	Cefpirome	Cefuroxime	Cefixime
	Cefprozil	Cefepime	Cefoperazone	Cefmetazole
	Cefatrizine	Cefetamet	Cefdinir	Ceftibuten
	Cefadroxil	Cefteram		Moxalactam

0.5-6.5% higher chance of allergy in amoxicillin-allergic patients

 Pichichero, Pediatrics 2005;**115**:1048-1057

Skin Testing

- If reaction to a penicillin or a cephalosporin was not IgE-mediated and not serious, safe to administer repeated courses of that antibiotic (e.g. vomiting, diarrhoea or non-specific rash)
- IgE-mediated reactions likely to become more severe with time and result in anaphylaxis (e.g. bronchospasm, angioedema, hypotension, urticaria or a pruritic rash)
- Penicillin skin testing ~60% predictive for clinical hypersensitivity
  - Only really helpful if the penicillin and cephalosporin share similar side chains
- Value of cephalosporin skin testing is questionable
  - Individual degradation components have not been identified
  - Skin testing is usually conducted with the native compound

 Cormier *et al.*, Paediatr Child Health 2007;**12**:387-388; Pichichero, Pediatrics 2005;**115**:1048-1057

Summary of Recommendations

Cephalosporin generation	Cross-reactivity issue	OK to use
1st	(+) anaphylaxis to penicillin	+/-
1st, 2nd	Similar side chain	No
1st	(-) anaphylaxis to penicillin and different side chain	Yes
2nd	Different side chain	Yes
3rd or higher	Not applicable	Yes

- There are three management options for patients with a history of penicillin allergy with positive penicillin skin test responses
  - Receive a non-β-lactam antibiotic
  - Receive a cephalosporin through graded challenge
  - Receive a cephalosporin through rapid desensitization

 Cormier *et al.*, Paediatr Child Health 2007;**12**:387-388

Non-Cephalosporin Treatment Options

Reliable option

Unavailable in Australia

- Spectinomycin 2 g IM stat (not available in Australia)

Sub-optimal options

Give as dual therapy & try to obtain in vitro susceptibility data

- Gentamicin 240 mg IM stat
- Azithromycin 2 g po stat
- Ciprofloxacin 500 mg po stat
- Rifampicin 900 mg po stat
- Aztreonam 1 g IM stat

 Cormier *et al.*, Paediatr Child Health 2007;**12**:387-388; Pichichero, Pediatrics 2005;**115**:1048-1057

The G-TOG Trial — Gentamicin

- Blinded 2-arm multicentre non-inferiority randomised trial in 14 English Sexual Health clinics
- 720 patients randomized
  - IM gentamicin 240 mg (n=358) + oral azithromycin 1 g
  - IM ceftriaxone 500 mg (n=362) + oral azithromycin 1 g
- **Primary outcome:** bacteriological clearance of *N. gonorrhoeae* at all infected sites by a negative NAAT at 2 weeks post treatment
  - Primary outcome data for 598 (82%) patients (ceftriaxone, 306; gentamicin 292)
  - Clearance at 2 weeks: 299/306 (98%) ceftriaxone, 267/292 (91%) gentamicin
  - Gentamicin has substantially lower efficacy in oro-pharynx (80% vs. 98% clearance)
- **Gentamicin failed to show non-inferiority to ceftriaxone**

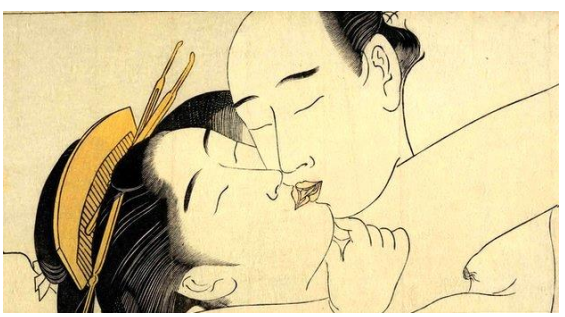
 Brittain *et al.*, Trials 2016;**17**:558; Ross *et al.*, Sex Transm Infect 2017;**93**(Suppl 2):A42-A43

Emergence of Extensively Drug Resistant *Neisseria gonorrhoeae* (XDR-NG), Central Japan, 2009

Is *Neisseria gonorrhoeae* Initiating a Future Era of Untreatable Gonorrhea?: Detailed Characterization of the First Strain with High-Level Resistance to Ceftriaxone▽†

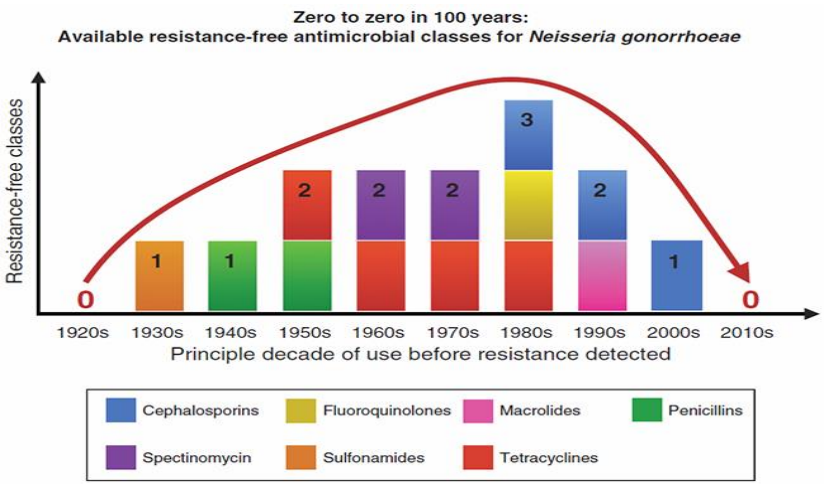
Makoto Ohnishi,[1] Daniel Golparian,[2] Ken Shimuta,[1] Takeshi Saika,[3] Shinji Hoshina,[4] Kazuhiro Iwasaku,[5] Shu-ichi Nakayama,[1] Jo Kitawaki,[5] and Magnus Unemo[2]*

H041 strain



 Ohnishi M *et al.* , Antimicrob Agents Chemother 2011;**55**:3538-3545

Available Resistance-Free Antimicrobial Classes for *Neisseria gonorrhoeae*



Lahra *et al.*, Microbiology Australia 2016;10.1071/MA16058

WHO Priority Pathogens List for Research & Development of New Antibiotics (2017)

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant
Pseudomonas aeruginosa, carbapenem-resistant
Enterobacteriaceae, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

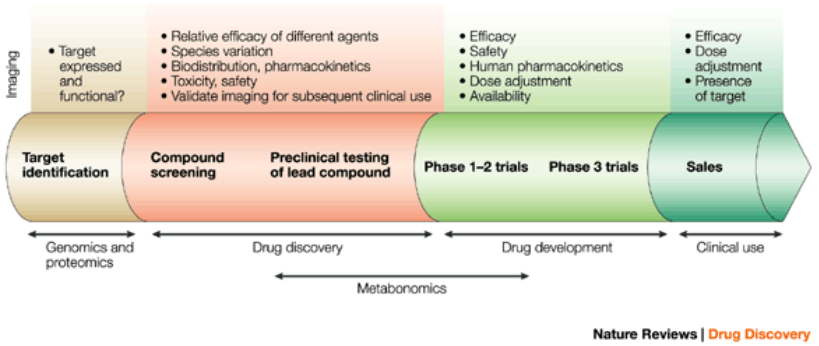
Enterococcus faecium, vancomycin-resistant
Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant
Helicobacter pylori, clarithromycin-resistant
Campylobacter, fluoroquinolone-resistant
Salmonella spp., fluoroquinolone resistant
Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible
Haemophilus influenzae, ampicillin-resistant
Shigella spp., fluoroquinolone-resistant

http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1

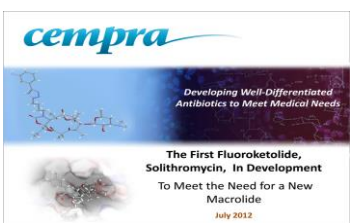
Pipe Line for the Introduction of New Drugs



15 years and $800 million from target to product

5,000-10,000 compounds are screened for every 5 drugs that enter clinical trials and for every 1 drug that obtains FDA approval

Solithromycin (CEM-101)



- Novel fluoroketolide undergoing clinical development for treatment of community-acquired pneumonia, gonorrhoea and other infections
- Active against gonococci (including XDR strains H041and F89) as well as *C. trachomatis* and *M. genitalium*
- Less prone to generate *in vivo* resistance c.f. other macrolides
- Gonococci with MIC ≥ 256 mg/L will fail Rx (high-level AZM^R)
- 2-centre open-label non-comparative **Phase 2** safety completed

Golparian *et al.*, Antimicrob Agents Chemother 2012;**56**:2739-2742;
Hook *et al.*, Clin Infect Dis 2015;**61**:1043-1048

Solithromycin vs. Ceftriaxone Gonorrhoea Treatment Trial (Solitaire-U Trial)

- **Phase 3** open-label randomized multi-centre study (Solitaire-U) in USA (Cleveland) and Australia (Melbourne/Sydney)
- Solithromycin 1g stat vs. ceftriaxone 500mg/azithromycin 1g stat
  - 262 men/women enrolled initially - up to 76 extra women/adolescents were included through an R&D agreement with NIAID (slow recruitment)
  - Analysis of the first 262 participants demonstrated that solithromycin failed to show non-inferiority to standard of care

Drug	Modified intention to treat (mITT)	Microbiologically evaluable (ME) population
Solithromycin	80.5%	91.3%
Ceftriaxone/Azithromycin	84.5%	100%

Note: Primary end-point was culture negative at day 7-8
(*N. gonorrhoeae* NAAT at day 21 was also performed as a molecular test of cure)

Zoliflodacin (ETX0914, AZD0914)

- Novel oral spiropyrimidinetrione with dual DNA topoisomerase II inhibitory activity targeting the *gyrB* and *parE* genes
- **Phase 2:** Study conducted in partnership with NIAID
  - Demonstrated high microbiological cure rates at 6 +/- 2days (98% of 49 patients receiving 2g and 100% of 47 patients receiving 3g vs 100% of 21 in the ceftriaxone arm)
  - Good tolerability and minimal side effects (12% - 20/21 mild, 1 mod)
  - No resistance at baseline and no development of resistance on treatment
- Licensure in the US and the EU will require a single **Phase 3** study with approximately 600 patients
- Formulation development on track for **Phase 3** – Entasis/Global Antibiotic & Research Development Partnership (GARDP)

Gepotidacin (GSK2140944)

- Novel triazaacenaphthylene antimicrobial with DNA topoisomerase II inhibitory activity targeting the *gyrA* and *par*C genes
- Claimed that there is no cross-resistance with fluoroquinolones due to different binding to the DNA-protein complex at a location away from that of fluoroquinolones
- However gepotidacin MIC_{90} reported as higher in ciprofloxacin resistant isolates
- **Phase 1**: Safety profile consistent with other marketed antibiotics and there were no significant changes in cardiac parameters

Gepotidacin (GSK2140944)

- **Phase 2**: Open-label randomized multi-centre dose-ranging (1.5g/3g) study with negative culture at 3-7 days post-Rx as primary outcome
  - 106 randomized patients (101men/5 women) enrolled with either positive *N. gonorrhoeae* NAAT or culture results
  - 105/106 received treatment
  - 69 participants had positive baseline cultures - microbiological success good for both treatment groups: 1.5g (29/30, 97%) and 3g (37/39, 95%)
  - Isolates from 2/105 patients developed resistance between baseline and test-of-cure (D86N in ParC and A92T in GyrA)
  - Most side-effects were gastro-intestinal (mostly mild/moderate)
- **Phase 3** study under consideration

Conclusions

- Wherever possible, use ceftriaxone to treat gonorrhoea
- Ceftriaxone allergy is rare and the drug can be given to patients with a history of IgE-mediated penicillin or amoxicillin/ampicillin drug allergy
- Clinicians working in remote clinical settings may prefer to have therapy administered in a hospital environment if there is a history of anaphylaxis/past ITU admission
- In rare situations where ceftriaxone is contra-indicated, patients are best managed in consultation with a Sexual Health specialist
- Some sub-optimal alternatives exist and could be given as dual therapy to maximise the chance of clinical cure – new and better drugs are on the way!