Mechanism of imipenem Resistance in Acinetobacter baumannii Isolates from a Regional Hospital in Taiwan

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ABSTRACT

Acinetobacter baumannii is an opportunistic pathogen causing nosocomial infections in immunocompromised and elderly patients. Imipenem is antibiotic of choice to treat such infections. However, the fast emerging drug-resistant A. baumannii poses difficulty in the treatment usage. In order to elucidate the resistance mechanisms, 20 imipenem-resistant A. baumannii clinical isolates from a regional hospital in Taiwan were collected and examined in this study. E-test analysis showed all isolates were susceptible to colistin, and twelve isolates were intermediately resistant to tigecycline. All isolates were resistant to imipenem, ciprofloxacin, and ceftazidime. PCR amplification and sequence analysis identified blaOXA-23, bla OXA-66 and blaADC-25 in these isolates. The upstream ISAba1 contributing to its downstream gene expression, is always found in blaOXA-23 and blaADC-25, and in blaOXA-66 of three isolates. Further sequence analysis showed that blaOXA-23 was carried by transposon Tn2006. The imipenem resistance in the isolates of A. baumannii was likely due to the expression of either blaOXA-23 or blaOXA-66.We concluded that imipenem resistance in A. baumannii isolates from the regional hospital was likely due to the hpper-expression of OXA-type β-lactamases. Colistin still remained active in vitro (MIC 0.38 - 0.75 μg / ml).

Keywords : Acinetobacter baumannii, imipenem, β-lactamases, blaOXA-23, blaOXA- 66, blaADC-25, ISaba1

Table of Contents

REFERENCES

1. Ambler, R. P. 1980. The structure of beta-lactamases. Philos.Trans.R.Soc.Lond B Biol.Sci. 289:321-331. 2. Arakawa, Y., N. Shibata, K. Shibayama, H. Kurokawa, T. Yagi, H. Fujiwara, and M. Goto. 2000. Convenient test for screening metallo-beta-lactamase-producing gram-negative bacteria by using thiol compounds. J.Clin.Microbiol. 38:40-43. 3. Bertini, A., L. Poirel, S. Bernabeu, D. Fortini, L. Villa, P. Nordmann, and A. Carattoli. 2007. Multicopy blaOXA-58 gene as a source of high-level resistance to carbapenems in Acinetobacter baumannii. Antimicrob.Agents Chemother. 51:2324-2328. 4. Brown, S. and S. Amyes. 2006. OXA (beta)-lactamases in Acinetobacter: the story so far. J.Antimicrob.Chemother. 57:1-3. 5. Bush, K., G. A. Jacoby, and A. A. Medeiros. 1995. A functional classification scheme for beta-lactamases and its correlation with molecular structure. Antimicrob.Agents Chemother. 39:1211-1233. 6. Chen, C. M., P. Y. Liu, S. C. Ke, H. J. Wu, and L. T. Wu. 2009. Investigation of carbapenem-resistant Acinetobacter baumannii isolates in a district hospital in Taiwan. Diagn.Microbiol.Infect.Dis. 63:394-397. 7. Chen, T. L., R. C. Wu, M. F. Shaio, C. P. Fung, and W. L. Cho. 2008. Acquisition of a plasmid-borne blaOXA-58 gene with an upstream IS1008 insertion conferring a high level of carbapenem resistance to Acinetobacter baumannii. Antimicrob.Agents Chemother. 52:2573-2580. 8. Corvec, S., N. Caroff, E. Espaze, C. Giraudeau, H. Drugeon, and A. Reynaud. 2003. AmpC cephalosporinase hyperproduction in Acinetobacter baumannii clinical strains. J.Antimicrob.Chemother. 52:629-635. 9. Corvec, S., L. Poirel, T. Naas, H. Drugeon, and P. Nordmann. 2007. Genetics and expression of the carbapenem-hydrolyzing oxacillinase gene bla in OXA-23 - 44 - Acinetobacter baumannii. Antimicrob.Agents Chemother. 51:1530-1533. 10. Dijkshoorn, L., A. Nemec, and H. Seifert. 2007. An increasing threat in hospitals: multidrug-resistant Acinetobacter baumannii. Nat.Rev.Microbiol. 5:939-951. 11. Dorsey, C. W., A. P. Tomaras, and L. A. Actis. 2002. Genetic and phenotypic analysis of Acinetobacter baumannii insertion derivatives generated with a transposome system. Appl.Environ.Microbiol. 68:6353-6360. 12. Figueiredo, S., L. Poirel, J. Croize, C. Recule, and P. Nordmann. 2009. In vivo selection of reduced susceptibility to carbapenems in Acinetobacter baumannii related to ISAba1-mediated overexpression of the natural bla(OXA-66) oxacillinase gene. Antimicrob.Agents Chemother. 53:2657-2659. 13. Fischbach, M. A. and C. T. Walsh. 2009. Antibiotics for emerging pathogens. Science 325:1089-1093. 14. Heritier, C., L. Poirel, and P. Nordmann. 2006. Cephalosporinase over- expression resulting from insertion of ISAba1 in Acinetobacter baumannii. Clin.Microbiol.Infect. 12:123-130. 15. Hu, W. S., S. M. Yao, C. P. Fung, Y. P. Hsieh, C. P. Liu, and J. F. Lin. 2007. An OXA-66/OXA-51-like carbapenemase and possibly an efflux pump are associated with resistance to imipenem in Acinetobacter baumannii. Antimicrob.Agents Chemother. 51:3844-3852. 16. Hujer, K. M., N. S. Hamza, A. M. Hujer, F. Perez, M. S. Helfand, C. R. Bethel, J. M. Thomson, V. E. Anderson, M. Barlow, L. B. Rice, F. C. Tenover, and R. A. Bonomo. 2005. Identification of a new allelic variant of the Acinetobacter baumannii cephalosporinase, ADC-7 beta-lactamase: defining a unique family of class C enzymes. Antimicrob.Agents Chemother. 49:2941-2948. 17. Kado, C. I. and S. T. Liu. 1981. Rapid procedure for detection and isolation of large and small plasmids. J.Bacteriol. 145:1365-1373. 18. Karageorgopoulos, D. E., T. Kelesidis, I. Kelesidis, and M. E. Falagas. 2008. Tigecycline for the treatment of multidrug-resistant (including carbapenem- resistant) Acinetobacter infections: a review of the scientific evidence. J.Antimicrob.Chemother. 62:45-55. 19. Koeleman, J. G., J. Stoof, D. J. Biesmans, P. H. Savelkoul, and C. M. Vandenbroucke-Grauls. 1998. Comparison of amplified ribosomal DNA restriction analysis, random amplified polymorphic DNA analysis, and amplified fragment length polymorphism fingerprinting for identification of Acinetobacter genomic species and typing of Acinetobacter baumannii. J.Clin.Microbiol. 36:2522-2529. 20. Lee, Y. T., L. Y. Huang, D. H. Chiang, C. P. Chen, T. L. Chen, F. D. Wang, C. P. Fung, L. K. Siu, and W. L. Cho. 2009. Differences in phenotypic and genotypic characteristics among imipenem-non-susceptible Acinetobacter isolates belonging to different genomic species in Taiwan. Int.J.Antimicrob.Agents 34:580-584. 21. Loehfelm, T. W., N. R. Luke, and A. A. Campagnari. 2008. Identification and characterization of an Acinetobacter baumannii biofilm-associated protein. J.Bacteriol. 190:1036-1044. 22. Lu, P. L., M. Doumith, D. M. Livermore, T. P. Chen, and N. Woodford. 2009. Diversity of carbapenem resistance mechanisms in Acinetobacter baumannii from a Taiwan hospital: spread of plasmid-borne OXA-72 carbapenemase. J.Antimicrob.Chemother. 63:641-647. 23. Magnet, S., P. Courvalin, and T. Lambert. 2001. Resistance-nodulation-cell division-type efflux pump involved in aminoglycoside resistance in Acinetobacter baumannii strain BM4454. Antimicrob.Agents Chemother. 45:3375-3380. 24. Mak, J. K., M. J. Kim, J. Pham, J. Tapsall, and P. A. White. 2009. Antibiotic resistance determinants in nosocomial strains of multidrug-resistant Acinetobacter baumannii. J.Antimicrob.Chemother. 63:47-54. 25. Mammeri, H., L. Poirel, N. Mangeney, and P. Nordmann. 2003. Chromosomal integration of a cephalosporinase gene from Acinetobacter baumannii into Oligella urethralis as a source of acquired resistance to beta-lactams. Antimicrob.Agents Chemother. 47:1536-1542. 26. Massova, I. and S. Mobashery. 1998. Kinship and diversification of bacterial penicillin-binding proteins and beta-lactamases. Antimicrob.Agents Chemother. 42:1-17. 27. mier-Piolle, L., S. Magnet, S. Bremont, T. Lambert, and P. Courvalin. 2008. AdeIJK, a resistance-nodulation-cell division pump effluxing multiple antibiotics in Acinetobacter baumannii. Antimicrob.Agents Chemother. 52:557-562. 28. Peleg, A. Y., J. Adams, and D. L. Paterson. 2007. Tigecycline Efflux as a Mechanism for Nonsusceptibility in Acinetobacter baumannii. Antimicrob.Agents Chemother. 51:2065-2069. 29. Peleg, A. Y., H. Seifert, and D. L. Paterson. 2008. Acinetobacter baumannii: emergence of a successful pathogen. Clin.Microbiol.Rev. 21:538-582. 30. Poirel, L., S. Marque, C. Heritier, C. Segonds, G. Chabanon, and P. Nordmann. 2005. OXA-58, a novel class D {beta}-lactamase involved in resistance to carbapenems in Acinetobacter baumannii. Antimicrob.Agents Chemother. 49:202-208. 31. Queenan, A. M. and K. Bush. 2007. Carbapenemases: the versatile beta- lactamases. Clin.Microbiol.Rev. 20:440-58, table. 32. Segal, H., R. K. Jacobson, S. Garny, C. M. Bamford, and B. G. Elisha. 2007. Extended -10 promoter in ISAba-1 upstream of blaOXA-23 from Acinetobacter baumannii. Antimicrob.Agents Chemother. 51:3040-3041. 33. Segal, H., E. C. Nelson, and B. G. Elisha. 2004. Genetic environment and transcription of ampC in an Acinetobacter baumannii clinical isolate. Antimicrob.Agents Chemother. 48:612-614. 34. Seward, R. J. and K. J. Towner. 1998. Molecular epidemiology of quinolone resistance in

Acinetobacter spp. Clin.Microbiol.Infect. 4:248-254. 35. Walsh, T. R., M. A. Toleman, L. Poirel, and P. Nordmann. 2005. Metallo-beta-lactamases: the quiet before the storm? Clin.Microbiol.Rev. 18:306-325. 36. Wu, T. L., L. H. Su, H. S. Leu, C. H. Chiu, Y. P. Chiu, J. H. Chia, A. J. Kuo, and C. F. Sun. 2002. Molecular epidemiology of nosocomial infection associated with multi-resistant Acinetobacter baumannii by infrequent-restriction-site PCR. J.Hosp.Infect. 51:27-32. 37. Zarrilli, R., M. Crispino, M. Bagattini, E. Barretta, P. A. Di, M. Triassi, and P. Villari. 2004. Molecular epidemiology of sequential outbreaks of Acinetobacter baumannii in an intensive care unit shows the emergence of carbapenem resistance. J.Clin.Microbiol. 42:946-953. 38. Zarrilli, R., D. Vitale, P. A. Di, M. Bagattini, Z. Daoud, A. U. Khan, C. Afif, and M. Triassi. 2008. A plasmid-borne blaOXA-58 gene confers imipenem resistance to Acinetobacter baumannii isolates from a Lebanese hospital. Antimicrob.Agents Chemother. 52:4115-4120.