Penicillin/ampicillin efficacy among children with severe pneumonia due to penicillin-resistant pneumococcus (MIC=4 μg ml^{-1})

Antimicrobials and dosing regimens that have equivalent bacteriological efficacy against susceptible pathogens can have significantly different bacteriological success rates against resistant strains of the same species (Dagan, 2003). Pneumococcal strains are the most frequent pathogens identified among children with bacterial pneumonia and resistance to penicillin poses a potential problem of choosing the initial antibiotic treatment for these patients (Sinaniotis & Sinaniotis, 2005). Discordance between *in vivo* treatment efficacy and *in vitro* antimicrobial resistance has been reported in pneumococcal infection treated with penicillin (Rothermel, 2004). The aim of this study was to assess the association between resistance to penicillin *in vitro* and treatment failure of children with severe pneumococcal pneumonia treated with intravenous penicillin/ampicillin.

This was a multicentre, prospective observational study conducted in 12 centres in Argentina, Brazil and the Dominican Republic. Children aged 3–59 months hospitalized with severe pneumonia according to the World Health Organization (WHO) guidelines (WHO, 1990) were included. Any confounding variable such as other concomitant infection, signs of very severe disease (severe malnutrition, stridor in calm child, somnolence, convulsions, nasal flaring, central cyanosis), underlying disease that could interfere with response to pneumonia treatment or known penicillin allergy excluded initially eligible patients. *Streptococcus pneumoniae* was recovered from blood or pleural fluid. Bacteriological identification was performed according to standard procedures (Facklam & Washington, 1991) and resistance to penicillin was investigated by the identification of the MIC following the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2007). The patients received empirically either penicillin G (200 000 IU kg^{-1} per day) or ampicillin (150 mg kg^{-1} per day) divided into four doses and daily evaluation was registered in a standardized questionnaire until discharge. Treatment failure was defined as absence of improvement (persistence of fever, tachypnoea, dyspnoea or hypoxaemia) after at least 48 h of antibiotic therapy or deterioration of patients (development of pneumothorax, pneumatocele, pleural effusion for those without pleural effusion on admission, respiratory failure or sepsis) during antimicrobial therapy. Written informed consent from parents or legal guardians of the patients was obtained before enrolment. The study was approved by the Ethics Committee of every participating centre and by the ethical review board of the WHO. Details of the methods and the results regarding children infected with pneumococcal strains with MIC $\geqslant 2$ μg ml^{-1} or MIC <2 μg ml^{-1} have already been published (Cardoso *et al.*, 2008).

The study group included 240 patients, out of which 51 (21 %) presented treatment failure. The final multiple logistic regression analysis included 236 patients because of missing data for the variable 'previous antibiotic use'. The median age of the study group was 15.6 months (mean=19.9 months) and 133 (55 %) were males. Table 1 shows the frequency of therapeutic failure by MIC. Table 2 shows the multivariate analysis of treatment failure in patients with pneumococcal strains with different MIC values. Regardless of the small number in the highest MIC group, it is noteworthy that the difference in treatment failure frequency was not significant when children infected with pneumococcal strains with different MICs were compared (P=0.31). There was no strain with MIC >4 μg ml^{-1}.

In vitro bacteriological efficacy can be predicted by pharmacokinetic/ pharmacodynamic parameters and time that the drug concentration is over the MIC for 40–50 % of the dosing interval is a good predictor of bacteriological efficacy for penicillin (Jacobs, 2003). The aim of antimicrobial therapy in respiratory tract infections should be bacterial eradication, and penicillin resistance in pneumococcal pneumonia can be overcome by increasing the dose, hence increasing the time during which serum concentrations are above the MIC (Aguado-García *et al.*, 2004).

Table 1. Frequency of therapeutic failure by MIC for pneumococcal strains among children with severe pneumonia treated with penicillin/ampicillin

Fisher, P=0.935.

MIC (μg ml^{-1})	Outcome		
	Success (n=189)	Failure (n=51)	Total
0.06	94	26 (22 %)	120
0.12	13	4 (24 %)	17
0.25	7	1 (12 %)	8
0.5	5	2 (28 %)	7
1	24	8 (25 %)	32
2	40	8 (17 %)	48
4	6	2 (25 %)	8

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Table 2. Prognostic factors for treatment failure among children admitted with severe pneumonia with isolated *Streptococcus pneumoniae* treated with penicillin/ampicillin

Variable	Success (n=187)	Failure (n=49)	OR (95 % CI)*		P†
			Unadjusted	Adjusted	
MIC					0.31
⩽0.06 μg ml^{-1}	94	25	1	1	
0.125–1 μg ml^{-1}	49	14	1	1.18 (0.52–2.70)	
2 μg ml^{-1}	39	8	1	0.90 (0.35–2.34)	
4 μg ml^{-1}	5	2	1.55 (0.29–8.24)	2.53 (0.42–15.30)	
Age (months)			1.01 (0.99–1.03)	1.00 (0.98–1.03)	0.85
Pleural effusion on admission	90 (48 %)	35 (71 %)	2.69 (1.36–5.33)	2.94 (1.43–6.07)	0.003
Lethargy on admission	50 (27 %)	21 (43 %)	2.06 (1.07–3.94)	2.28 (1.14–4.65)	0.02
Previous antibiotic use	42 (22 %)	9 (18 %)	0.78 (0.35–1.73)	0.72 (0.30–1.69)	0.45

*OR, Odds ratio; CI, confidence interval.
†Log-likelihood ratio test.

The results presented herein are from a further analysis exploring the issue of association between resistance *in vitro* and treatment failure *in vivo*. Now we provide clinical evidence that penicillin G IV (200 000 IU kg^{-1} per day) or ampicillin IV (150 mg kg^{-1} per day) divided into four doses are efficacious options for treating children with pneumonia due to pneumococcal strains with penicillin MIC up to 4 μg ml^{-1}. Attention must be paid to complications (pleural effusion) or the degree of severity (lethargy) when those patients fail to improve after receiving penicillin G or ampicillin at the dosing regimen used in this study. The treatment failure definition used was conservative and strictly applied to the initial 48 h of treatment (Ayieko & English, 2007).

Up to the year 2007, the CSLI recommended interpretation of the penicillin MIC as: ⩽0.06 μg ml^{-1}, susceptible; 0.12–1 μg ml^{-1}, intermediately susceptible; ⩾2 μg ml^{-1}, resistant (CLSI, 2007). Nonetheless, since the year 2000, the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group (DRSP) argued that penicillin susceptibility categories should be shifted upward for pneumococcal pneumonia so that the susceptible category includes all isolates with MIC of no greater than 1 μg ml^{-1}, the intermediate category includes isolates with MIC of 2 μg ml^{-1}, and the resistant category includes isolates with MIC of no less than 4 μg ml^{-1} (Heffelfinger *et al.*, 2000). The DRSP suggested the aforementioned classification in order to parallel penicillin resistance categories with clinical outcomes (Heffelfinger *et al.*, 2000). Our results corroborate the upward shift of penicillin susceptibility categories that was recommended as of the year 2008 (CLSI, 2008). It is possible to speculate that patients with pneumonia with pneumococcal strains with MIC=4 μg ml^{-1} improve by receiving either penicillin G (200 000 IU kg^{-1}) or ampicillin (150 mg kg^{-1}) per day. Studies including a greater number of such patients are needed to better clarify this issue.

Cristiana M. Nascimento-Carvalho,[1] Maria-Regina Cardoso,[2] Maria-Cristina Brandileone,[3] Fernando Ferrero,[4] Paulo Camargos,[5] Eitan Berezin,[6] Raul Ruvinsky,[7] Clemax Sant'Anna,[8] Maria-Fátima March,[8] Jesus Feris-Iglesias,[9] Rubem Maggi,[10] Yehuda Benguigui[11] and the CARIBE Group†, the CARIBE Group

[1]Department of Paediatrics, School of Medicine, Federal University of Bahia, Salvador, Brazil

[2]Faculty of Public Health, São Paulo University, São Paulo, Brazil

[3]Bacteriology Branch, Adolfo Lutz Institute, São Paulo, Brazil

[4]Hospital de Niños Elizalde, Buenos Aires, Argentina

[5]Department of Pediatrics, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil

[6]Santa Casa de São Paulo Medical School, São Paulo, Brazil

[7]Hospital Municipal Durand, Buenos Aires, Argentina

[8]Martagão Gesteira Paediatric Institute, Rio de Janeiro, Brazil

[9]Hospital Infantil Dr Robert Reid Cabral, Santo Domingo, Dominican Republic

[10]Instituto Materno Infantil de Pernambuco, Recife, Brazil

[11]Child and Adolescent Health Unit, Pan American Health Organization, Washington, DC, USA

Correspondence:
Cristiana M. Nascimento-Carvalho
(nascimentocarvalho@hotmail.com)

†CARIBE Group (in alphabetical order): Argentina: Carlos Pascua, Carmen Martiarena, Julio Pace, Mabel Regueira, María José Rial, María Agosti, Norma Gonzalez, Paulina Tagliaferri, Raquel Cosiglio, Sandra Grenon, Silvia Ayala; Brazil: Antônio Cardoso, Claudia Marques, Eduardo Just, Fernando Oliveira, Geraldo Leocádio Filho, Karla Bomfim, Leda Freitas-Souza, Marcelo Otsuka, Marinalva Coelho, Mônica Tura, Silvana Casagrande; Dominican Republic: Hilma Coradín, Jacqueline Sánchez.

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