We believe that patients with severe combined immunodeficiency and any form of mild local changes at the BCG injection site should be given single or double anti-TB therapy, which should be continued until complete immunologic reconstitution occurs after bone marrow transplant. Severe local BCG infection with regional lymph node involvement needs at least triple anti-TB therapy followed by long-term prophylaxis. Disseminated BCG infection needs anti-TB therapy, including >4 anti-TB drugs, until the patient fully recovers.

Acknowledgments

E.A.B. thanks Peter Folb, Dina Pfeiffer, and Adwoa BentSi-Enhill for encouragement in writing this article.

The investigation was supported by grant EURO-POLICY-primary immunodeficiency SP23-CT-2005-006411 and national project no. PBZ-KBN-119/PO5/04.

Ewa Anna Bernatowska,*
Beata Wolska-Kusnierz,*
Malgorzata Pac,*
Magdalena Kurenko-Deptuch,*
Zofia Zwolska,†
Jean-Laurent Casanova,‡
Barbara Piatosa,*
Jacques van Dongen,§
Kazimierz Roszkowski,†
Bozena Mikoluc,¶
Maja Klaudel-Dreszler,*
and Anna Liberek¶

*Children’s Memorial Health Institute, Warsaw, Poland; †National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland; ‡University Rene Descartes, Paris, France; §University Medical Center, Rotterdam, the Netherlands; and ¶Medical University of Białystok, Białystok, Poland

References

1. Newport MJ, Huxley CM, Huston S, Hawrylowicz CM, Oostra BA, Williams R, et al. A mutation in the interferon-γ receptor gene and susceptibility to mycobacterial infection. N Engl J Med. 1996;335:1941–9.

2. Casanova JL, Jouanguy E, Lamhamedi S, Blanche S, Fischer A. Immunological conditions of children with BCG disseminated infection. Lancet. 1995;346:581.

3. Casanova JL, Blanche S, Emile JF, Jouanguy E, Lamhamedi S, Altare F, et al. Idiopathic disseminated bacillus Calmette-Guérin infection: a French national retrospective study. Pediatrics. 1996;98:774–8.

4. Fieschi C, Dupuis S, Catherinot E, Feinberg J, Bustamante J, Breiman A, et al. Low penetrance, broad resistance, and favourable outcome of interleukin 12 receptor β1 deficiency: medical and immunological implications. J Exp Med. 2003;197:527–35.

5. Liberek A, Korzon M, Bernatowska E, Kurenko-Deptuch M, Rydlewksa M. Vaccination-related Mycobacterium bovis BCG infection. Emerg Infect Dis. 2006;12:860–2.

6. Heyderman RS, Morgan G, Levinsky R, Strobel S. Successful bone marrow transplantation and treatment of BCG infection in two patients with severe combined immunodeficiency. Eur J Pediatr. 1991;150:477–80.

7. Gonzalez B, Moreno S, Burdach R, Vanluzenta MT, Herinque A, Ramos MJ. Clinical presentation of bacillus Calmette-Guérin infections in patients with immunodeficiency syndromes. Pediatr Infect Dis J. 1989;8:201–6.

8. Wolska-Kusnierz B, Pac M, Pietrucha B, Heropolitanska-Pliszka E, Klaudel-Dreszler M, Kurenko-Deptuch M, et al. Twenty five years of investigation into primary immunodeficiency diseases in the Department of Immunology, Children’s Memorial Health Institute, Warsaw. Central European Journal of Immunology. 2005;30:104–14 [cited 2007 Mar 19]. Available from http://www.termedia.pl/magazine.php?magazine_id=10&article_id=6799&magazine_subpage=ABSTRACT.

9. Bonilla FA, Bernstein IL, Khan DA, Ballas ZJ, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and the management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005;94 (5 Suppl 1):S1–63.

10. Folb PI, Bernatowska E, Chen R, Clemens J, Dodoo AN, Ellenberg SS, et al. A global perspective on vaccine safety and public health: the Global Advisory Committee on Vaccine Safety. Am J Public Health. 2004;94:1926–31.

Address for correspondence: Ewa Anna Bernatowska, Children’s Memorial Health Institute, Department of Immunology, Av. Dziesci Polskich, 20 Warsaw, 04-730 Mazovia, Poland; email: bernatowskac@yahoo.com

Clindamycin-resistant Streptococcus pneumoniae

To the Editor: Antimicrobial medications classified as macrolides (e.g., erythromycin) and lincosamides (e.g., clindamycin) show strong activity against streptococci and are commonly used to treat community-acquired infections caused by Streptococcus pneumoniae. Moreover, these drugs are the recommended alternatives for patients who cannot tolerate β-lactams.

Two main macrolide-resistant S. pneumoniae phenotypes have been reported (1). The first has a high level of resistance to all macrolides, lincosamides, ketolides, and streptogramins B due to ribosomal dimethylation, 23S rRNA mutations, or ribosomal protein mutations (MLSb, MSb, ML, MKSb, and K phenotypes). The second is characterized by a low-level resistance (e.g., MIC 2–4 mg/L) to only 14- and 15-member ring macrolides (M phenotype) because of mef gene–mediated active drug efflux mechanism.

In January 2005, an erythromycin-susceptible but clindamycin-resistant pneumococcal strain was obtained from a conjunctival swab of a 10-month-old female outpatient attending the daycare center of the Clinic and Laboratory of Infectious Diseases, Siena University, Siena, Italy. To our knowledge, such a phenotype has not been reported in the international literature for S. pneumoniae, although a similar phenotype of S. agalactiae was described by Malbruny et al. (2).

The S. pneumoniae isolate was identified by standard procedures (3) and confirmed by PCR for the common capsule gene cpsA (4). Serotyping, performed by Quellung reaction, showed a 35F serotype. Susceptibility testing was carried out by disk diffusion and confirmed with E-test according to Clinical and Laboratory...
Standard Institute standards (5,6) for penicillin, ceftriaxone, ciprofloxacin, erythromycin, clindamycin, linezolid, and quinupristin-dalfopristin. For telithromycin, because an E-test strip was unavailable, a microbroth dilution method was used.

The strain was susceptible to ceftriaxone (MIC 0.125 mg/L), ciprofloxacin (MIC 0.125 mg/L), erythromycin (MIC 0.125 mg/L), linezolid (MIC 1.5 mg/L), quinupristin/dalfopristin (MIC 0.5 mg/L), and telithromycin (MIC <0.0035 mg/L); it was not susceptible to penicillin (MIC 0.125 mg/L) and was resistant to clindamycin (MIC 1 mg/L). A triple disk-diffusion test with erythromycin, clindamycin, and josamycin was performed to test resistance inducibility. No inducible pattern was shown.

To understand the possible resistance mechanism, MICs for 2 lincosamides (clindamycin and lincomycin) were determined by using a microbroth dilution method in the presence and absence of 10 mg/L of the efflux pump inhibitor reserpine (Sigma Chemicals, St Louis, MO, USA), as described (7); S. pneumoniae ATCC 49619 and S. mitis 21A29 (mefE+) were used as controls (8). The MICs remained unchanged in the presence of reserpine: 1 mg/L for clindamycin and 4 mg/L for lincomycin.

The strain was screened for ermTR, ermB or mefA, and mefE determinants as described (8,9). All PCR controls gave the expected results. No PCR product was obtained for the studied isolate.

Preliminary data did not show classic macrolide resistance determinants for S. pneumoniae. Low-level lincosamide resistance suggests the presence of some efflux mechanism, even if no inhibition by reserpine was observed. Moreover, no mutations of ribosomal proteins and of known binding sites for lincosamides in rRNA (1) were shown by sequencing of L22, L4, and 23S rRNA domain II and V genes with primers described by Canu et al. (10). Although these findings are preliminary and the molecular basis for resistance is the subject of ongoing investigation, the identification of this S. pneumoniae phenotype may affect clinical management of pneumococcal infections, especially in the treatment of patients intolerant of β-lactams.

Acknowledgments

We thank Elisabetta Mantengoli for useful suggestions on gene sequencing and Sanofi Aventis for providing telithromycin.

Strain serotyping was performed at Streptococcal Reference Unit of Respiratory and Systemic Infection Laboratory, Centre for Infections, Health Protection Agency, London, UK.

Francesca Montagnani,*1 Alessandra Zanchi,*1 Lucia Stolzluizi,* Leonardo Croci,* and Carla Cellesi*

*Clinica e Laboratorio di Malattie Infettive, Università degli Studi di Siena, Italy

References

1. Edelstein PH. Pneumococcal resistance to macrolides, lincosamides, ketolides, and streptogramin B agents: molecular mechanisms and resistance phenotype. Clin Infect Dis. 2004;38:S122–7.
2. Malbruny B, Werno AM, Anderson TP, Mordoch DR, Leclercq R. A new phenotype of resistance to lincosamide and streptogramin A-type antibiotics in Streptococcus agalactiae in New Zealand. J Antimicrob Chemother. 2004;54:1040–4.
3. Rouff KL, Whitey RA, Beighton D. Streptococcus. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Yolken RH, editors. Manual of clinical microbiology. 8th ed. Washington: American Society for Microbiology; 2003. p. 405–21.
4. Lawrence ER, Griffiths DB, Martin SA, George RC, Hall LM. Evaluation of semi-automated multiplex PCR assay for determination of Streptococcus pneumoniae serotypes and serogroups. J Clin Microbiol. 2003;41:601–17.

*Contributed equally to this work.

1Contributed equally to this work.