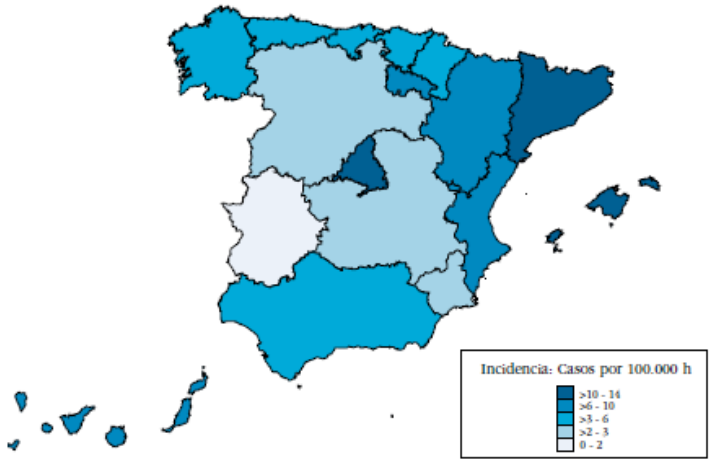
Infecciones por Neisseria gonorrhoeae en nuestro medio. Actitud terapéutica .

Dra. Leire Gil. Medicina Interna Infecciosas. HUSE. 8 de mayo 2015

Vigilancia de Infección gonocócica. España. 2012
Incidencia por Comunidades Autónomas



Fuente: Enfermedades de Declaración Obligatoria (EDO)

http://gesdoc.isciii.es/gesdoccontroller?action=download&id=21/01/2015-3962d0c4cd

Enferm Infecc Microbiol Clin. 2013;31(9):579–583

Enfermedades Infecciosas y Microbiología Clínica
www.elsevier.es/eimc

Original

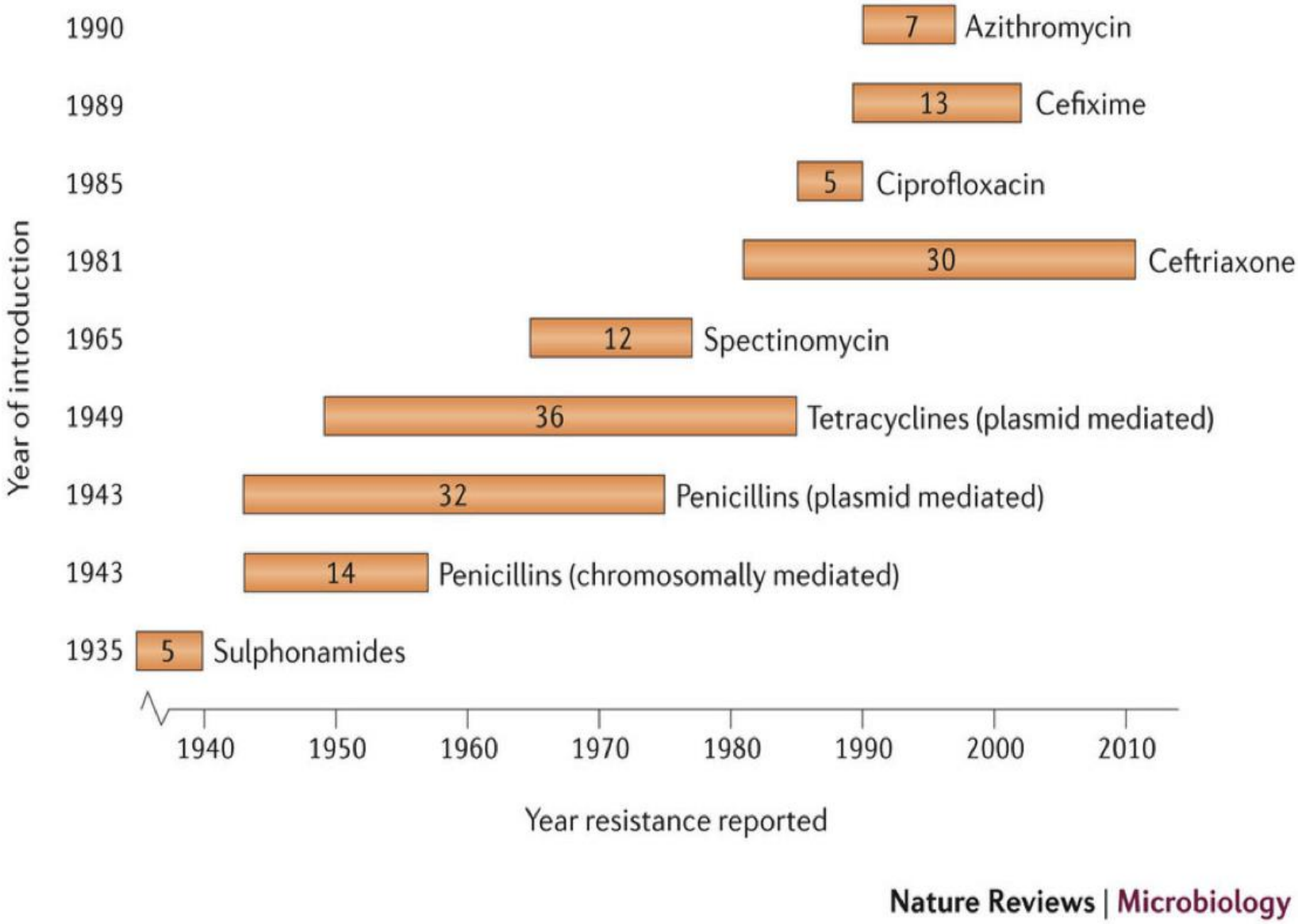
Neisseria gonorrhoeae: resistencias antimicrobianas y estudio de la dinámica poblacional. Situación en 2011 en Barcelona

Judit Serra-Pladevall[a,*], María Jesús Barberá-Gracia[b], Glòria Roig-Carbajosa[c], Rosa Juvé-Saumell[d], Juan José Gonzalez-Lopez[a], Rosa Bartolomé-Comas[a] y Antònia Andreu-Domingo[a]

Infección gonocócica en Islas Baleares.
Tasas /100.000 hab 2003-2013

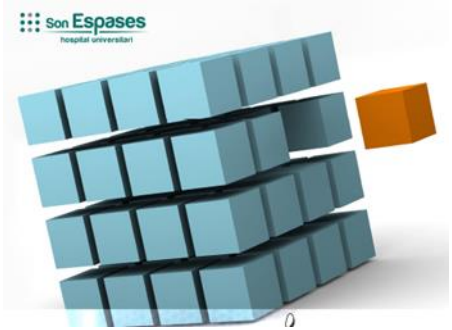
Fulls setmanals de Vigilància Epidemiològica 28/2014. Servei d'Epidemiologia. Direcció General de Salut Pública iConsum. Conselleria de Salut. Illes Balears.

Sesgos:
1.- Búsqueda activa de casos asintomáticos
2.- Técnicas diagnósticas más sensibles: PCR.



Nature Reviews Microbiology 12, 223–229 (2014)

En anteriores episodios:



- **Fluoroquinolonas**

  -Elevadas resistencias / fallos de tratamiento

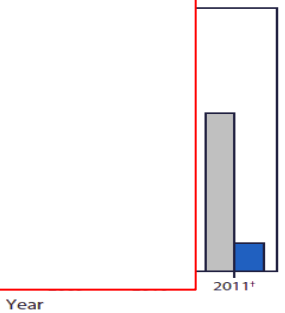
NO recomendadas como régimen de elección

1.- Excepto ante imposibilidad de administrar cefalosporinas IM (no disposición/ negativa del paciente)

2.- Alergia a penicilinas/cefalosporinas

3.- Conocimiento de antibiograma previo a tratamiento de la infección.

(n = 32,794)
0.125 µg/mL)
nococcal
elevated
in 2006 to



http://www.cdc.gov/mmwr/preview/mmwrhtml/Mm6131a3/htm#box

d

si

a

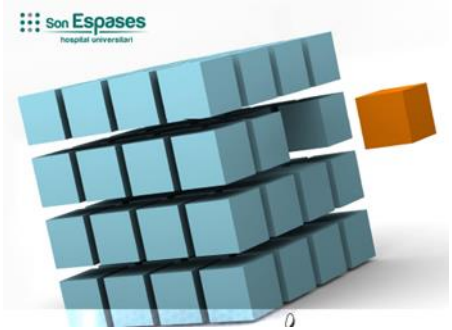
-Descritos casos de fallos de tratamiento y alto nivel de resistencia en Europa , además discrepancias de eficacia y sensibilidad in vivo vs in vitro.

Accesible con referencias bibliográficas en http://iusti.org/regions /Europe/pdf/2012/Gonorrhoea_2012.pdf

Emergence of gonococcal strains with resistance to azithromycin in Spain

L. Arreaza[1], F. Vázquez[2], B. Alcalá[1], L. Otero[3], C. Salcedo[1] and J. A. Vázquez[1]*

Journal of Antimicrobial Chemotherapy (2003) **51**, 190–191
DOI: 10.1093/jac/dkg027



Plan estratégico ECDC

Acciones/estrategia para disminuir las CMIs y mejorar susceptibilidad

- Optimización de terapia antimicrobiana
  1.- Aumento de dosis de antibióticos conocidos
  2.- Asociación de antibióticos:

  →búsqueda de sinergia/influencia sobre CMIs

  3.- Nuevos antibióticos: gentamicina, ertapenem, solitromicina

- Además de intensificar estudios epidemiológicos/sensibilidades antibióticas/estudios de contacto/reportar fallo de tratamiento

Actions

ECDC and IUSTI to review guidance on the management of gonorrhoea treatment failures and recommendations for a test of cureCase definitions for antibiotic treatment failure

Working case definition for confirmed treatment failure: clinical and laboratory criteria

A gonorrhoea patient who returns for test of cure or who has persistent genital symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose)
AND remains positive for one of the following tests for N. gonorrhoeae:
- presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment;
OR
isolation of N. gonorrhoeae by culture taken at least 72 hours after completion of treatment;
OR
positive nucleic acid amplification test (NAAT) taken two to three weeks after completion of treatment
AND
denies sexual contact during the post-treatment follow-up period
AND
decreased susceptibility to cephalosporin used for treatment*:
- cefixime: MIC>0.12 mg/L**
- ceftriaxone: MIC>0.12 mg/L**

- Ideally, the pre- and post-treatment isolates should be examined with an appropriate and highly discriminatory molecular epidemiological typing method (to confirm an identical strain)
- and with genetic methods (to confirm the resistance determinants in order to show that the strain is truly resistant).

** These thresholds are in accordance with EUCAST tentative breakpoints.

Working case definition for probable treatment failure: clinical and laboratory criteria

A gonorrhoea patient who returns for test of cure or who has persistent genital symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose)
AND remains positive for one of the following tests for N. gonorrhoeae:
- presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment;
OR
isolation of N. gonorrhoeae by culture taken at least 72 hours after completion of treatment;
OR
positive nucleic acid amplification test (NAAT) taken two to three weeks after completion of treatment
AND
denies sexual contact during the post-treatment follow-up period.

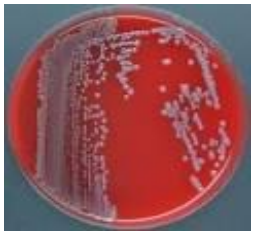
IUSTI
INTERNATIONAL UNION AGAINST SEXUALLY TRANSMITTED INFECTIONS

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

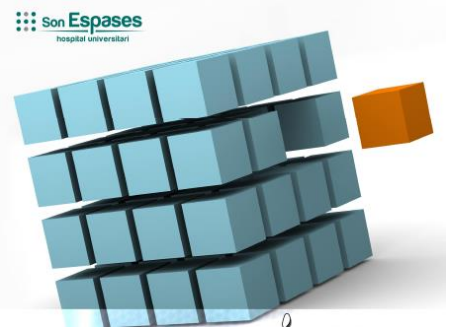
World Health Organization

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Instituto de Salud Carlos III

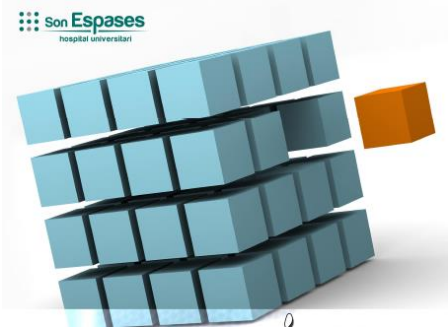


Recomendaciones /guias



GUIA	AÑO	RECOMENDACIÓN	COMENTARIOS
CDC	2012 **Uncomplicated urogenital, anorectal, and pharyngeal gonorrhea**	**Ceftriaxone 250 mg IM** **PLUS** **Azithromycin 1 g orally in a single dose** **or doxycycline 100 mg orally twice daily for 7 days*** Treatment failure after treatment with alternative regimens should be treated with ceftriaxone 250 mg as a single intramuscular dose and azithromycin 2 g orally as a single dose and should receive infectious disease consultation. The case should be reported to CDC through the local or state health department.	***Cefixime 400 mg in a single oral dose PLUS** **Azithromycin 1 g orally in a single dose** **or doxycycline 100 mg orally twice daily for 7 days*** PLUS **Test-of-cure in 1 week** Allergy : Azitromicin 2gr single oral dose * Because of the high prevalence of tetracycline resistance among Gonococcal Isolate Surveillance Project isolates, particularly those with elevated minimum inhibitory concentrations to cefixime, the use of azithromycin as the second antimicrobial is preferred.

Accesible en:
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm#box



2012 European Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults // IUSTI. Org // WHO

Revision date: 1 November 2012
Proposed date for review: 1 November 2014

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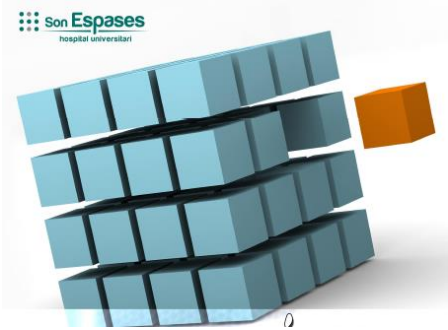
	Recomendación	Alternativas
Uncomplicated N. gonorrhoeae infections of the urethra, cervix and when the antimicrobial sensitivity of the infection is unknown	Ceftriaxone 500 mg intramuscularly (IM) as a single dose together with azithromycin 2 g as single oral dose *Pregnancy/bresatfeeding Ceftriaxone 500 IM single dose	Cefixime 400 mg oral as a single dose together with azithromycin 2 g as a single oral dose Spectinomycin 2 g IM as a single dose together with azithromycin 2 g as a single oral dose if resistance to extended-spectrum cephalosporins is identified or suspected, or history of penicillin annafilaxis
Uncomplicated gonococcal infection of the pharynx	Ceftriaxone 500 mg IM as a single dose together with azithromycin 2 g oral single dose	Azithromycin 2 g as a single oral dose penicilin anaphilaxys Ciprofloxacin 500 mg as a single oral dose or ofloxacin 400 mg as a single oral dose
Genital, anorectal and pharyngeal gonococcal infection **when extended-spectrum cephalosporin resistance identified**	Ceftriaxone 1 g IM as a single dose together with azithromycin 2 g oral single dose [	**Gentamicin 240 mg IM** as a single dose together with azithromycin 2 g oral as single dose [IV, C].

El papel de la gentamicina en el tratamiento del gonococo



RESEARCH Open Access

The effectiveness of gentamicin in the treatment of *Neisseria gonorrhoeae*: a systematic review

Hathorn *et al. Systematic Reviews* 2014, **3**:104
http://www.systematicreviewsjournal.com/content/3/1/104

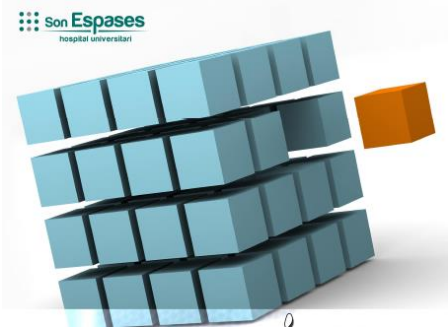
Table 1 Characteristics of included studies

Author	Methods	Participants	Intervention		Primary outcome	Evaluation of re-infection
			Gentamicin	Comparator		
Hira et al. (1984) [36]	Quasi-random (treatment assigned to alternate consecutive patients)	Men with uncomplicated gonorrhoea infection (gram-negative diplococci on urethral smear), Lusaka, Zambia	Single-dose gentamicin 280 mg intramuscular injection (n = 302)	Single-dose kanamycin 2 g intramuscular injection (n = 113)	Cure	All patients advised to abstain from sexual activity for 2 weeks after therapy.
					Patients in whom *N. gonorrhoea* persisted or re-appeared (as determined by a positive result of a smear or culture) in the absence of sexual activity during the follow-up period were considered to be treatment failure	Patients excluded if reported sexual activity during 2 weeks follow-up period with or without persistent or re-appearing gonorrhoea on culture
Iskandar et al. (1978) [33]	RCT (randomly allocated to 3 groups of 30 patients)	Men with acute gonorrhoea infection (gonorrhoea on Gram stain of urethral smears), Egypt	Single-dose gentamicin 240 mg intramuscular injection (n = 30)	Co-trimoxazole (Bactrim, Roche) 8 tablets daily divided into 2 doses for 2 days (n = 30). Trimethoprim-sulphametrol (Lidaprim, Ciba) 8 tablets divided into 2 doses for 2 days (n = 30)	Cure	One case of re-infection reported in which there was a history of re-exposure.
					Cases with negative smears plus resolution of discharge on day 7 were considered cured	Safe sex advice and assessment of re-infection not described
Pareek and Chowdhury (1981) [35]	Non-randomised, comparator study	Men with urethral gonorrhoea infection (culture positive and beta lactamase detected), Riyadh, Saudi Arabia	Single-dose gentamicin 160 mg intramuscular injection (n = 20)	Single-dose spectinomycin 2 g intramuscular injection (n = 20)	Cure Patients in whom culture on days 3, 7 and 14 post treatment were negative were considered cured	Safe sex advice, definition and assessment of re-infection not described
Yoon et al. (1988) [34]	RCT (random numbered tickets used to divide patients into 2 groups)	Men with uncomplicated gonococcal urethritis (Gram stain and 'bacteriological test of urethral secretions'), Seoul, Korea	Single-dose gentamicin 240 mg intramuscular injection (n = 137)	Single-dose kanamycin 2 g intramuscular injection (n = 137)	Cure Cases with negative Gram stain and bacteriological test (undefined) of urethral secretions	All patients advised to avoid sexual intercourse during the period of treatment. Definition and assessment of re-infection not described
Lule et al. (1994) [28]	RCT (computerised randomisation)	Men presenting with urethral discharge +/−dysuria and gram-negative intracellular diplococci on urethral smear and/or positive culture, Malawi	Single-dose gentamicin 240 mg intramuscular injection (n = 40)	Amoxicillin 3 gm, probenecid 1 gm, and clavulanate 125 mg by mouth once (n = 60)	To determine the relative contribution of gonorrhoea and chlamydia to urethritis in Malawi	Safe sex advice not described
				Amoxicillin 3 gm, probenecid 1 gm, and clavulanate 125 mg, by mouth once and doxycycline 100 mg BD for 7 days (n = 56)	To evaluate the effectiveness of five antibiotic therapies for urethritis	6/48 (12.5%) patients with persistent gonococcal infection at follow-up reported having sex between initial and follow-up visits compared to 21 of 249 (8.4%) men for whom gonococcal infection was not detected at follow-up (p = 0.4)
				Ciprofloxacin 250 mg by mouth once (n = 59)	Cure not defined. An assessment of symptoms and signs, urethral Gram stain and culture were obtained at 8–10 days post treatment	
				Co-trimoxazole (trimethoprim 320 mg/sulphamethoxazole 1,600 mg) by mouth for 2 days (n = 28)		

Guias españolas

GUIA	AÑO	ENTIDAD	RECOMENDACIÓN	ALTERNATIVAS
Guia terapeútica antimicrobiana	2014	Infección uretral/endocervical /faringea /anal no complicada	Ceftriaxona 250-500mg ó cefixima 400mg vo + Azitromicina 1-2 gr en MD	* Si áreas con > 5% de prevalencia de cepas con CMI elevadas a ceftriaxona ; Ceftriaxona 500mg + Azitromicina 2gr.
GESIDA	2010	Infección uretral/endocervical	-Cefixima: 400 mg vo -Ceftriaxona: 125-250 mg IM (A) -Cefuroxima axetilo: 1 gr vo -Ciproflox/ Oflox (A) /levoflox/norflox vo -Espectinomicina: 2 gr IM (A) - Azitromicina 1-2 gr vo	
Grupo de trabajo sobre ITS	2011		**Ceftriaxona 250 mg IM, dosis única ó Cefixima 400 mg, dosis única**	

El papel del ertapenem en el tratamiento del gonococo

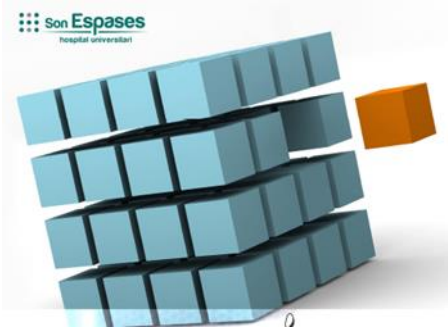


AAC

In Vitro Activity of Ertapenem versus Ceftriaxone against *Neisseria gonorrhoeae* Isolates with Highly Diverse Ceftriaxone MIC Values and Effects of Ceftriaxone Resistance Determinants: Ertapenem for Treatment of Gonorrhea?

Unemo, Magnus et al. Antimicrobial Agents and Chemotherapy July 2012 Volume 56 Number 7; p. 3603-3609

- El ertapenem no se tuvo ventajas frente a la ceftriaxona en las cepas de CMI más bajas , in vitro.
- Las cepas con CMIs más altas a ceftriaxona (0.5 a 4 ug/ml) se correspondieron con CMIs más bajas a ertapenem 0.016 a 0.064ug/ml.
- Podría ser una opción en tratamiento DUAL para gonococia, pero se requieren estudios genéticos para conocer la posbilidad de aparición de carbapenemasas / otros mecanismos de resistencia por parte del gonococo hacia el ertapenem así como estudios in vivo de eficacia /seguridad.



In Vitro Activity of the New Fluoroketolide Solithromycin (CEM-101) against a Large Collection of Clinical *Neisseria gonorrhoeae* Isolates and International Reference Strains, Including Those with High-Level Antimicrobial Resistance: Potential Treatment Option for Gonorrhea?

Daniel Golparian,[a] Prabhavathi Fernandes,[b] Makoto Ohnishi,[c] Jörgen S. Jensen,[d] and Magnus Unemo[a]

Antimicrobial Agents and Chemotherpy 2012; p2739-2742

- Eficacia **in vitro** del fluoroketólido frente a cepas de diferentes orígenes geográficos algunas de ellas con elevadas resistencias a cefalosporinas .

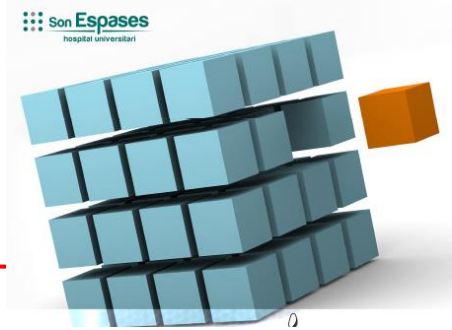
- Actividad también frente *a Chlamydia y Mycoplasma genitalium*

- Ptes estudios in vivo toxicidad/farmacocinética.

TABLE 1 MICs of solithromycin, relative to MICs of antimicrobials previously or currently used for treatment of gonorrhea and MICs of telithromycin (first developed ketolide), against 246 clinical *N. gonorrhoeae* isolates and international reference strains

Antimicrobial	MIC (μg/ml)[a] Range	50%[c]	90%[d]	Resistance (%)[b]
Solithromycin[e]	0.001–32	0.125	0.25	ND
Azithromycin	0.001–>256	0.5	8	37.8[f]
Telithromycin	0.001–>256	0.25	1	ND
Erythromycin	0.064–>2[f]	>2[f]	>2[f]	94.3
Cefixime	<0.016–8	0.032	0.25	6.5
Ceftriaxone	<0.002–4	0.016	0.125	1.2
Ampicillin	<0.016–>256	1	16	24.4
Ciprofloxacin	0.002–>32	4	>32	64.2[h]
Spectinomycin	4–>1,024	16	16	2.0[f]
Tetracycline	0.125–256	4	64	69.5

Además del tratamiento…..



1. ***Estudio de contactos:***

   - Evaluación y tratamiento de parejas en 60 dias previos a la infección : prevención transmisibilidad y cronificación.

   - HTSX : posibilidad de utilizar a paciente como transmisor del régimen antibiótico

2. ***TEST DE CURA* a la semana**

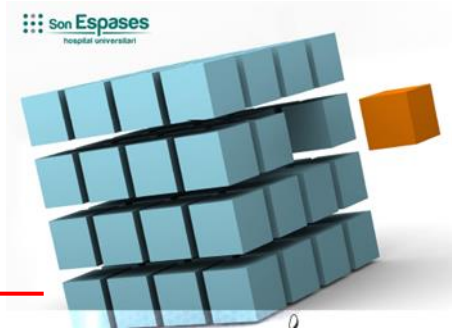
En pacientes que no se ha administrado el régimen de elección, persistencia de sintomatologia, embarazadas o lozalización **no genital** de la infección (sobre todo a nivel faringeo):

- *Cultivo vs PCR*

3.- ***Notificar*** fallos de tratamiento al organismo responsable

Locorregional (epidemiologia caib) --- Carlos III--- ECDC

take home messages



1.El aumento de la resistencia de *Neisseria gonorrhoeae* a fármacos de primera línea tiene importantes implicaciones en la **salud pública**, ya que la efectividad del tratamiento es esencial en la reducción de la morbilidad, de las complicaciones y de la expansión de la infección en la población.

2.**Importancia** de la toma de muestras (cultivo) para conocer la epidemiologia de nuestro medio y adecuar los tratamientos.

3.La evaluación los **contactos** implicaría el conocimiento de cepas para **sensibilidades y estudio de posibles brotes**

4.- Además es posible que la **uniformidad de tratamientos** implique a la larga un **efecto en las CMI** de los antibióticos utilizados (ej cefalosp+ azitrom)

Pero si las hubiera en nuestro medio:

Ceftriaxona 250mg IM + Azitromicina 1 gr

Estudio prospectivo

“Análisis de la tendencia en la tendencia de la infección por gonococo en Mallorca y su relación con los parámetros de sensibilidad antibiótica”

Gracias.