CESPER 2023

C’è da modificare qualcosa nella terapia dello streptococco A ?

PEDIATRIA BELLUNO

Giangiacomo Nicolini

Caso clinico

18/9/2023

Derek ha 5 anni

Anamnesi patologica prossima

* Dalla mattina precedente comparsa di febbre
* Dalla sera precedente comparsa di dolore e tumefazione al testicolo dx
* Dalla mattina della visita comparsa di tumefazione al pene, con successiva comparsa di ematomi a pene/testicoli e a livello cutaneo

Anamnesi patologica remota

* Un anno fa angioedema massivo post COVID
* No allergie nemmeno a livello familiare

Esame obiettivo

* OF iperemico, tonsille sanguinanti, senza essudato, non linfonodi; ematoma alla radice del pene e allo scroto, alle caviglie e arti inferiori, con noduli sottocutanei duri e dolenti appena comparsi
* T 37.9°C, parametri regolari.

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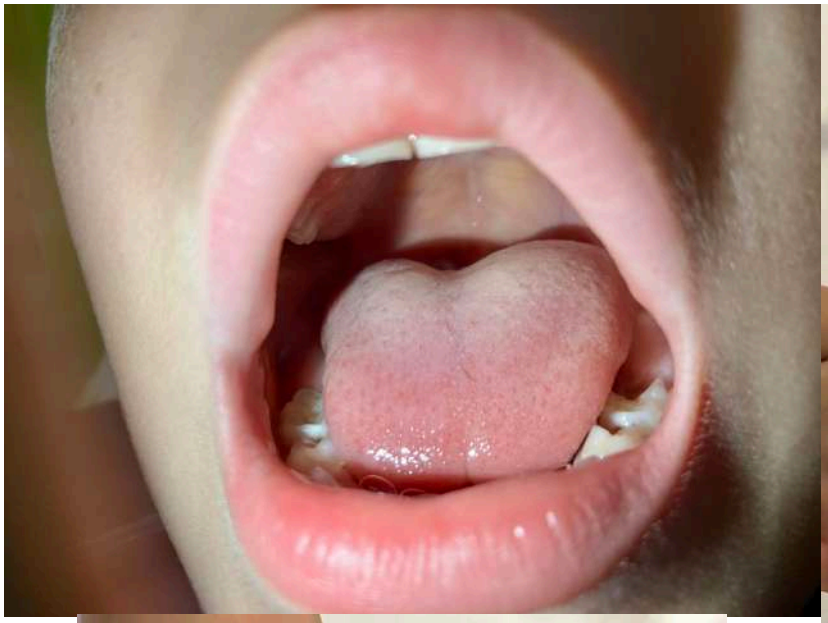
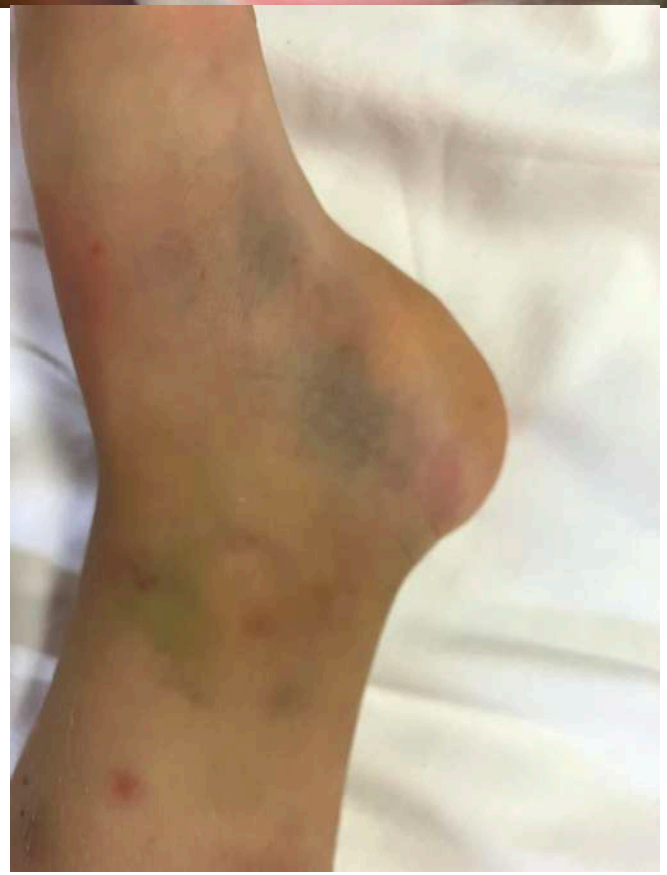
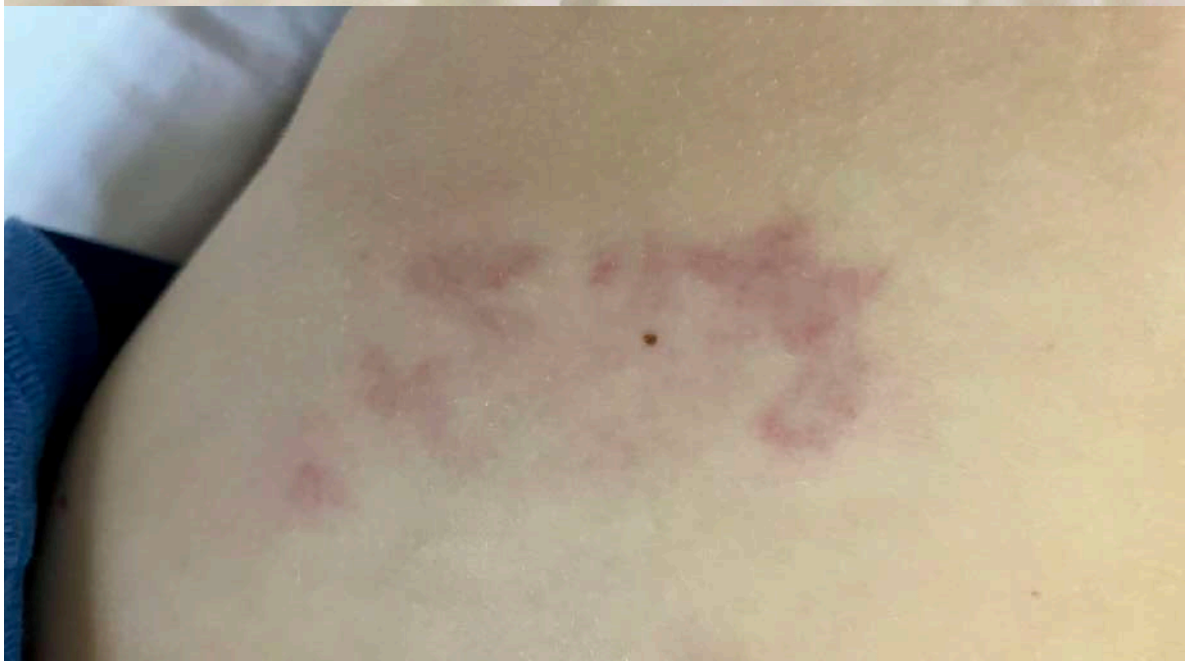




Il Tampone rapido per GAS risulta

POSITIVO



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Domanda: quale terapia?

- Amoxicillina 50 mg/Kg/die in 2 somministrazioni
- Cefalosporina orale (cefaclor)
- Amoxicillina 50 mg/Kg/die in 3 somministrazioni
- Azitromicina 10 mg/Kg/die

Domanda: per quanti giorni?

- 10 giorni
- 10 giorni se amoxi, 7 se cefaclor o azitro
- 5 - 7 giorni
- 7 giorni se amoxi, 5 se cefalo, 3 se azitro

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Faringotonsillite da GAS Possibili obiettivi e domande

1. Curare la patologia acuta?
2. Per impedire l'evoluzione dei sintomi verso complicanze suppurative o non suppurative?
3. Se si, con cosa? Se sì, per quanto?
4. Possiamo evitare/prevenire/trattare le ricadute e le infezioni ricorrenti?
5. Possiamo eradicare GAS dalla gola sterilizzando i portatori?
6. Come trattare le I - GAS?

Barbieri *et al. Italian Journal of Pediatrics* (2019) 45:103
https://doi.org/10.1186/s13052-019-0696-9

Italian Journal of Pediatrics

RESEARCH Open Access

CESPER 2023

Antibiotic prescriptions in acute otitis media and pharyngitis in Italian pediatric outpatients

E. Barbieri[1*], D. Donà[2,3], A. Cantarutti[4,5], R. Lundin[3], A. Scamarcia[6], G. Corrao[4,5], L. Cantarutti[6] and C. Giaquinto[2,3,4,6]

Table 3 Distribution of first line treatment antibiotic therapy for GABHS pharyngitis. Pedianet, Italy, 2010–2015

	GABHS pharyngitis (*N* = 37,929)					
	No test- No result/Dubious result		Positive test		Total	
	N	(%)	N	(%)	N	(%)
Amoxicillin	10,602	(42.5)	5438	(55.8)	16,040	(46.3)
CV-Amoxicillin	8004	(32.1)	2341	[24]	10,345	(29.8)
Cephalosporins - III gen.	4022	(16.1)	1127	(11.6)	5149	(14.9)
Cephalosporins - II gen.	1349	(5.4)	389	[4]	1738	[5]
Macrolides/Lincosamides	925	(3.7)	449	(4.6)	1374	[4]
Other[a]	20	(0.1)	5	(0.1)	25	(0.1)
Total treated	24,922	(90.2)	9749	(94.7)	34,671	(91.4)
Total not treated	2708	(9.8)	550	(5.3)	3258	(8.6)

[a]Clofoctol

Antibiotico vs terapia sintomatica

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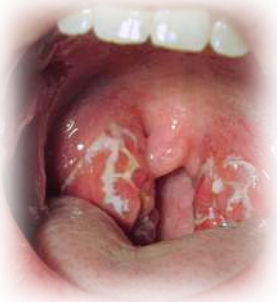
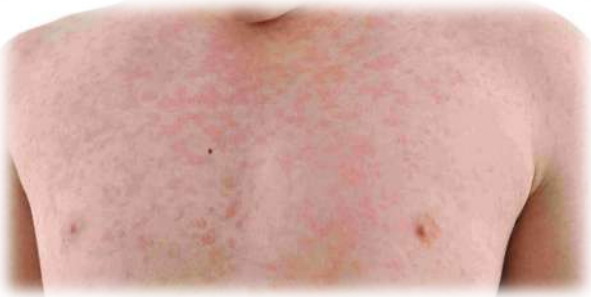
* Riduce gravità e durata della sintomatologia?
* Riduce il rischio di recidive?
* Riduce il rischio di complicanze suppurative?
* Riduce il rischio di complicanze non suppurative?





Complicanze

Suppurative

* Ascesso peritonsillare, parafaringeo, o retrofaringeo
* Otite media
* Sinusite
* Mastoidite
* Rare: Tromboflebite vena giugulare, meningite, polmonite, foci settici

Non Suppurative

* Malattia reumatica
* Glomerulonefrite acuta

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Antibiotics for treatment of sore throat in children and adults (Review)

Spinks A, Glasziou PP, Del Mar CB

Cochrane Library

Cochrane Database of Systematic Reviews

Background

Sore throat is a common reason for people to present for medical care and to be prescribed antibiotics. Overuse of antibiotics in primary medicine is a concern, hence it is important to establish their efficacy in treating sore throat and preventing secondary complications.

Objectives

To assess the effects of antibiotics for reducing symptoms of sore throat for child and adult patients.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs of antibiotics versus control assessing typical sore throat symptoms or complications amongst children and adults seeking medical care for sore throat symptoms.

Main results

We included 29 trials with 15,337 cases of sore throat. The majority of included studies were conducted in the 1950s, during which time the rates of serious complications (especially acute rheumatic fever) were much higher than today. Although clinical antibiotic trials for sore throat and respiratory symptoms are still being conducted, it is unusual for them to include placebo or 'no treatment' control arms, which is a requirement for inclusion in the review.

The age of participants ranged from younger than one year to older than 50 years, but most participants across all studies were adults. Although all studies recruited patients presenting with symptoms of sore throat, few of them distinguished between bacterial and viral aetiology. Bias may have been introduced through non-clarity in treatment allocation procedures and lack of blinding in some studies. Harms from antibiotics were poorly or inconsistently reported, and were thus not quantified for this review.

Antibiotics for treatment of sore throat in children and adults (Review)

Spinks A, Glasziou PP, Del Mar CB

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1. Symptoms

Throat soreness and headache at day three were reduced by using antibiotics, although 82% of participants in the placebo or no treatment group were symptom-free by one week. The reduction in sore throat symptoms at day three (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.60 to 0.80; 16 studies, 3730 participants; moderate-certainty evidence) was greater than at one week in absolute numbers (RR 0.50, 95% CI 0.34 to 0.75; 14 studies, 3083 participants; moderate-certainty evidence) due to many cases in both treatment groups having resolved by this time. The number needed to treat for an additional beneficial outcome (NNTB) to prevent one sore throat at day three was less than six; at week one it was 18. Compared with placebo or no treatment, antibiotics did not significantly reduce fever at day three (RR 0.75, 95% CI 0.53 to 1.07; 8 studies, 1443 participants; high-certainty evidence), but did reduce headache at day three (RR 0.49, 95% CI 0.34 to 0.70; 4 studies, 1020 participants; high-certainty evidence).

2. Suppurative complications

Whilst the prevalence of suppurative complications was low, antibiotics reduced the incidence of acute otitis media within 14 days (Peto odds ratio (OR) 0.21, 95% CI 0.11 to 0.40; 10 studies, 3646 participants; high-certainty evidence) and quinsy within two months (Peto OR 0.16, 95% CI 0.07 to 0.35; 8 studies, 2433 participants; high-certainty evidence) compared to those receiving placebo or no treatment, but not acute sinusitis within 14 days (Peto OR 0.46, 95% CI 0.10 to 2.05; 8 studies, 2387 participants; high-certainty evidence).

3. Non-suppurative complications

There were too few cases of acute glomerulonephritis to determine whether there was a protective effect of antibiotics compared with placebo against this complication (Peto OR 0.07, 95% CI 0.00 to 1.32; 10 studies, 5147 participants; low-certainty evidence). Antibiotics reduced acute rheumatic fever within two months when compared to the control group (Peto OR 0.36, 95% CI 0.26 to 0.50; 18 studies, 12,249 participants; moderate-certainty evidence). It should be noted that the overall prevalence of acute rheumatic fever was very low, particularly in the later studies.

Authors' conclusions

Antibiotics probably reduce the number of people experiencing sore throat, and reduce the likelihood of headache, and some sore throat complications. As the effect on symptoms can be small, clinicians must judge on an individual basis whether it is clinically justifiable to use antibiotics to produce this effect, and whether the underlying cause of the sore throat is likely to be of bacterial origin. Furthermore, the balance between modest symptom reduction and the potential hazards of antimicrobial resistance must be recognised. Few trials have attempted to measure symptom severity. If antibiotics reduce the severity as well as the duration of symptoms, their benefit will have been underestimated in this meta-analysis. Additionally, more trials are needed in low-income countries, in socio-economically deprived sections of high-income countries, as well as in children.

CESPER 2023

ORIGINAL ARTICLES

www.jpeds.com • The Journal of Pediatrics

(J Pediatr 2012;160:832-6)

Population-Based Study of Incidence and Clinical Characteristics of Rheumatic Fever in Abruzzo, Central Italy, 2000-2009

Luciana Breda, MD[1], Valentina Marzetti, MD[1], Stefania Gaspari, MD[1], Marianna Del Torto, MD[1], Francesco Chiarelli, PhD[1], and Emma Altobelli, MD[2]

Criteri di Jones: basso rischio in presenza di un'incidenza annuale di MR inferiore a 2 per 100.000 bambini in età scolare

Acute Rheumatic Fever: Where Do We Stand? An Epidemiological Study in Northern Italy

February 2021 | Volume 8 | Article 621668

Achille Marino[1], Rolando Cimaz[2,3], Maria Antonietta Pelagatti[4], Giulia Tattesi[4], Andrea Biondi[4], Laura Menni[5], Marco Sala[5], Patrizia Calzi[6], Francesco Morandi[7], Francesca Cortinovis[7], Anna Cogliardi[8], Claudia Addis[8], Roberto Bellù[8], Massimo Andreotti[1] and Tiziana Varisco[1]*

Toward the Knowledge of the Epidemiological Impact of Acute Rheumatic Fever in Italy

published: 15 December 2021

Antonino Maria Quintilio Alberio[1†], Filippo Pieroni[1†], Alessandro Di Gangi[1], Susanna Cappelli[1], Giulia Bini[1], Sarah Abu-Rumeileh[2], Alessandro Orsini[3], Alice Bonuccelli[3], Diego Peroni[1], Nadia Assanta[4], Carla Gaggiano[5], Gabriele Simonini[2] and Rita Consolini[6]*

frontiers in Pediatrics

Paese		Incidenza annuale (per 100.000 persone)
Italia	Abruzzo (Breda et al., 2012)	4.1
	Lombardia(Marino et al., 2021)	5.7
	Toscana(Alberio et al., 2021)	0.9-7.33
Stati Uniti(Bradley-Hewitt et al., 2019)		0.61
Galles (Saunders et al., n.d.)		0.81
Israele (Tal et al., 2022)		0.54 per 1000 ospedalizzazioni
Turchia(Gürses et al., 2021)		3.3-14.4
Uganda (Okello et al., 2021)		13-25
India(Kumar et al., 2014)		8.7
Australia (Katzenellenbogen et al., 2020)		Indigeni 71.9 non-Indigeni 0.6
Nuova Zelanda(Bennett et al., 2021)		Non indigeni 1.6 Maori 35.9 Isole del Pacifico 79.6

GL nel mondo

CESPER 2023

Al momento in Italia l'indicazione è di identificare e trattare le tonsilliti da GAS

Tuttavia diventa fondamentale implementare nuovi studi per identificare la attuale prevalenza di Malattia Reumatica

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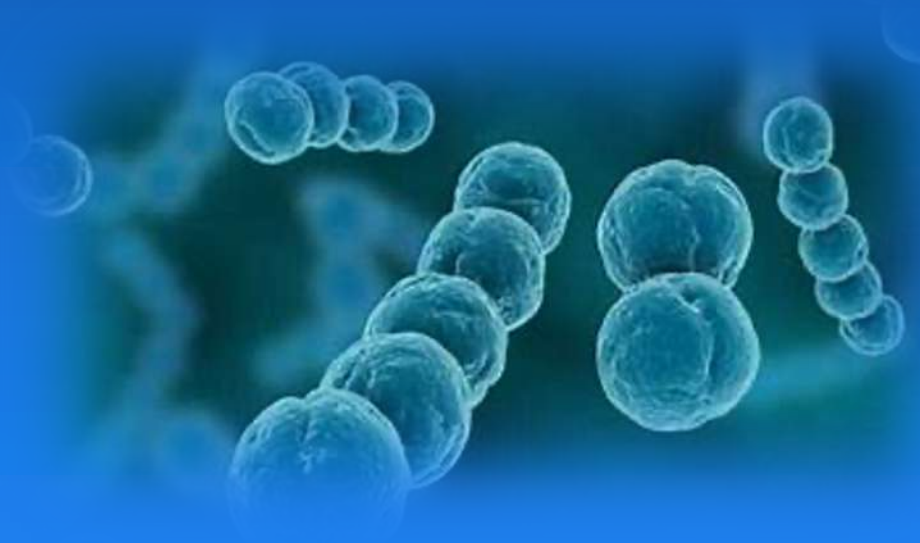
GAS e resistenze



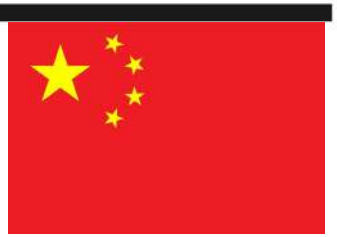
Current Clinical Pharmacology, 2020, *15*, 125-131

RESEARCH ARTICLE

BENTHAM SCIENCE

Severe Group A and Group B Streptococcus Diseases at a Pediatric ICU: Are they Still Sensitive to the Penicillins?

CESPER 2023



Kam L. Hon[2,*], Tai C. Chow[2], Tsun S. Cheung[2], Wai T. Lam[2], Lok T. Hung[2], King W. So[1], I.P. Margaret[3] and Su Y. Qian[4]

[1]Department of Paediatrics, The Chinese University of Hong Kong, Central Ave, Hong Kong; [2]Faculty of Medicine, The Chinese University of Hong Kong, Central Ave, Hong Kong; [3]Department of Microbiology, The Chinese University of Hong Kong, Central Ave, Hong Kong; [4]Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China

***Methods*:** All children admitted to PICU of a teaching hospital between October 2002 and May 2018 with laboratory-proven GAS and GBS isolations were included.

***Results*:** There were 19 patients (0.7% PICU admissions) with streptococcal isolations (GAS, n=11 and GBS, n=8). Comparing to GAS, GBS affected infants were younger (median age 0.13 versus 5.47 years, 95% CI, 1.7-8.5, p=0.0003), and cerebrospinal fluids more likely positive (p = 0.0181). All GAS and GBS were sensitive to penicillin (CLSI: MICs 0.06 – 2.0 μg/mL), with the majority of GAS sensitive to clindamycin and erythromycin, and half of the GBS resistant to clindamycin and erythromycin. Co-infections were prevalent, but viruses were only isolated with GAS (p=0.024). Isolation of GAS and GBS was associated with nearly 40% mortality and high rates of mechanical ventilation and inotropic supports. All non-survivors had high mortality (PIM2) and sepsis scores.

***Conclusions*:** Severe GAS and GBS are rare but associated with high mortality and rates of mechanical ventilation and inotropic supports in PICU. The streptococci are invariably sensitive to penicillin.

JOURNAL OF MEDICAL MICROBIOLOGY

RESEARCH ARTICLE

Ubukata *et al.*, *Journal of Medical Microbiology* 2020;69:443–450
DOI 10.1099/jmm.0.001158

MICROBIOLOGY SOCIETY

CESPER 2023

Changes in epidemiologic characteristics and antimicrobial resistance of *Streptococcus pyogenes* isolated over 10 years from Japanese children with pharyngotonsillitis

Kimiko Ubukata[1,*], Takeaki Wajima[2], Miyuki Morozumi[1], Megumi Sakuma[1], Takeshi Tajima[3], Keita Matsubara[4], Koju Itahashi[5] and Satoshi Iwata[1,6]

Methodology. GAS isolated from paediatric patients with pharyngotonsillitis during Period I (mid-2007 to 2008, *n*=235), Period II (2012, *n*=210), and Period III (2018, *n*=189) were analysed for *emm* type, multilocus sequence type (MLST), antibiotic susceptibility, and macrolide (ML)- and quinolone (QL)-resistance genes.

Results. Over 20% of isolates represented *emm*1 and *emm*12 types, remaining common in all three periods. Among other *emm* types, *emm*4 was common in Period I, *emm*28 and *emm*89 in Period II, and *emm*3 and *emm*89 in Period III. All isolates remained highly susceptible to penicillins and cephalosporins. Isolates possessing *mefA*, *ermA*, or *ermB* genes mediating ML resistance increased from 34.9% in Period I to 60.9% in Period II, but fell to 27.5% in Period III. QL-resistant isolates with amino acid substitutions affecting ParC and/or GyrA gradually increased from 11.5 to 14.3%. Specific sequence types identified by MLST and *emm* typing were associated closely with ML or QL resistance.

Conclusion. Our findings indicate that even in ambulatory care, antibiotic choice for these infections should be based on rapid identification and characterization of causative pathogens.

REVIEW ARTICLE

OMAN MEDICAL JOURNAL [2021], VOL. 36, NO. 1: e222

Group A *Streptococcus* Antibiotic Resistance in Iranian Children: A Meta-analysis

Farzad Khademi[1]*, Hamid Vaez[2], Amirhossein Sahebkar[3,4,5] and Ramezan Ali Taheri[6]

Results: Our analysis indicated the following prevalence pattern for *S. pyogenes* antimicrobial resistance in Iran: 4.2% to penicillin, 38.3% to amoxicillin, 5.4% to erythromycin, 12.0% to azithromycin, 12.6% to clarithromycin, 12.4% to clindamycin, 15.3% to rifampicin, 8.1% to ceftriaxone, 17.6% to cefixime, 36.9% to ampicillin, 14.1% to vancomycin, 8.4% to chloramphenicol, 30.4% to tetracycline, 8.8% to cefotaxime, 82.8% to trimethoprim/sulfamethoxazole, 39.6% to gentamicin, 11.9% to ofloxacin, 28.3% to carbenicillin, 3.1% to ciprofloxacin, 6.1% to imipenem, 18.2% to cephalothin, 57.6% to tobramycin, 49.3% to kanamycin, 79.0% to cloxacillin, 12.9% to cephalexin, 10.7% to cefazolin, and 89.5% to amoxicillin-clavulanic acid. ***Conclusions:*** Our findings suggest penicillin (in non-allergic children) and macrolides, lincosamides, and narrow-spectrum cephalosporins (in penicillin-allergic children) as the treatments of choice in Iran.

Journal of Microbiology, Immunology and Infection (2021) 54, 1086—1093

Available online at www.sciencedirect.com

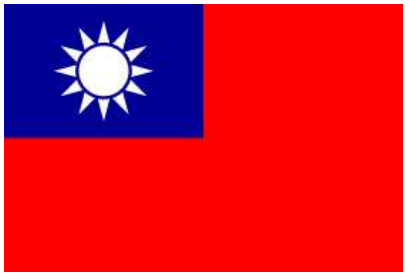
ScienceDirect

journal homepage: www.e-jmii.com

CESPER 2023

Original Article

Emergence of macrolide-resistant *Streptococcus pyogenes emm*12 in southern Taiwan from 2000 to 2019



Wei-Chun Tsai [a,1], Ching-Fen Shen [a], Ya-Lan Lin [a], Fan-Ching Shen [b], Pei-Jane Tsai [c,d], Shu-Ying Wang [d,e], Yee-Shin Lin [d,e], Jiunn-Jong Wu [f], Chia-Yu Chi [a,b,g,**], Ching-Chuan Liu [a,d,*]

Results: A total of 320 GAS from 339 children were enrolled. Most of the children (75%) were under 9 years of age. The most common diagnosis was scarlet fever (225, 66.4%), and the frequency increased from 54.8% in the 1st to 77.9% in the 2nd decade ($p < 0.0001$). There was a significant increase in resistance to erythromycin and azithromycin from 18.1%, 19.3% in the 1st to 58.4%, 61.0% in the 2nd decade ($p < 0.0001$). This was associated with clonal expansion of the GAS *emm*12-ST36 which carrying *erm*(B) and *tet*(M) from 3.0% in the 1st to 53.2% in the 2nd decade ($p < 0.0001$).

Eur J Clin Microbiol Infect Dis (2015) 34:1797–1802
DOI 10.1007/s10096-015-2414-x

ARTICLE

Decline in macrolide resistance rates among *Streptococcus pyogenes* causing pharyngitis in children isolated in Italy

G. Gherardi[1] · D. Petrelli[2] · M. C. Di Luca[2,7] · F. Pimentel de Araujo[1,8] · P. Bernaschi[3] · A. Repetto[4] J. Bellesi[5] · L. A. Vitali[6]

In Italy, based on regional studies mainly, macrolide resistance rates steadily increased from 9 % in 1992 to 53 % in 1997 [24]. Over the period 2000–2009, the rates continued to remain high in Central Italy, varying between 16 % and 36 % [10, 11]. In those years, Italy was among the regions with the highest levels of erythromycin resistance in Europe. According to the present study, we witnessed, for the first time, a decline in macrolide resistance rates in Central Italy, among GAS isolates over the period 2012–2013, down to 7.4 %.

Macrolide resistance gene/phenotype	No. of resistant strains (%)		
	2012	2013	2012+2013
mef(A)/M	14 (50 %)	4 (25 %)	18 (40.9 %)
erm(A)/iMLS$_B$	0	3 (18.75 %)	3 (6.8 %)
erm(B)/cMLS$_B$	14 (50 %)	9 (56.25 %)	23 (52.3 %)

CESPER 2023

Journal of Medical Microbiology (2015), **64**, 1186–1195 DOI 10.1099/jmm.0.000146

CESPER 2023

Evolution of macrolide resistance in *Streptococcus pyogenes* over 14 years in an area of central Italy

Raffaela Olivieri,[1,2]† Matteo Morandi,[1,3]† Alessandra Zanchi,[1] Giacinta Tordini,[1] Gianni Pozzi,[1,2] Andrea De Luca[1,3] and Francesca Montagnani[1,3]

2744 *S. pyogenes* isolates

2000–2013. The total resistance rate to erythromycin of the isolates was 17.9 %. A maximum of erythromycin resistance emerged in 2000 (38.6 %), followed by a significant decrease to 5.2 % in 2012 ($P<0.0001$). Molecular analysis revealed the presence and co-presence of known genetic resistance determinants *mefA*, *mefE*, *ermTR* and *ermB*, in line with phenotypes. PFGE analysis identified genetically related groups in 2000 and 2007–2008, mainly the MLS and M phenotypes, respectively.

CESPER 2023

Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe

*Mike Sharland, Celine Pulcini, Stephan Harbarth, Mei Zeng, Sumanth Gandra, Shrey Mathur, *Nicola Magrini, on behalf of the 21st WHO Expert Committee on Selection and Use of Essential Medicines*

www.thelancet.com/infection **Vol 18 January 2018**

Access

Amoxicillin
Amoxicillin and clavulanic acid
Ampicillin
Benzathine benzylpenicillin
Benzylpenicillin
Cefalexin or cefazolin
Chloramphenicol
Clindamycin
Cloxacillin
Doxycyline
Gentamicin or amikacin
Metronidazole
Nitrofurantoin
Phenoxymethylpenicillin
Procaine benzylpenicillin
Spectinomycin
Sulfamethoxazole and trimethoprim

Core access antibiotics

Azithromycin
Cefixime
Cefotaxime
Ceftriaxone
Ciprofloxacin
Clarithromycin
Piperacillin and tazobactam
Meropenem
Vancomycin

* Antibiotics that are also in the Watch group

Watch

Anti-pseudomonal penicillins with beta-lactamase inhibitor (eg, piperacillin and tazobactam)
Carbapenems or penems (eg, faropenem, imipenem and cilastatin, meropenem)
Cephalosporins, third generation (with or without beta-lactamase inhibitor; eg, cefixime, cefotaxime, ceftazidime, ceftriaxone)
Glycopeptides (eg, teicoplanin, vancomycin)
Macrolides (eg, azithromycin, clarithromycin, erythromycin)
Quinolones and fluoroquinolones (eg, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin)

Reserve

Aztreonam
Cephalosporins, fourth generation (eg, cefepime)
Cephalosporins, fifth generation (eg, ceftaroline)
Daptomycin
Fosfomycin (intravenous)
Oxazolidinones (eg, linezolid)
Polymyxins (eg, colistin, polymyxin B)
Tigecycline

Published in final edited form as:
Clin Infect Dis. 2020 June 24; 71(1): 201–204. doi:10.1093/cid/ciz1000.

Streptococcus pyogenes pbp2x Mutation Confers Reduced Susceptibility to β-Lactam Antibiotics

Kirsten S. Vannice[1,2], **Jessica Ricaldi**[3], **Srinivas Nanduri**[3], **Ferric C. Fang**[4], **John B. Lynch**[4], **Chloe Bryson-Cahn**[4], **Theodore Wright**[4], **Jeff Duchin**[2], **Meagan Kay**[2], **Sopio Chochua**[3], **Chris A. Van Beneden**[3], **Bernard Beall**[3]

Two near-identical clinical *Streptococcus pyogenes* isolates of *emm* subtype *emm43.4* with a *pbp2x* missense mutation (T553K) were detected. Minimum inhibitory concentrations (MICs) for ampicillin and amoxicillin were 8-fold higher, and the MIC for cefotaxime was 3-fold higher than for near-isogenic control isolates, consistent with a first step in developing β-lactam resistance.

S. pyogenes

* Ampicillina S
* (Amoxiclavulanato) S
* Macrolidi +-
* Cefalosporine orali S

CESPER 2023

Quale antibiotico?

CESPER 2023

Different antibiotic treatments for group A streptococcal pharyngitis (Review)

van Driel ML, De Sutter AIM, Thorning S, Christiaens T

2021,

Background

Antibiotics provide only modest benefit in treating sore throat, although their effectiveness increases in people with positive throat swabs for group A beta-haemolytic streptococci (GABHS). It is unclear which antibiotic is the best choice if antibiotics are indicated. This is an update of a review first published in 2010, and updated in 2013, 2016, and 2020.

Objectives

To assess the comparative efficacy of different antibiotics in: (a) alleviating symptoms (pain, fever); (b) shortening the duration of the illness; (c) preventing clinical relapse (i.e. recurrence of symptoms after initial resolution); and (d) preventing complications (suppurative complications, acute rheumatic fever, post-streptococcal glomerulonephritis). To assess the evidence on the comparative incidence of adverse effects and the risk-benefit of antibiotic treatment for streptococcal pharyngitis.

Main results

We included 19 trials reported in 18 publications (5839 randomised participants): six trials compared penicillin with cephalosporins; six compared penicillin with macrolides; three compared penicillin with carbacephem; one compared penicillin with sulphonamides; one compared clindamycin with ampicillin; and one compared azithromycin with amoxicillin in children. All participants had confirmed acute GABHS tonsillopharyngitis, and ages ranged from one month to 80 years. Nine trials included only, or predominantly, children.

CESPER 2023

Different antibiotic treatments for group A streptococcal pharyngitis (Review)

van Driel ML, De Sutter AIM, Thorning S, Christiaens T 2021,

Cochrane Library

Cephalosporins versus penicillin

We are uncertain if there is a difference in symptom resolution (at 2 to 15 days) for cephalosporins versus penicillin (odds ratio (OR) for absence of symptom resolution 0.79, 95% confidence interval (CI) 0.55 to 1.12; 5 trials; 2018 participants; low-certainty evidence). Results of the sensitivity analysis of evaluable participants differed (OR 0.51, 95% CI 0.27 to 0.97; 5 trials; 1660 participants; very low-certainty evidence). We are uncertain if clinical relapse may be lower for cephalosporins compared with penicillin (OR 0.55, 95% CI 0.30 to 0.99; number needed to treat for an additional beneficial outcome (NNTB) 50; 4 trials; 1386 participants; low-certainty evidence). Very low-certainty evidence showed no difference in reported adverse events.

Macrolides versus penicillin

We are uncertain if there is a difference between macrolides and penicillin for resolution of symptoms (OR 1.11, 95% CI 0.92 to 1.35; 6 trials; 1728 participants; low-certainty evidence). Sensitivity analysis of evaluable participants resulted in an OR of 0.79, 95% CI 0.57 to 1.09; 6 trials; 1159 participants). We are uncertain if clinical relapse may be different (OR 1.21, 95% CI 0.48 to 3.03; 6 trials; 802 participants; low-certainty evidence).

Azithromycin versus amoxicillin

Amoxicillin 1° choice

Based on one unpublished trial in children, we are uncertain if resolution of symptoms is better with azithromycin in a single dose versus amoxicillin for 10 days (OR 0.76, 95% CI 0.55 to 1.05; 1 trial; 673 participants; very low-certainty evidence). Sensitivity analysis for per-protocol analysis resulted in an OR of 0.29, 95% CI 0.11 to 0.73; 1 trial; 482 participants; very low-certainty evidence). We are also uncertain if there was a difference in relapse between groups (OR 0.88, 95% CI 0.43 to 1.82; 1 trial; 422 participants; very low-certainty evidence). Adverse events were more common with azithromycin compared to amoxicillin (OR 2.67, 95% CI 1.78 to 3.99; 1 trial; 673 participants; very low-certainty evidence).

Carbacephem versus penicillin

There is low-certainty evidence that compared with penicillin, carbacephem may provide better symptom resolution post-treatment in adults and children (OR 0.70, 95% CI 0.49 to 0.99; NNTB 14.3; 3 trials; 795 participants).

Studies did not report on long-term complications, so it was unclear if any class of antibiotics was better in preventing serious but rare complications.

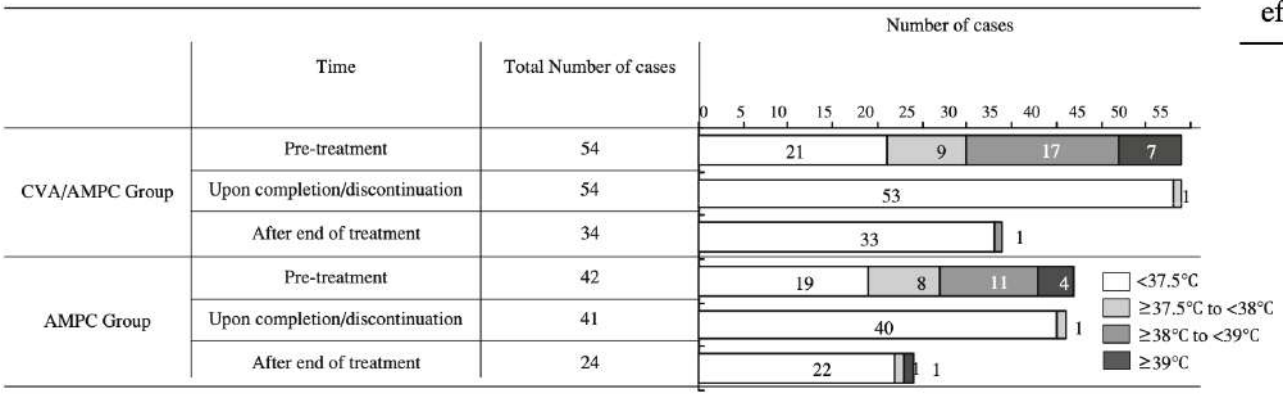
J Infect Chemother (2013) 19:12–19
DOI 10.1007/s10156-012-0444-1

ORIGINAL ARTICLE

Comparison of clinical efficacy between 3-day combined clavulanate/amoxicillin preparation treatment and 10-day amoxicillin treatment in children with pharyngolaryngitis or tonsillitis

Haruo Kuroki · Naruhiko Ishiwada · Nobue Inoue · Nobuyasu Ishikawa · Hiroshi Suzuki · Kyoko Himi · Tomomichi Kurosaki

Judgment	CVA/AMPC group Number of cases (%)	AMPC group Number of cases (%)
Total	54	42
Markedly effective	50 (92.6)	37 (88.1)
Effective	3 (5.6)	2 (4.8)
Slightly effective	1 (1.94)	2 (4.8)
Ineffective	0 (0)	1 (2.4)
Markedly effective	50 (92.6)	37 (88.1)
Markedly effective + effective	53 (98.1)	39 (92.9)



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Clinical and Bacteriologic Efficacy of Amoxycillin b.d. (45 mg/kg/day) Versus Amoxycillin t.d.s (40 mg/kg/day) in Children with Group A b-hemolytic Streptococcal Tonsillopharyngitis

Journal of Chemotherapy

A. AGUILAR, J. TINOCO, M. MACIAS, L. HUICHO, J. LEVY, H. TRUJILLO, P. LOPEZ, M. PEREIRA, S. MAQBOOL, Z.A. BHUTTA, R.A. SACY & S. DEACON

This randomized, observer-blind, multicenter, parallel-group study compared the clinical and bacteriologic efficacy and safety of amoxycillin, 45 mg/kg/day b.d. and amoxycillin, 40 mg/kg/day t.d.s. after 7 days of treatment in 517 children with acute bacterial tonsillopharyngitis. At the end of treatment, a successful clinical response was recorded in more than 96% of patients in each of the treatment groups. A similar result was obtained at follow-up. Among those patients who were bacteriologically evaluable at the end of treatment, a successful bacteriologic response was achieved in more than 94% in each treatment group. Both treatments were well tolerated. Drug-related adverse events were recorded in just 12 patients (4.6%) in the b.d. group and six (2.4%) in the t.d.s. group. The study demonstrated that a twice-daily regimen of amoxycillin, 45 mg/kg/day, was as effective and as well tolerated as the standard three-times-daily regimen of amoxycillin, 40 mg/kg/day, in the treatment of acute bacterial tonsillopharyngitis in children.

Quale antibiotico

* gold standard è Amoxicillina
* Dosaggio: 40 - 50 mg/Kg/die in 2-3 somministrazioni
* Non sussiste NESSUN motivo per prescrivere amoxiclavulanato, cefalosporine o macrolidi in prima battuta
* In caso di allergia: cefalosporine di I generazione in prima battuta, altrimenti cefalosporine di II o III generazione, clindamicina. Macrolidi SOLO se allergia IgE mediata

CESPER 2023

Per quanto tempo?

Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children (Review)

Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA

Main results

Twenty studies were included with 13,102 cases of acute GABHS pharyngitis. Compared to standard duration treatment, the short duration treatment had shorter periods of fever (mean difference (MD) -0.30 days, 95% CI -0.45 to -0.14) and throat soreness (MD -0.50 days, 95% CI -0.78 to -0.22); lower risk of early clinical treatment failure (OR 0.80, 95% CI 0.67 to 0.94); no significant difference in early bacteriological treatment failure (OR 1.08, 95% CI 0.97 to 1.20), or late clinical recurrence (OR 0.95, 95% CI 0.83 to 1.08). However, the overall risk of late bacteriological recurrence was worse in the short duration treatment (OR 1.31, 95% CI 1.16 to 1.48), although no significant differences were found when studies of low dose azithromycin (10mg/kg) were eliminated (OR 1.06, 95% CI 0.92 to 1.22). Three studies reported long duration complications with no statistically significant difference (OR 0.53, 95% CI 0.17 to 1.64).

Authors' conclusions

Three to six days of oral antibiotics had comparable efficacy compared to the standard duration 10 day oral penicillin in treating children with acute GABHS pharyngitis. In countries with low rates of rheumatic fever, it appears safe and efficacious to treat children with acute GABHS pharyngitis with short duration antibiotics. In areas where the prevalence of rheumatic heart disease is still high, our results must be interpreted with caution.

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Figure 1. Funnel plot of comparison: 2 Clinical efficacy, outcome: 2.1 Clinical treatment failure (early).

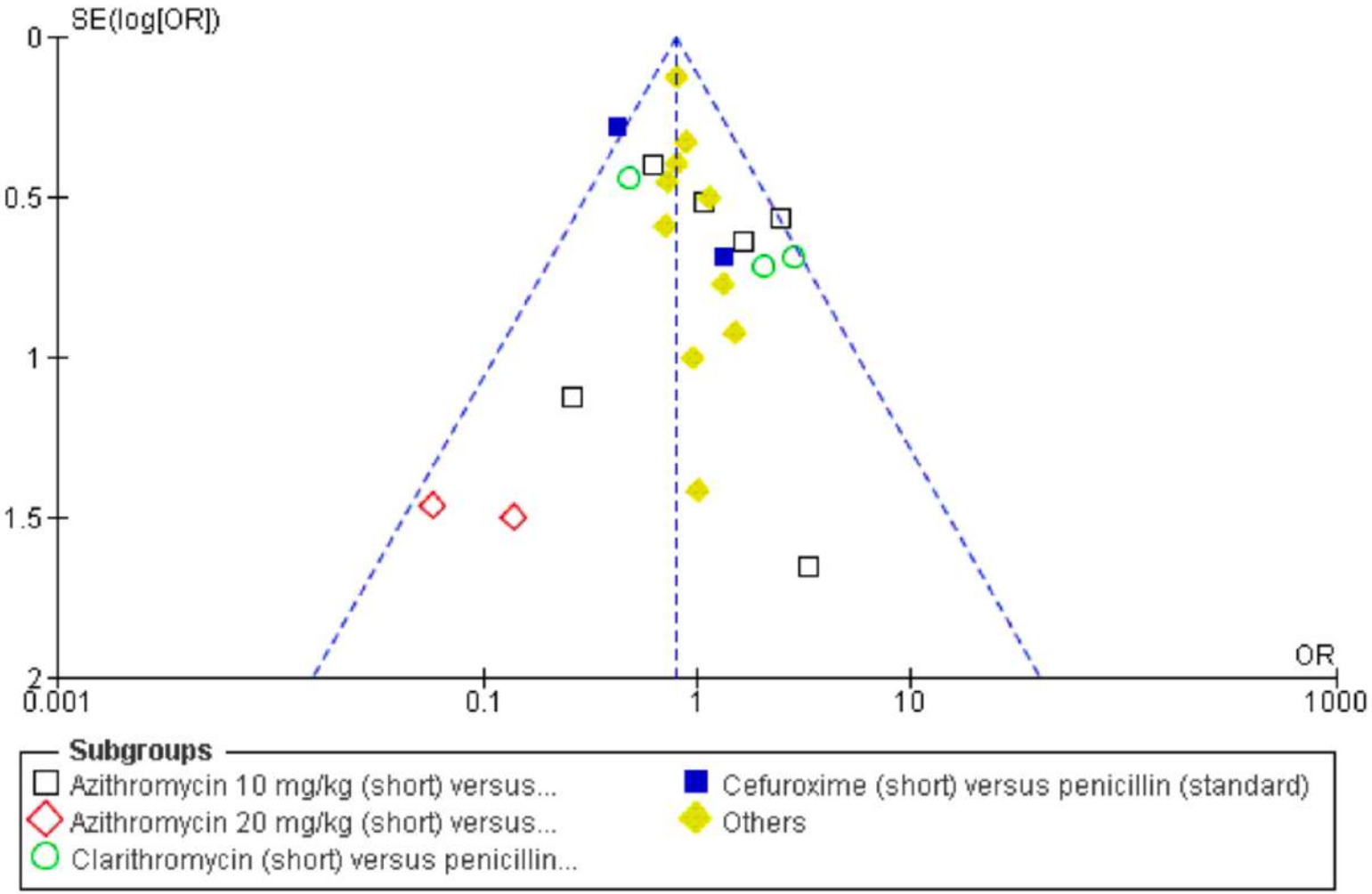

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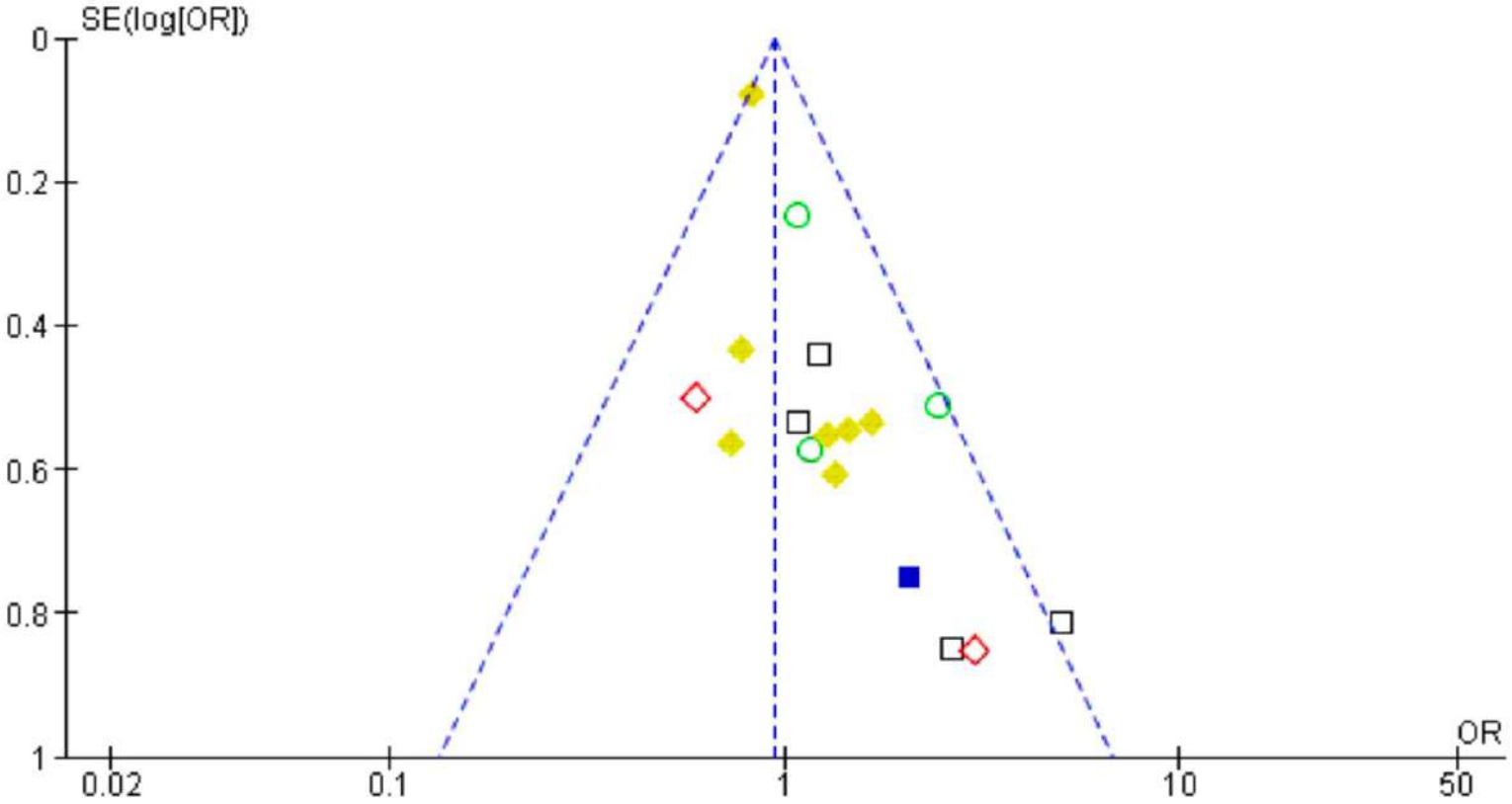
Figure 2. Funnel plot of comparison: 2 Clinical efficacy, outcome: 2.2 Clinical treatment failure (late).



Evaluation of 3-day azithromycin or 5-day cefaclor in comparison with 10-day amoxicillin for treatment of tonsillitis in children

Peng Li, Genqin Jiang, and Xiaofei Shen

Published at www.nrcresearchpress.com/cjpp on 31 July 2019.

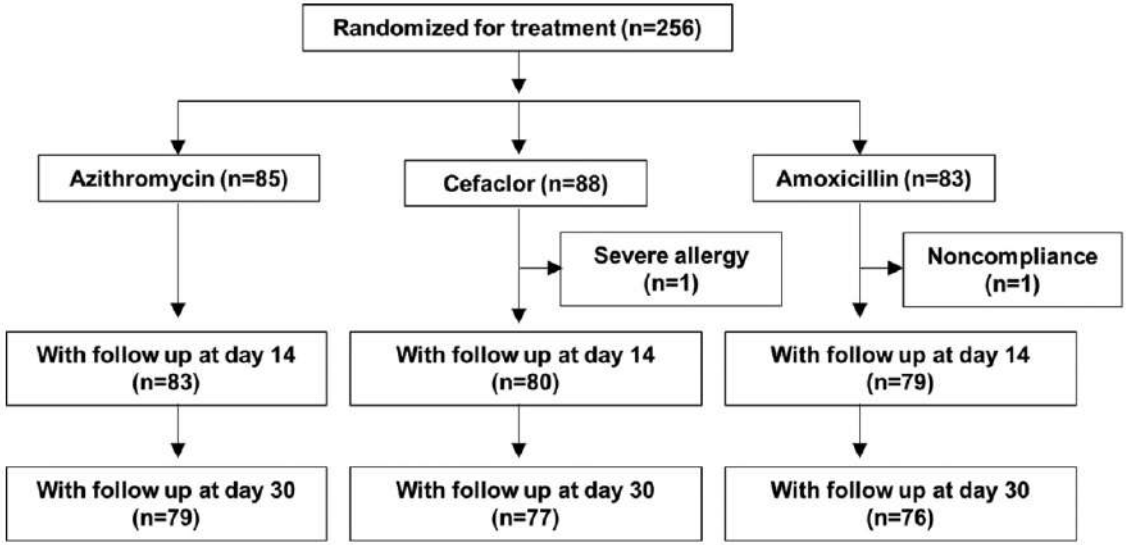


Table 2. Clinical efficacy and microbiologic outcome at day 14 (per-protocol-assessable patients).

Clinical efficacy and microbiologic outcome	No. of patients (%)			*p*		
	Azithromycin	Cefaclor	Amoxicillin	Azithromycin vs. cefaclor	Azithromycin vs. amoxicillin	Cefaclor vs. amoxicillin
Clinical efficacy	*n*=83	*n*=79	*n*=78			
Success	80 (96.4)	73 (92.4)	71 (91.0)	0.3198[a]	0.2002[a]	0.7538[b]
Failure	3 (3.6)	6 (7.6)	7 (9.0)			
Microbiologic outcome	*n*=83	*n*=79	*n*=78			
Eradication	78 (94.0)	71 (89.9)	69 (88.5)	0.3367[b]	0.2146[b]	0.7759[b]
Failure	5 (6.0)	8 (10.1)	9 (11.5)			

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Penicillin V four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study

the bmj | *BMJ* 2019;367:l5337 | doi: 10.1136/bmj.l5337

Gunilla Skoog Ståhlgren,[1] Mia Tyrstrup,[2,3] Charlotta Edlund,[1] Christian G Giske,[4,5] Sigvard Mölstad,[3] Christer Norman,[6] Karin Rystedt,[7,8] Pär-Daniel Sundvall,[8,9] Katarina Hedin[3,10]

INTERVENTIONS

Penicillin V 800 mg four times daily for five days (total 16 g) compared with the current recommended dose of 1000 mg three times daily for 10 days (total 30 g).

MAIN OUTCOME MEASURES

Primary outcome was clinical cure five to seven days after the end of antibiotic treatment. The non-inferiority margin was prespecified to 10 percentage points. Secondary outcomes were bacteriological eradication, time to relief of symptoms, frequency

CONCLUSIONS

Penicillin V four times daily for five days was non-inferior in clinical outcome to penicillin V three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci. The number of relapses and complications did not differ between the two intervention groups. Five day treatment with penicillin V four times daily might be an alternative to the currently recommended 10 day regimen.

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Table 2 | Primary and secondary endpoints for per protocol, modified intention to treat*, and subgroup populations. Values are numbers (percentages) unless stated otherwise

Endpoint	5 days	10 days	Difference† (95% CI)
Primary endpoint: clinical cure at test of cure:			
PP population (n=397)	181/202 (89.6)	182/195 (93.3)	−3.7 (−9.7 to 2.2)
MITT population (n=422)‡	190/212 (89.6)	197/210 (93.8)	−4.2 (−9.9 to 1.5)
Subgroup analyses: clinical cure at test of cure:			
Men PP (n=142)	64/72 (88.9)	66/70 (94.3)	−5.4 (−15.9 to 5.1)
Women PP (n=255)	117/130 (90.0)	116/125 (92.8)	−2.8 (−10.4 to 4.8)
Age <18 years PP (n=101)	48/53 (90.6)	46/48 (95.8)	−5.3 (−16.9 to 6.4)
Age ≥18 years PP (n=296)	133/149 (89.3)	136/147 (92.5)	−3.3 (−10.5 to 4.0)
Centor score 3 PP (n=194)	94/100 (94.0)	90/94 (95.7)	−1.7 (−9.0 to 5.5)
Centor score 4 PP (n=203)	87/102 (85.3)	92/101 (91.1)	−5.8 (−15.6 to 4.0)
Secondary endpoints (PP):			
Bacteriological eradication at test of cure (n=376)	156/194 (80.4)	165/182 (90.7)	−10.2 (−17.8 to −2.7)
Relapse within one month (n=359)	8/179 (4.5)	7/180 (3.9)	0.6 (−4.1 to 5.3)
Complication by three month follow-up (n=387)	0/198 (0.0)	4/189 (2.1)	−2.1 (−4.7 to 0.5)
New tonsillitis by three month follow-up (n=386)	6/197 (3.0)	13/189 (6.9)	−3.8 (−8.7 to 1.0)

MITT=modified intention to treat; PP=per protocol.
*Includes every patient who received at least one dose of study drug.
†5 days−10 days (percentage points).
‡Missing data (six patients in the five day group and 13 in the 10 day group) imputed as clinical cure.

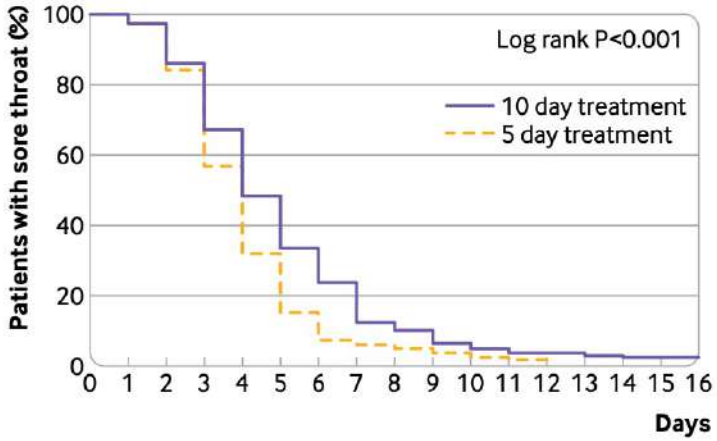

Fig 2 | Time to first day of relief of sore throat according to patient diaries for five day and 10 day groups (per protocol population, n=381)

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Short-term antibiotic therapy for the most common bacterial respiratory infections in infants and children

frontiers | Frontiers in Pharmacology

Nicola Principi[1], Giovanni Autore[2], Alberto Argentiero[2] and Susanna Esposito[2]*

TYPE Review
PUBLISHED 06 June 2023
DOI 10.3389/fphar.2023.1174146

Despite many cases can spontaneously solve, official guidelines worldwide recommend antibiotic therapy in all of the documented cases of ASF. Antibiotic therapy reduces the spread of the pathogen and the risk of developing acute suppurative and long-term non-suppurative complications, including acute rheumatic fever (ARF) (Centers for Disease Control and Prevention, 2023).

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Short-term antibiotic therapy for the most common bacterial respiratory infections in infants and children

frontiers | Frontiers in Pharmacology

Nicola Principi[1], Giovanni Autore[2], Alberto Argentiero[2] and Susanna Esposito[2]*

Official guidelines and experts worldwide agree in defining oral penicillin V or amoxicillin (where penicillin V is lacking) as the drugs of choice to treat children with ASF (Chiappini et al., 2012; Pelucchi et al., 2012; Shulman et al., 2012). These agents, despite largely prescribed for several decades, remain highly effective against *S. pyogenes*, and are safe, well tolerated, cheap and, due to their narrow spectrum of activity, at low risk of favoring development of AMR. Alternatives for children with penicillin allergy are second or third generation oral cephalosporin macrolides or clindamycin (Chiappini et al., 2012; Pelucchi et al., 2012; Shulman et al.,

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Less agreement there is on the duration of the therapy. In most of the official guidelines a 10-day course of one of the first-line drugs is recommended (Chiappini et al., 2011). However, several experts believe that alternative strategies may need to be employed in order to achieve safe reduction in antimicrobial therapy. These include administering different antibiotics such as oral cephalosporins or macrolides, increasing penicillin V or amoxicillin dosage, modifying their time schedule of administration. The approval by Food and Drug Administration (FDA) of the United States of cefdinir and cefpodoxime for a 5-day course of therapy for ASF is one of the best examples in this regard (Holm et al., 2020).

Short-term antibiotic therapy for the most common bacterial respiratory infections in infants and children

Nicola Principi[1], Giovanni Autore[2], Alberto Argentiero[2] and Susanna Esposito[2]*

frontiers | Frontiers in Pharmacology

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- available studies do not definitively support the use of short-term therapy for ASF
- even if one or more cephalosporins or macrolides given for a shorter period were definitively found as effective as to the traditional penicillin V 10-day course, the increased risk of drug- related adverse events and the increased economic cost of therapy should make physicians seriously consider the opportunity to use these newer antibiotics. As pointed out by World Health Organization macrolides and cephalosporins are broad spectrum drugs and should be prescribed only when the first-line drugs, as in this case penicillin V or amoxicillin, fail.
- To improve knowledge on short- term therapy of ASF, short-term administration of penicillin V or amoxicillin, eventually with increased daily dosage or with different total daily dose fractioning, should be further studied.

Terapia: durata ottimale

Considerando che:

* L'antibiotico considerato come gold standard è amoxicillina
* Gli studi che paragonano amoxicillina 5 – 7 gg verso 10 gg non ne documentano una inferiorità di successo
* La durata ottimale di un trattamento con amoxicillina vs *S. pyogenes* può essere di 5 – 7 giorni nei Paesi a basso rischio di malattia reumatica, mentre di 10 giorni nei Paesi ad elevato rischio di MR
* Serviranno ulteriori studi di conferma, specie per capire la reale prevalenza di MR in Italia

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Le ricadute e le infezioni ricorrenti

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-018-3245-3

REVIEW

CrossMark

CESPER 2023

Antibiotics for recurrent acute pharyngo-tonsillitis: systematic review

Holger Munck[1] · Anders W. Jørgensen[1] · Tejs Ehlers Klug[1]

Received: 22 January 2018 / Accepted: 26 March 2018

1. Can antibiotic treatment prevent future attacks of acute pharyngotonsillitis (APT) in patients with recurrent APT (RAPT)?
   - Two studies found that clindamycin and cefpodoxime, respectively, were effective in preventing future APT episodes and in eradicating group A streptococci from the tonsils of RAPT patients. One study found that long-term azithromycin had no effect on the number of APT episodes

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-018-3245-3

REVIEW

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Holger Munck[1] · Anders W. Jørgensen[1] · Tejs Ehlers Klug[1]

Received: 22 January 2018 / Accepted: 26 March 2018

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2. Which antibiotic regimen is preferable in the treatment of APT in patients with RAPT?
   - Two studies reported superior clinical and microbiological effects of clindamycin and amoxicillin with clavulanate, respectively, compared to penicillin. The four studies showing superior effects of clindamycin and amoxicillin with clavulanate were assessed to have high risk of bias. Hence, the level of evidence was moderate.
3. Which antibiotic regimen is preferable in the treatment of relapsing APT?
   - No studies reporting on Q3 were included

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IDSA
Infectious Diseases Society of America

Table 5. Treatment Regimens for Chronic Carriers of Group A Streptococci

Route, Drug	Dose or Dosage	Duration or Quantity	Recommendation Strength, Quality[a]	Reference
Oral				
Clindamycin	20–30 mg/kg/d in 3 doses (max = 300 mg/dose)	10 d	Strong, high	[119]
Penicillin and rifampin	Penicillin V: 50 mg/kg/d in 4 doses × 10 d (max = 2000 mg/d); rifampin: 20 mg/kg/d in 1 dose × last 4 d of treatment (max = 600 mg/d)	10 d	Strong, high	[118]
Amoxicillin–clavulanic acid	40 mg amoxicillin/kg/d in 3 doses (max = 2000 mg amoxicillin/d)	10 d	Strong, moderate	[120]
Intramuscular and oral				
Benzathine penicillin G (intramuscular) plus rifampin (oral)	Benzathine penicillin G: 600 000 U for <27 kg and 1 200 000 U for ≥27 kg; rifampin: 20 mg/kg/d in 2 doses (max = 600 mg/d)	Benzathine penicillin G: 1 dose; rifampin: 4 d	Strong, high	[81]

Abbreviation: Max, maximum.

[a]See Table 1 for a description.

Lo stato di portatore

Presenza di Streptococco gr A a livello del faringe, testimoniato da un tampone faringeo positivo, in assenza di infezione, flogosi concomitante e di una risposta immunologica all'agente stesso (Gerber et al.2009)

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Clinical Features of Group A *Streptococcus* in Children With Pharyngitis: Carriers versus Acute Infection

Anne-Marie Rick, MD, MPH,† Haniah A. Zaheer, BS, ‡ and Judith M. Martin, MD*†*

The Pediatric Infectious Disease Journal • Volume 39, Number 6, June 2020

Background: Among children with pharyngitis who test positive for group A *Streptococcus* (GAS), 10%–25% are GAS carriers. Current laboratory methods cannot distinguish acute infection from colonization.

Methods: We examined 2 separate longitudinal studies of children with symptomatic pharyngitis associated with a positive GAS throat culture (illness culture). In cohort 1, children presented with pharyngitis symptoms to a clinician, then had follow-up cultures at regular intervals. In cohort 2, throat cultures were performed at regular intervals and with pharyngitis symptoms. Illness cultures were categorized as acute infection or carrier based on follow-up culture results. In cohort 2, carriers were further categorized as a GAS carrier with a new *emm*-type or a GAS carrier with a previous *emm*-type based on typing data from prior culture results. For each cohort, symptoms were compared at the time of illness culture between carriers and those with acute infection.

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Clinical Features of Group A *Streptococcus* in Children With Pharyngitis: Carriers versus Acute Infection

Anne-Marie Rick, MD, MPH,† Haniah A. Zaheer, BS, ‡ and Judith M. Martin, MD*†*

Results: Cohort 1 (N = 75 illness cultures): 87% of the children were classified as acutely infected versus 13% carriers. Carriers were more likely to have upper respiratory (URI) symptoms [odds ratio (OR): 5.5; 95% confidence interval (CI): 1.4–22.1], headache (OR: 6.0; 95% CI: 1.2–40.5) or vomiting (OR: 5.5; 95% CI: 1.2–24.5). Cohort 2 (N = 122 illness cultures): 79% were acutely infected and 21% were carriers. Children determined to be carriers with a previous detected *emm*-type were more likely to have URI symptoms compared with those with acquisition of a new *emm*-type.
Conclusions: Children with symptomatic pharyngitis and GAS on throat culture identified as carriers were more likely to present with URI and atypical symptoms than children who were acutely infected.

Diversi studi confermano che lo stato di portatore può persistere da settimane a mesi, ma si associa a un rischio minimo di complicanze, suppurative e non suppurative,
e la probabilità di trasmissione è bassissima !
Pertanto, non è raccomandata la ricerca né il trattamento dei soggetti portatori di GAS

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

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Systematic review

The association between bacteria colonizing the upper respiratory tract and lower respiratory tract infection in young children: a systematic review and meta-analysis

Shantelle Claassen-Weitz [1,*], Katherine Y.L. Lim [2], Christopher Mullally [2], Heather J. Zar [3,4,5], Mark P. Nicol [1,6]

1) Division of Medical Microbiology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
2) Marshall Centre for Infectious Diseases Research and Training, School of Biomedical Sciences, University of Western Australia, Perth, Australia
3) Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, Cape Town, South Africa
4) SAMRC Unit on Child & Adolescent Health, University of Cape Town, Cape Town, South Africa
5) Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
6) Division of Infection and Immunity, School of Biomedical Sciences, University of Western Australia, Perth, Australia

Conclusions: Detection of *H. influenzae* or *Klebsiella* spp. in the URT was associated with LRTI, while evidence for association with *S. pneumoniae* was less conclusive. Longitudinal studies assessing URT microbial communities, together with environmental and host factors are needed to better understand pathogenesis of childhood LRTI. **Shantelle Claassen-Weitz, Clin Microbiol Infect 2021;27:1262**

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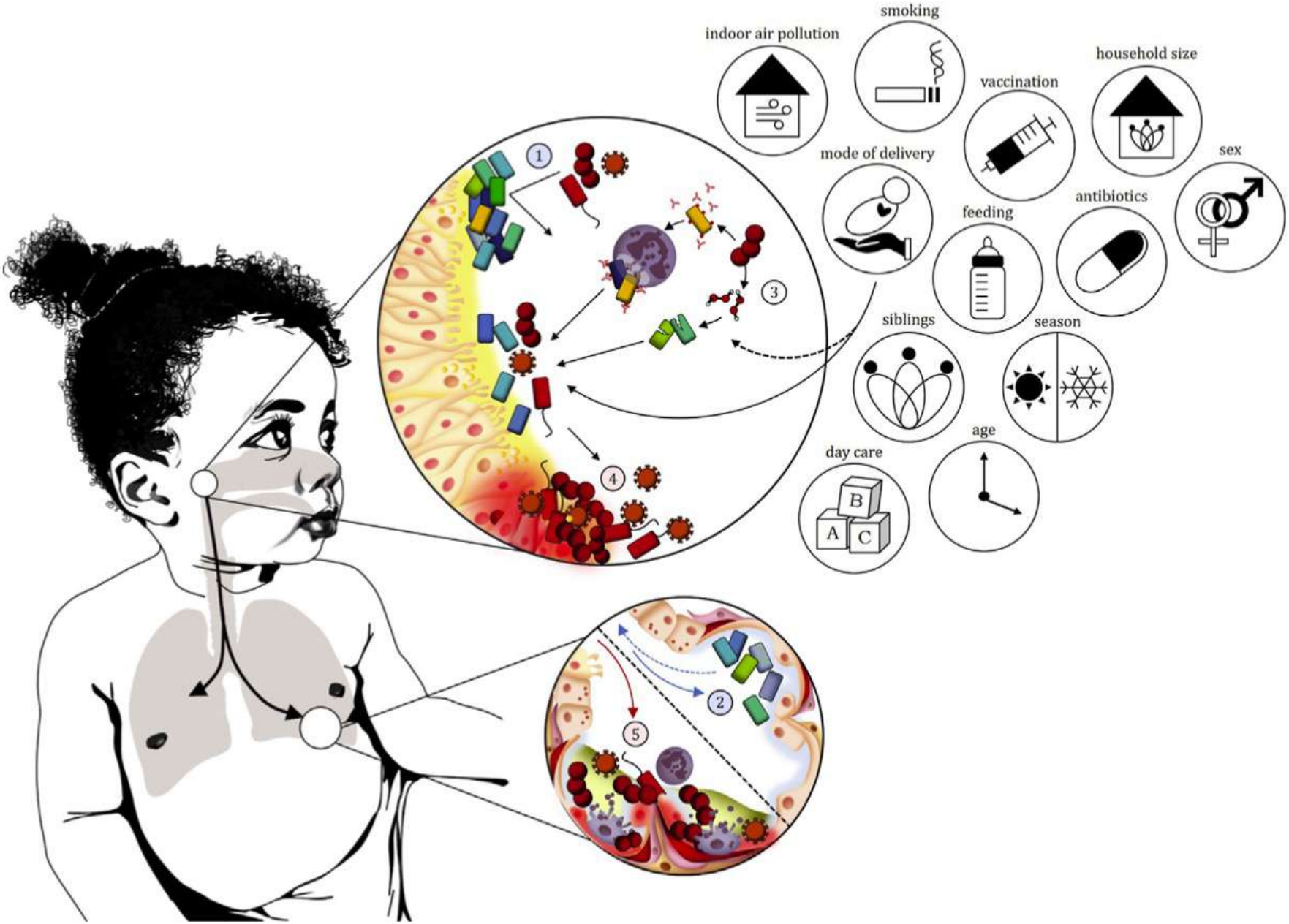

Imbalances in upper respiratory tract (URT) bacterial communities may result in translocation of dysbiotic bacterial communities to the lower respiratory tract (LRT), causing infection. (1) Commensal bacteria with low pathogenic potential confer colonization resistance against potential pathogens. (2) Bacterial communities from the URT translocate to the lungs where they are detected as stable resident or transient LRT communities. (3) Bacterial–bacterial interactions in the URT may be competitive or synergistic allowing potential pathogens to colonize. Environmental exposures may influence bacterial–bacterial and bacterial–host interactions, or directly impact on select bacteria within the community. (4) Perturbations of the bacterial community (dysbiosis), resulting from pathogen exposure, viral-bacterial, bacterial-bacterial interactions and environmental risk factors, may result in inflammation and damage to the URT epithelium. (5) Dysbiotic bacterial communities translocate to the LRT and cause inflammation and damage to the respiratory epithelium.

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Gli antibiotici nelle IGAS

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La recrudescenza delle infezioni (anche) da streptococco beta-emolitico di gruppo A?

FEDERICO MARCHETTI

UOC di Pediatria e Neonatologia, Ospedale di Ravenna, AUSL della Romagna

Medico e Bambino 1/2023

Nel trattamento nulla cambia, alla luce del fatto che i ceppi di SBEA al momento documentati sono quelli noti e di normale circolazione negli ultimi anni, sensibili al trattamento con amoxicillina alla dose convenzionale di 50 mg/kg/die in due somministrazioni e per una durata, nella FTA, di 5- 6 giorni

EMERGING INFECTIOUS DISEASES®

ISSN: 1080-60

EID Journal > Volume 29 > Early Release > Main Article

Volume 29, Number 10—October 2023

Dispatch

Expansion of Invasive Group A *Streptococcus* $M1_{UK}$ Lineage in Active Bacterial Core Surveillance, United States, 2019–2021

CESPER 2023

Characteristic	M1 iGAS, no. (%) cases		
	$M1_{UK}$, n = 86	Non-$M1_{UK}$, n = 1,747	p value†
Strain feature‡			
Antimicrobial susceptibility			
Penicillin nonsusceptible	0	0	1.000
Erythromycin nonsusceptible	0	21 (1.2)	0.621
Clindamycin nonsusceptible	0	20 (1.1)	1.000
Tetracycline nonsusceptible	0	18 (1)	1.000
Levofloxacin nonsusceptible	0	9 (0.5)	1.000

frontiers in Pediatrics

MINI REVIEW
published: 20 August 2021
doi: 10.3389/fped.2021.697938

Invasive Group A Streptococcal Infections: Benefit of Clindamycin, Intravenous Immunoglobulins and Secondary Prophylaxis

Delphine Laho[1,2], *Sophie Blumental*[1], *Anne Botteaux*[2] *and Pierre R. Smeesters*[1,2,3,4*]

Results: This review includes two meta-analyses, two randomized controlled trials, four prospective studies, five retrospective studies, and microbiological studies. To reduce mortality and morbidity, it appears useful to add clindamycin to β-lactams in severe clinical presentations, including necrotizing fasciitis or streptococcal toxic shock syndrome, and immunoglobulins for the latter two presentations. The high risk of secondary infection in household contacts justifies the need of taking preventive measures.

Conclusions: Both clinical studies and available experimental evidence suggest that adding clindamycin and immunoglobulins as adjunctive therapies in the management of invasive group A streptococcal infections may reduce mortality. Household contacts should be warned about the increased risk of secondary infection, and chemoprophylaxis may be considered in certain situations.

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Countries/ Recommendations	IVIG	Clindamycin	Secondary prophylaxis
Common recommendations	None	None	• For all: inform close contacts • Seek medical attention promptly if symptoms occur • Antibiotics to close contacts if they present any symptoms of a localized infection with GAS (angina, fever, skin infection, etc.) (1, 10–13)
USA	Infection refractory to aggressive treatment or a non-drainable focus or an oliguria persistence with pulmonary oedema (14)	Severe GAS infection° (14)	• Chemoprophylaxis to household contacts who have a high risk of iGAS (age ≥ 65 years, HIV infection, diabetes, cancer, heart disease, addiction, corticosteroids, Native American origin), or death (10, 14) • Penicillin + rifampicin • Clindamycin • Azithromycin (10, 14)
Canada	Severe GAS infection° or infection refractory to aggressive treatment (15)	Severe GAS infection° (15)	• Chemoprophylaxis to close contacts of a patient with a severe iGAS° • Chemoprophylaxis to close contacts if two or more cases occur in a community within 1 month • chemoprophylaxis to close contacts if a case in a child care center occurs at the same time as a chickenpox outbreak • 1st choice: 1st generation cephalosporins • If beta-lactams allergy: clindamycin or macrolides (15)
United Kingdom	No consensus	No consensus	• Chemoprophylaxis to a mother or her child if either has an iGAS during the neonatal period (the first 28 days of life) • Chemoprophylaxis to close contacts if two or more cases occur in a community within 1 month • 1st choice: oral penicillin • If beta-lactams allergy: azithromycin (12)
Ireland	STSS or NF if associated with organ failure (16)	Suspected severe infection° (16)	• Chemoprophylaxis to a mother or her child if either has an iGAS during the neonatal period (the first 28 days of life) • Chemoprophylaxis to close contacts if two or more cases occur in a community within 1 month • 1st choice: oral penicillin • If beta-lactams allergy: azithromycin (16)

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France	STSS or NF	NF, STSS, or toxin signs (rash, digestive or hemodynamic disorders) (17)	• Chemoprophylaxis to close contacts at risk of iGAS or complications (age ≥ 65 years, chickenpox, extensive skin lesions (including burns), drug addiction, progressive pathology (diabetes, cancer, hematology, HIV infection, heart failure), oral corticosteroid treatment (defined as doses > 5 mg/kg/day prednisone for more than 5 days or doses equivalent to or >0.5 mg/kg/day prednisone for ≥30 days) • 1st choice: 2nd or 3rd generation cephalosporins • If beta-lactams allergy: clindamycin or macrolides • If macrolide-resistant GAS: oral penicillin + rifampin (13)
Australia	No consensus	No consensus	• Chemoprophylaxis to close contacts of patient with a severe iGAS° • Chemoprophylaxis to a mother or her child if either develops an iGAS in the neonatal period (the first 28 days of life) • Chemoprophylaxis to close contacts if two or more cases occur in a community within 3 months • 1st choice: benzathine penicillin (intramuscular) • 2nd choice if oral therapy preferred: cephalexin • If beta-lactams allergy: macrolides • If macrolide-resistant GAS or pregnant women: clindamycin (11)
Belgium (Flanders)	No consensus	No consensus	• Chemoprophylaxis to all household contacts of the index case • 1st choice: azithromycin • If macrolide-resistant GAS or pregnant women: clindamycin (18)
Our recommendations	All hemodynamically unstable patients and/or admitted to intensive care unit and/or having STSS or NF	For all hospitalized iGAS infections	• Chemoprophylaxis to all household members of the patient • Chemoprophylaxis to people at high risk of complications or deaths related to iGAS • 1st choice: first-generation cephalosporins • If beta-lactams allergy: macrolides • If macrolide-resistant GAS or pregnant women: clindamycin

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Effectiveness of adjunctive clindamycin in β-lactam antibiotic-treated patients with invasive β-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study

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21: 697–710

Ahmed Babiker, Xiaobai Li, Yi Ling Lai, Jeffrey R Strich, Sarah Warner, Sadia Sarzynski, John P Dekker, Robert L Danner, Sameer S Kadri

Background Clindamycin is strongly recommended as an adjunctive treatment to β-lactam antibiotics in patients with severe invasive group A β-haemolytic streptococcal (iGAS) infections. However, there is little evidence of a benefit in the use of clindamycin in humans, and its role, if any, in treating patients with invasive non-group A/B β-haemolytic streptococcal (iNABS) infections is unclear.

In the iGAS cohort, in-hospital mortality in propensity-matched patients who received adjunctive clindamycin (18 [6·5%] of 277 patients) was significantly lower than in those who did not (55 [11·0%] of 500 patients; aOR 0·44 [95% CI 0·23–0·81]). This survival benefit was maintained even in patients without shock or necrotising fasciitis (six [2·6%] of 239 patients treated with adjunctive clindamycin *vs* 27 [6·1%] of 422 patients not treated with adjunctive clindamycin; aOR 0·40 [0·15–0·91]).

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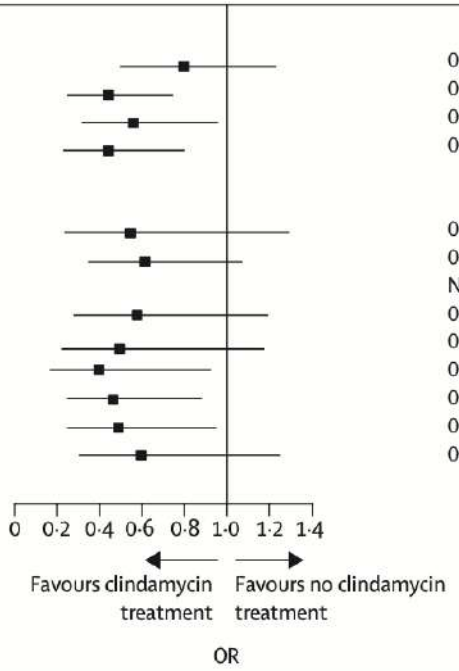
	Clindamycin treatment		No clindamycin treatment		p value	OR (95% CI)
	Patients	Mortality (%)	Patients	Mortality (%)		
Primary analysis						
Unmatched, unadjusted	343	28 (8·2%)	736	74 (10·1%)	0·32	0·80 (0·50–1·24)
Unmatched, adjusted*					0·0031	0·44 (0·25–0·75)
Propensity-matched (1:2), unadjusted	277	18 (6·5%)	500	55 (11·0%)	0·042	0·56 (0·32–0·96)
Propensity-matched (1:2), adjusted*					0·011	0·44 (0·23–0·81)
Subgroup analysis†						
Early clindamycin treatment	97	6 (6·2%)	500	55 (11·0%)	0·16	0·53 (0·22–1·28)
Proven invasive β-haemolytic streptococcal infection	153	18 (11·8%)	282	51 (18·1%)	0·087	0·60 (0·33–1·06)
Probable invasive β-haemolytic streptococcal infection	124	0	218	4 (1·8%)	1·00	NA‡
Intensive care unit patients	55	13 (23·6%)	90	32 (35·6%)	0·13	0·56 (0·26–1·18)
Vasopressor-dependent shock	37	12 (32·4%)	57	28 (49·1%)	0·11	0·48 (0·21–1·16)
Without vasopressor-dependent shock or necrotising fasciitis	239	6 (2·6%)	442	27 (6·1%)	0·043	0·40 (0·15–0·91)
Clindamycin treatment for >1 days	226	12 (5·3%)	500	55 (11·0%)	0·016	0·45 (0·23–0·87)
Clindamycin treatment for >2 days	183	10 (5·5%)	500	55 (11·0%)	0·032	0·47 (0·23–0·94)
Clindamycin treatment for >3 days	122	9 (6·9%)	500	55 (11·0%)	0·17	0·58 (0·29–1·24)



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VIEWPOINTS
CID 2019:69 (1 September)
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

The Path to Group A *Streptococcus* Vaccines: World Health Organization Research and Development Technology Roadmap and Preferred Product Characteristics

Johan Vekemans,[1] Fernando Gouvea-Reis,[1] Jerome H. Kim,[2] Jean-Louis Excler,[2] Pierre R. Smeesters,[3,4,5,6] Katherine L. O'Brien,[7] Chris A. Van Beneden,[8] Andrew C. Steer,[5,9,10] Jonathan R. Carapetis,[11] and David C. Kaslow[12]

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Only 2 candidate vaccines are actively under evaluation in human trials

- A phase 1 clinical trial of the MJ8VAX vaccine candidate developed by the Queensland Institute of Medical Research, Australia: the vaccine antigen is a 29-amino-acid–long peptide (J8) from the conserved carboxyl terminus region of the M protein , conjugated with diphtheria toxoid and adsorbed onto aluminium hy- droxide. More investigations are planned to further optimize immunogenicity.
- The 30-valent StreptAnova, developed at the University of Tennessee and at Dalhousie University, Canada, is an M protein based vaccine with 4 recombinant subunits, each containing 7 or 8 N-terminal fragments of 30 different *emm* types linked in tandem. The N-terminal fragment of the Spa18 antigen is also included in the construct.

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Grazie per l’attenzione!