Unità di Pediatria ad Alta Intensità di Cura
Università degli Studi di Milano
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

34 Congresso Nazionale di
ANTIBIOTICOTERAPIA
in età pediatrica

Caratteristiche degli antibiotici e durata ottimale della terapia

N. Principi, Milano

LA DURATA OTTIMALE DELLA TERAPIA ANTIBIOTICA

NICOLA PRINCIPI

Durata ottimale della terapia antibiotica: un problema insoluto perché di difficile soluzione (I)

- Sul piano teorico la durata della terapia antibiotica dovrebbe essere calcolata sulla base del tempo necessario ad ottenere l'eradicazione dei batteri che hanno determinato la malattia

- Poter verificare la scomparsa dell'agente infettivo è evenienza eccezionale. Di fatto, nella pratica quotidiana, questo è possibile con relativa facilità solo nelle faringotonsilliti e nelle infezioni delle vie urinarie

- L'eliminazione dell'agente infettivo non sempre corrisponde alla scomparsa delle lesioni ad esso dovute e gli indici laboratoristici o radiologici normalmente utilizzati per valutare l'andamento di una malattia danno, in genere, indicazioni sul decorso ma non sulla guarigione completa e sul rischio di recidiva

DURATA DELLA TERAPIA ANTIBIOTICA: LA TRADIZIONE

10 giorni di terapia sono un lungo periodo ed è noto che tanto più protratta è la terapia antibiotica tonto più è elevato il rischio di:

1) emergenza di resistenze batteriche

2) insorgenza di eventi avversi antibiotico-correlati

3) Limitata compliance con elevato rischio di fallimento terapeutico

Inoltre, il costo della terapia si incrementa proporzionalmente alla durata del trattamento.

Per questo motivo sono stati fatti tentativi di riduzione della durata della terapia

Durata della terapia antibiotica: un problema insoluto perché di difficile soluzione (II)

Assimilando tutte le patologie a quanto verificato per la tonsillite streptococcica (10 giorni con penicillina), le malattia batteriche vengono solitamente trattate per 7-14 giorni, con i periodi più lunghi per le forme considerate più gravi.

Esistono, però, numerose condizioni che possono portare a trattamento di durata diversa.

I principali fattori discussi in letteratura che hanno portato a suggerire variazioni rispetto a quanto tradizionalmente raccomandato sono:

- La sede dell'infezione
- Il tipo di patogeno in causa
- Le caratteristiche del paziente
- Il tipo di antibiotico usato

- !!!!!!!! Ma attenzione: alcune informazioni sono discutibili e possono indurre in errore !!!!!!!!

LA SEDE DELL'INFEZIONE

A) dati veri
B) dati falsi

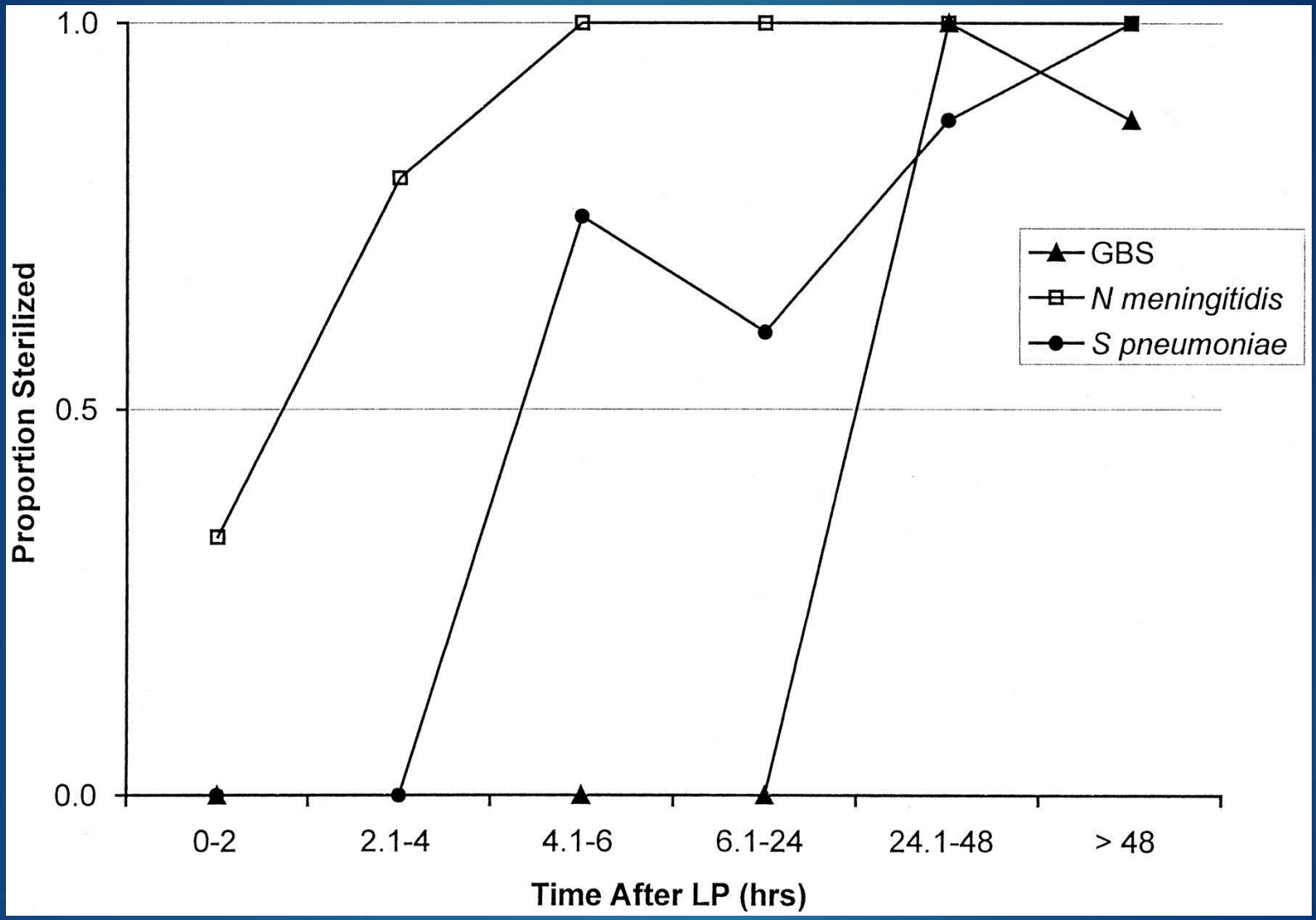
Recommended Duration of Intravenous Antibiotics for Meningitis in Children

From Schroeder AR and Ralston SL J Hosp Med 2014; 9:604

Pathogen	IDSA	NICE	Minimum Range Achieving Equivalent Outcomes in Recent Randomized Trials
Group B *Streptococcus*	14–21 days	14 days	None available
Neisseria meningititis	7 days	7 days	1–5 days
Haemophilus influenzae type b	7 days	10 days	4–5 days
Streptococcus pneumoniae	10–14 days	14 days	4–5 days

NOTE: **Abbreviations:** IDSA, Infectious Disease Society of America; NICE, National Institute for Clinical Excellence.

CSF sterilization



Kanegaye J T et al. Pediatrics 2001;108:1169-1174

PEDIATRICS®

Results of bacterial meningitis treatment according to the duration of antibiotic administration

(from Karageorgopoulus DE et al. Arch Dis Child 2009)

First author, year,	Clinical success, n/N (%)		Bacteriological success, n/N (%)		Mortality, n/N (%)		Adverse events, n/N (%)	
	Short course	Long course	Short course	Long course	Short course	Long course	Short course	Long course
Lin, 1985, USA[15]	31/35* (88.6)	29/35* (82.8)	35/35 (100)	34/34 (100)	0/35 (0)	0/35 (0)	17/35 (48.5)	15/35 (42.9)
Kavaliotis, 1989, Greece[16]	23/26 (88.5)	25/26 (96)	26/26 (100)	26/26 (100)	0/26 (0)	0/26 (0)	4/26 (15.4)	3/26 (11.5)
Martin, 1990, Switzerland[17]	39/47 (83)	37/45 (82.2)	47/47 (100)	45/45 (100)	0/47 (0)	0/45 (0)	NR§	NR§
Roine, 2000, Chile[18]	46/53* (86.8)	38/47* (80.8)	NR	NR	0/55 (0)	0/47 (0)	NR	NR
Singhi, 2002, India[19]	26/35 (74.3)	26/34 (76.5)	NR	NR	1/35 (2.8)¶	0/34 (0)	NR	NR

First author, year, ref	Nosocomial infections, n/N (%)		Length of hospital stay, mean (SD)		Hearing impairment, n/N (%)		Neurological complications, n/N (%)	
	Short course	Long course	Short course	Long course	Short course	Long course	Short course	Long course
Lin, 1985, USA[15]	6/35 (17.1)	5/35 (14.3)	9.9 (4.4)	11.6 (4.0)	8/27 (29.6)	8/25 (32)	1/35† (2.9)	2/35† (5.7)
Kavaliotis, 1989, Greece[16]	NR	NR	NR	NR	0/26 (0)	3/26 (11.5)	0/26 (0)	1/26 (3.8)
Martin, 1990, Switzerland[17]	NR	NR	At least 10	At least 10	NR	NR	4/47 (9)	5/45 (11)
Roine, 2000, Chile[18]	NR	NR	At least 7	At least 7	1/38 (2.6)	3/32 (9.4)	0/47 (0)	2/39 (5.1)
Singhi, 2002, India[19]	2/35 (5.7)	10/34 (29.4)	10.8 (6.0)	14.2 (7.2)	6/33 (18.2)	8/34 (23.5)	8/33 (24.2)‡	11/34 (32.4)‡

Short course: 4-7 days

Long course: 7-14 days

	5-day treatment group (n=496)	10-day treatment group (n=508)	Total	Risk difference (%; 95% CI)
Overall outcomes for all children				
Therapy successfully completed (10 days)	469 (95%)	485 (96%)	954	−0·92 (−3·6 to 1·8)
Antibiotic therapy modified after random assignment or therapy failure	17 (3%)	16 (3%)	33	0·3 (−1·9 to 2·5)
Changed diagnosis (to tuberculous meningitis)	2 (0%)	2 (0%)	4	0·009 (−0·7 to 0·7)
Adverse events to the study drug	0	0	0	..
Bacteriological failures	0	0	0	..
Another episode of meningitis	8 (2%)	13 (3%)	21	−0·95 (−2·7 to 8·2)
Relapse of meningitis	2 (0%)	0	2	−0·4 (−0·15 to 0·96)
Deaths related to meningitis only*	9 (2%)	6 (1%)	15	0·63 (−0·87 to 2·1)
Deaths due to any reason after cure (until follow-up at 6 months after enrolment)	22 (4%)	19 (4%)	41†	0·69 (−1·8 to 3·1)
Survival with sequelae	129 (26%)	138 (27%)	267	−1·2 (−6·6 to 4·3)
Hearing loss	105 (21%)	106 (21 %)	211	0·3 (−4·7 to 5·3)
Moderate or severe unilateral	22 (4%)	23 (5%)	45	0·09 (−2·7 to 2·5)
Moderate or severe bilateral	50 (10%)	45 (9%)	95	1·2 (−2·4 to 4·8)
Visual loss	4 (1%)	10 (2%)	14	−1·2 (−2·6 to 0·3)
Neurological sequelae including motor deficit, nerve palsies	21 (4%)	30 (6%)	51	−1·7 (−0·43 to 1·03)
Motor deficit	20 (4%)	29 (6%)	49	−1·6 (−4·3 to 0·98)
Cranial nerve palsy	4 (1%)	4 (1%)	8	0·02 (−1·1 to 1·1)
Afebrile seizures	3 (1%)	5 (1%)	8	−0·4 (−1·5 to 0·7)
Hydrocephalus	2 (0%)	6 (1%)	8	−0·8 (−1·9 to 0·3)
Developmental delay	25 (5%)	33 (7%)	58	−1·5 (−4·3 to 1·4)

Outcome of bacterial meningitis according to duration of antibiotic therapy with ceftriaxone

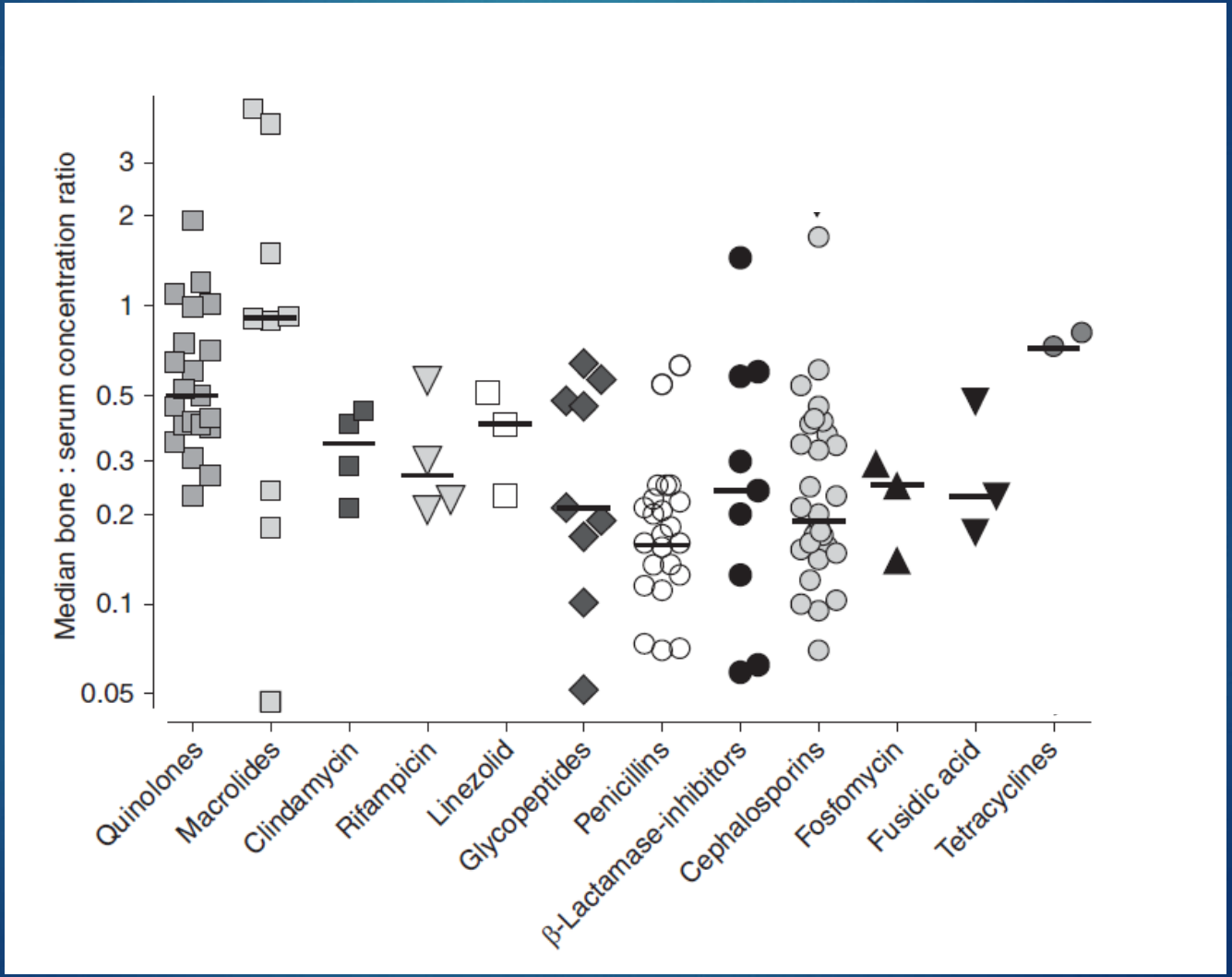
from Malyneux E, et al. Lancet 2011

Terapia antibiotica delle infezioni batteriche dell'osso

- Il trattamento deve essere molto prolungato (4-8 settimane) perché terapie più brevi sono associate ad aumentato rischio di evoluzione negativa **(Dagan R. Pediatr Infect Dis J 1993)**
- Un tempo veniva consigliata l'esclusiva somministrazione endovenosa. Oggi, sulla base, di studi clinici controllati si accetta che dopo un breve periodo di somministrazione endovenosa, si passi alla somministrazione orale

Penetrazione di vari antibiotici nell'osso

(da Landersdorfer CB, et al. Clin Pharmacokinet 2009)



Terapia dell'OMA

- Le cefalosporine orali di II e III generazione somministrate per 4-7 giorni sembrano consentire una possibilità di risoluzione dell'OMA analoga a quella dovuta all'uso di amoxicillina per 10 giorni

(Pchichero M e Casey R. Pediatr Infect Dis J 2002)

Bacteriological eradication rate (%) in studies involving shortened treatment regimens for maxillary sinusitis

(from Pichichero M. Pediatr Infect Dis J 2000)

Study Site, Year of Publication	Shortened Therapy (Drug, Duration)	Longer Therapy (Drug, Duration)
United States, 1995	77 (trimethoprim-sulfamethoxazole, 3 days)	76 (trimethoprim-sulfamethoxazole, 10 days)
United Kingdom, 1993*	86 (cefpodoxime, 5 days)	62 (amoxicillin/clavulanate, 5 days)
France, 1995	96 (cefpodoxime, 5 days)	97 (amoxicillin/clavulanate, 8 days)
United Kingdom, 1996	83 (cefpodoxime, 5 days)	86 (amoxicillin/clavulanate, 8 days)
France, 1996	91 (cefixime, 10 days)	94 (amoxicillin/clavulanate, 10 days)
United States, 1991	100 (azithromycin, 5 days)	100 (amoxicillin, 10 days)

* cefpodoxime statistically superior to amoxicillin/clavulanate

Il batterio

Treatment of tuberculosis in children

(from Berti E, et al. BMC Infect Dis 2014)

	Intensive phase (duration)	Continuation phase (duration)
TB disease (except meningitis and osteoarticular TB) in HIV-uninfected children with low risk of INH-resistance	INH + RIF + PZA (2 months)	INH + RIF (4 months)
TB disease (except meningitis and osteoarticular TB) in HIV-infected children and/or children with high risk of INH-resistance	INH + RIF + PZA + EMB (2 months)	INH + RIF (4 months)
Meningitis and osteoarticular TB	INH + RIF + PZA + EMB (2 months)	INH + RIF (10 months)
INH-monoresistance TB	RIF + PZA + EMB (2 months)[§]	RIF + PZA + EMB (4-7 months)[§]
	RIF + PZA + EMB (2 months)[#]	RIF + EMB (10 months) [#]
	RIF + PZA + EMB + FQN (2 months) [#]	RIF + EMB + FQN (4-7 months) [#]
RIF-monoresistance TB	INH+ PZA + EMB + FQN (2 months) [§]	INH + EMB + FQN (10-16 months) [§]
	INH + PZA + EMB (2 months) [#]	INH + EMB (16 months) [#]
MDR-resistance TB	Treatment regimens should be based on the drug susceptibility pattern of the *M. tuberculosis* isolated from child specimens or, more frequently, from the source case specimens.	

Il paziente

Variable	Induction therapy for ALL before day 77	Aggressive treatment for AL or NHL	Moderately aggressive treatment for AL, NHL, or HD	Maintenance treatment for AL or NHL	Allogeneic HSCT	Autologous HSCT	Aggressive treatment for ST	Moderately aggressive treatment for ST	All
No. neutropenic periods	93	252	167	58	123	171	727	201	1792
Duration of neutropenia, median days (IQR)	18 (8–29)	11 (7–19)	13 (8–23)	15 (8–28)	14 (5–23)	14 (8–22)	10 (7–16)	11.5 (7–17)	11 (7–20)
Primary febrile episodes									
No. (%) of neutropenic periods with a primary febrile episode	23 (25)	120 (48)	36 (21)	5 (9)	54 (44)	99 (58)	232 (32)	45 (22)	614 (34)
Duration from onset of neutropenia to onset of the febrile episode, median days (IQR)	3 (2–18)	4 (1–7)	3.5 (0–7)	5 (1–7)	4 (0–8)	2 (1–4)	3 (0–6)	2 (0–5)	3 (1–6)
Absolute PMN count at the onset of fever, median 10^6cells/L (IQR)	0.05 (0.05–0.30)	0.05 (0.04–0.14)	0.20 (0.05–0.46)	0.09 (0.09–0.33)	0.05 (0.00–0.34)	0.00 (0.00–0.05)	0.05 (0.02–0.20)	0.07 (0.05–0.39)	0.05 (0.00–0.20)
Diagnoses, no. (%) of primary febrile episodes									
FUO	18/23 (78)	91/120 (76)	27/36 (75)	5/5 (100)	36/54 (67)	76/99 (77)	198/232 (85)	32/45 (71)	483/614 (79)
MDI with bacteremia	1/23 (4)	17/120 (14)	3/36 (8)	0/5 (0)	11/54 (20)	11/99 (11)	13/232 (6)	3/45 (7)	59/614 (10)
MDI without bacteremia	1/23 (4)	2/120 (2)	1/36 (3)	0/5 (0)	4/54 (7)	4/99 (4)	4/232 (2)	3/45 (7)	19/614 (3)
CDI	2/23 (9)	5/120 (4)	5/36 (14)	0/5 (0)	1/54 (2)	6/99 (6)	16/232 (7)	5/45 (11)	40/614 (6)
Invasive mycosis	1/23 (4)	5/120 (4)	0/36 (0)	0/5 (0)	2/54 (4)	2/99 (3)	1/232 (<1)	2/45 (4)	13/614 (2)
Secondary febrile episodes									
No. of secondary febrile episodes/no. of primary febrile episodes (%)	4/23 (17)	45/120 (38)	0/36 (0)	0/5 (0)	18/54 (33)	5/99 (5)	16/232 (7)	1/45 (2)	89/614 (14)
Diagnoses, no. (%) of secondary febrile episodes									
FUO	2/4 (50)	24/45 (53)	0/0 (0)	0/0 (0)	12/18 (67)	1/5 (20)	13/16 (81)	1/1 (100)	53/89 (59)
MDI with bacteremia	0/4 (0)	13/45 (29)	0/0 (0)	0/0 (0)	3/18 (17)	3/5 (60)	2/16 (13)	0/1 (0)	21/89 (24)
MDI without bacteremia	0/4 (0)	0/45 (0)	0/0 (0)	0/0 (0)	1/18 (5)	0/5 (0)	1/16 (6)	0/1 (0)	2/89 (2)
CDI	1/4 (25)	2/45 (4)	0/0 (0)	0/0 (0)	1/18 (5)	1/5 (20)	0/16	0/1 (0)	5/89 (6)
Invasive mycosis	1/4 (25)	6/45 (13)	0/0 (0)	0/0 (0)	1/18 (5)	0/5 (0)	0/16 (0)	0/1 (0)	8/89 (9)
Total no. of febrile episodes	27	165	36	5	72	104	248	46	703
Total no. of days at risk	1982	4183	2816	995	2108	2754	10,034	3129	28,001
Rate, no. of febrile episodes per 30 days of neutropenia (95% CI)	0.41 (0.27–0.59)	1.18 (1.01–1.38)	0.38 (0.27–0.53)	0.12 (0.04–0.27)	1.02 (0.80–1.29)	1.13 (0.93–1.37)	0.76 (0.67–0.86)	0.45 (0.33–0.61)	0.76 (0.70–0.81)

NOTE. CDI, clinically documented infection; FUO, fever of unknown origin; HSCT, hemopoietic stem cell transplantation; IQR, interquartile range; MDI, microbiologically documented infection; PMN, granulocytes.

Bambini con tumore ad aumentato rischio infettivo

(da Castagnola E, et al. Clin Infect Dis 2007)

Il farmaco utilizzato

ACTA PAEDIATR SCAND 1985 Jul;74(4):584-8.

Single-dose netilmicin therapy of complicated and uncomplicated lower urinary tract infections in children.

Viganò A, et al.

Abstract

Thirty children (age 3 months to 10 years) with complicated and uncomplicated lower urinary tract infections were treated with a single intramuscular injection of netilmicin 4.5 mg/kg. The diagnosis of lower urinary tract infection was based on the absence of fever and the presence of normal values for erythrocyte sedimentation rate, C-reactive protein concentration and urinary excretion of N-acetyl-beta-D-glucosaminidase. Follow-up urine cultures in all children demonstrated a cure rate of 97% and reinfection and relapse rates each of 7% respectively. The subgroup (12 children) with radiological abnormalities of urinary tract showed a cure rate of 92%, and reinfection and relapse rates of 9% respectively. The rates of cure, reinfection and relapse in the complicated and uncomplicated urinary tract infections were not statistically different (p greater than 0.05). A pharmacokinetic study (performed in 5 children) demonstrated that netilmicin urinary concentrations were over the MIC's of the infecting organisms up to 96 hours after the single-dose injection. Netilmicin was well tolerated and no side effects appeared during treatment. Single-dose netilmicin therapy is an effective and safe regimen for complicated and uncomplicated urinary tract infections in children. The response to single-dose netilmicin therapy seems to be related to its prolonged urinary elimination

Recommendation 25

Considering that penicillin V is currently not available in Italy, amoxicillin administered at 50 mg/kg/d in 2 or 3 doses per day orally for 10 days is the first-choice treatment for GABHS pharyngitis (I-A).

Recommendation 26

Benzathine penicillin may be administered in noncompliant cases (children <27 kg, 600,000 IU; children ≥27 kg, 1,200,000 IU [as a single intramuscular dose]) (I-A).

Recommendation 27

Although not recommended routinely because of their high cost and wide spectrum of activity, a 5-day treatment course with a second-generation cephalosporin (cefaclor 40 mg/kg/d in 2 doses of cefuroxime axetil or 20–30 mg/kg/d in 2 doses; cefprozil 15–30 mg/kg/d in 2 doses) may be used in noncompliant cases (I-B).

Management of acute pharyngitis.

Guidelines of the Italian National Institute of Health

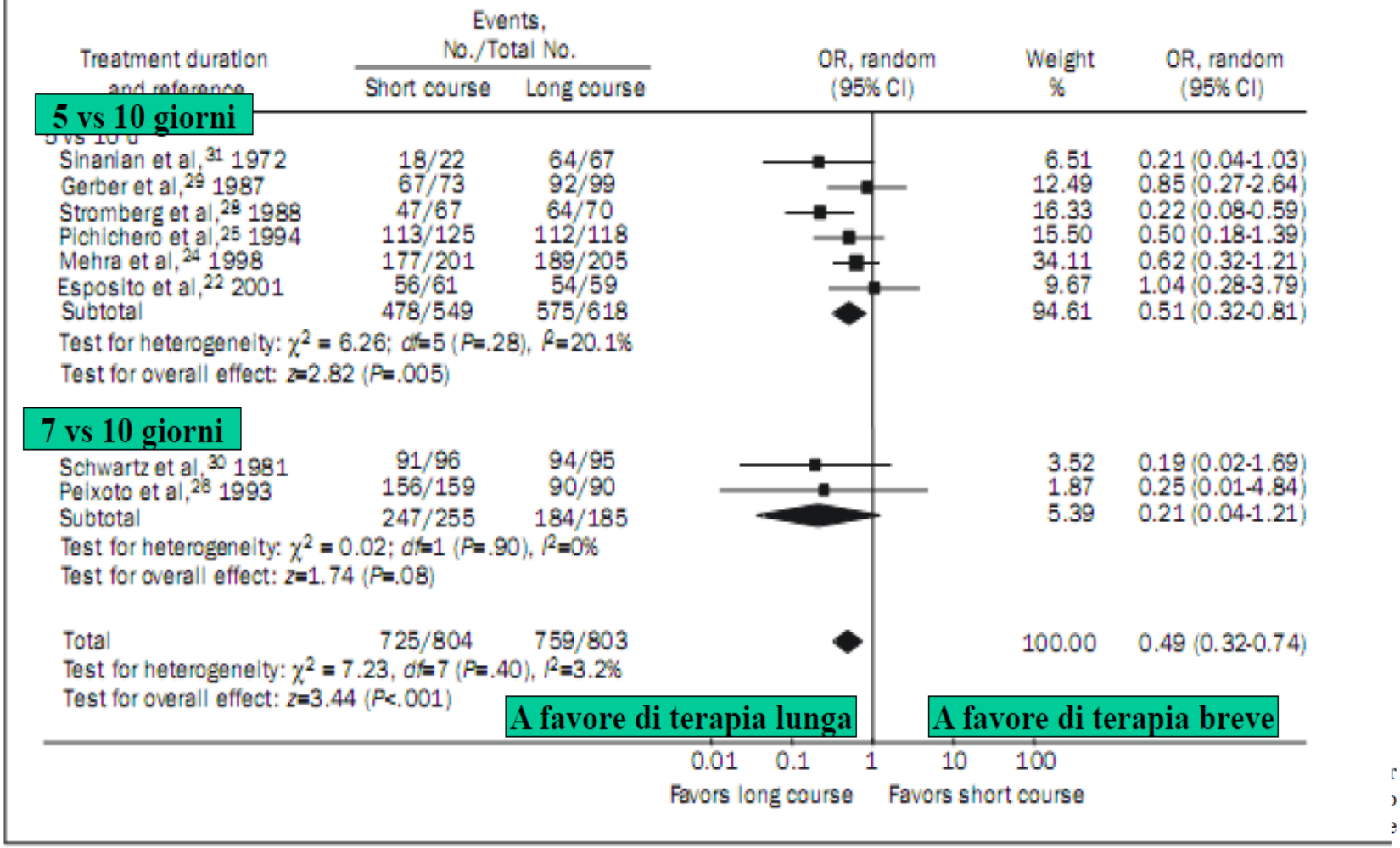
(from Chiappini e, et al. Clin Ther 2012)

Mayo Clinic Proceedings

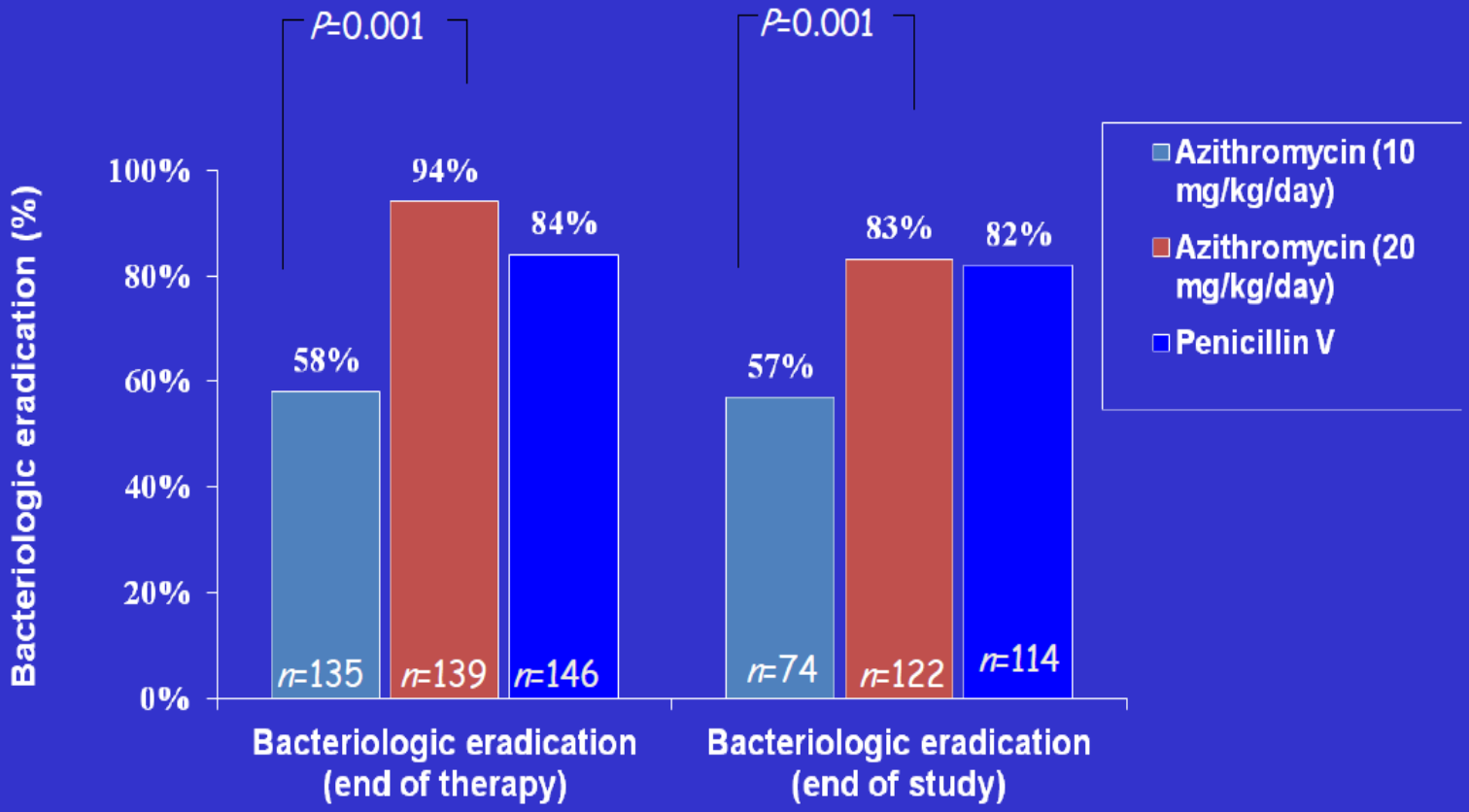
Effectiveness and safety of short-course vs long-course antibiotic therapy for group a beta hemolytic streptococcal tonsillopharyngitis: a meta-analysis of randomized trials

Falagas ME. Mayo Clin Proc 2008;82:880-89

Ogni antibiotico comparato verso se stesso, con diversa durata del trattamento



AZITHROMYCIN 20 mg/kg/day
Bacteriologic Efficacy
(Cohen R et al. 2002)



Cohen R et al. Pediatr Infect Dis J 2002; 21: 297-303

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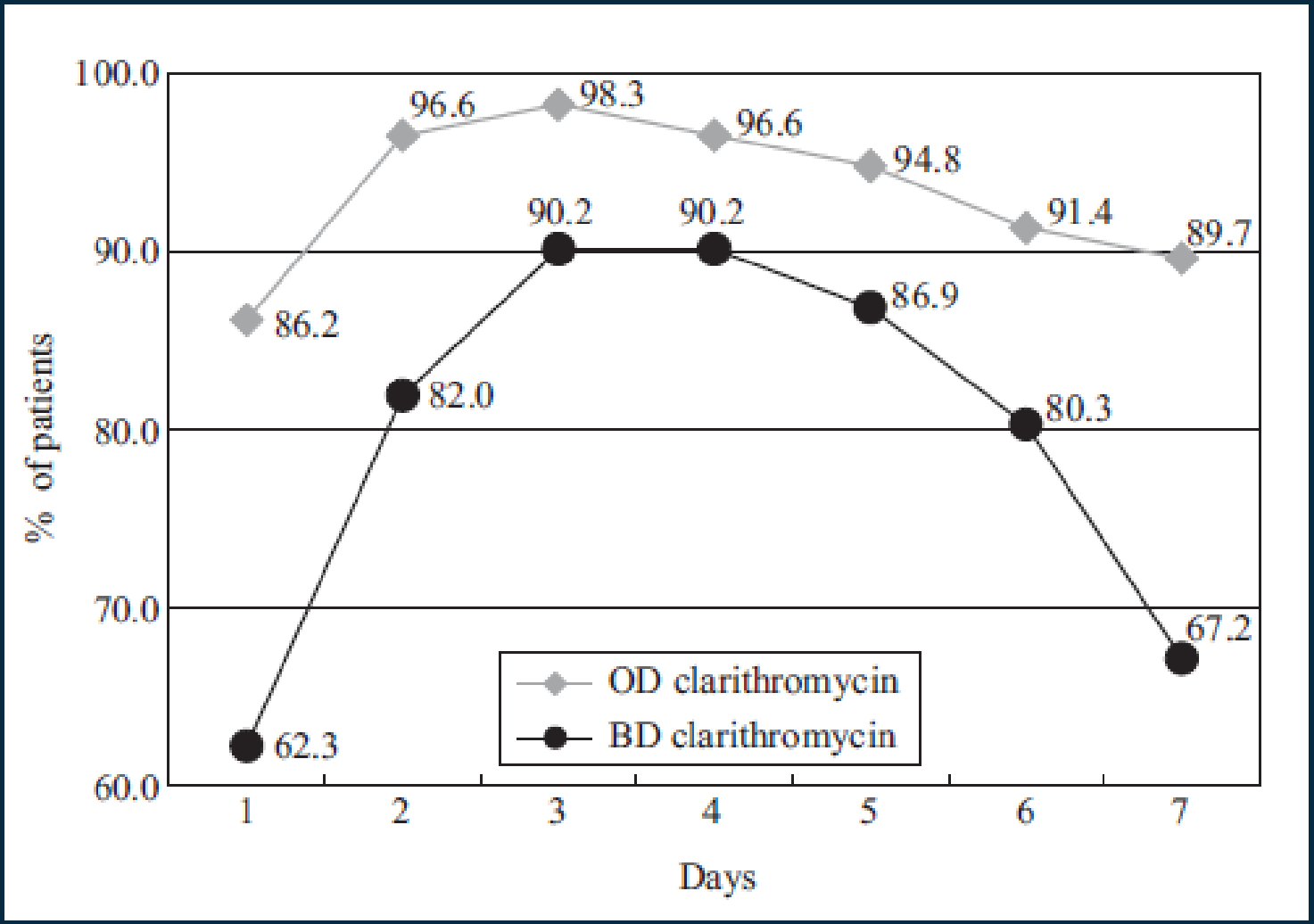
Patient compliance to antimicrobial therapy according to number of daily doses and length of treatment

(from Kardas P. J Antimicrob Chemother 2007)



PATIENT COMPLIANCE ACCORDING TO THE LENGHT OF PENICILLIN V ADMINISTRATION

(From Pichichero, Hosp Pract 1995)

STUDY	DAYS OF THERAPY	PATIENT COMPLIANCE (%)
Mahler et al., 1955	7	66
Bergman and Wemer, 1963	3 6 9	46 31 8
Leystina and Macaulay, 1966	9	89
Chamey et al., 1967	5 9	90 16
Green at al., 1969	9	68

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Impact of compliance on efficacy of antibiotic therapy

(from Rimoin AW, et al. Clin Pediatr 2011)

Country	Amox success (%)	IM BP Success (%)	% diff	95% CI	% diff	95% CI
Croatia (N=121)	70.3	66.7	3.6	-12.9, 20.2	2.5	-13.8, 18,9
EGYPT (N=247)	61.8	75.8	-14.0	-25.5, -2.59	-15.1	-26.6, -3,4

Benzatin penicillina: caratteristiche

- Spettro ristretto e, quindi, scarsa possibilità di modificare sensibilmente la flora saprofita e di selezionare stipiti resistenti (al contrario di tutti gli altri antibiotici usati per la patologia streptococcica)
- Capacità di determinare concentrazioni utili ad eradicare *Streptococcus pyogenes* fino a 3 settimane dopo la somministrazione
- Più bassa determinazione di eventi avversi sistemici
- Sicura aderenza alla terapia
- Iniezione intramuscolare