台灣一區域醫院鮑氏不動桿菌菌株對於 imipenem 的抗藥機制研究 = Mechanism of imipenem resistance in Acinetobacter baumannii

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摘 要

鮑氏不動桿菌 (Acinetobacter baumannii) 為一種伺機性的病 原菌，在醫院內常感染於免疫力不足與較年長的病人，而治療上 經常選擇 imipenem 做為治療此感染的抗生素；然而新的抗藥性 鮑氏不動桿菌的快速產生，因而造成了臨床用藥上的困難。本實 驗從台灣一區域醫院挑選了二十株對 imipenem 具有抗藥性的臨 床分離株做為研究的對象。使用E-test的抗藥性測試分析中發現， 對於 colistin 的測試二十株菌株皆為敏感型，對於 tigecycline 的 測試十二株菌株為中間型；而對於 imipenem、ciprofloxacin 與 ceftazidime 的測試二十株菌株皆為抗藥型。接著在PCR測試與定 序分析中發現二十株菌株皆有 blaOXA-23、blaOXA-66 與 blaADC-25 抗 藥基因存在；且在二十株菌株的 blaOXA-23 與blaADC-25 基因上游皆 有 ISAba1 的存在，而有三株菌株 blaOXA-66基因上游有 ISAba1 的存在，進一步分析 blaOXA-23 發現部分blaOXA-23 可能是由 transposon (Tn2006) 攜帶，而且位於質體上。而ISAba1的存在可 以導致下游的基因 blaOXA-23 與 blaOXA-66 表現量上升，因此鮑氏不 動桿菌對於 imipenem 的抗藥性是來自於基因 blaOXA-23 與blaOXA- 66。總結研究結果發現所收集的 imipenem 抗藥性菌株，皆含有 OXA-type β-lactamases 的抗藥基因，可以提供菌株對於 imipenem 產生抗藥性，並且利用 Real-time PCR 發現到其基因上游含有 ISAba1 可以使該基因表現量上升，進而可能導致菌株抗藥性上升 。對於這些菌株其抗生素的測試結果顯示，或許 colistin 對於這 些抗藥性菌株還是具有有效的抑菌效果（其MIC值介於0.38 ~ 0.75 μg / ml 之間）。

關鍵詞 : 鮑氏不動桿菌，imipenem ， β- 內醯胺?，blaOXA-23 ， blaOXA-66，blaADC-25，ISAba1

目錄

參考文獻

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.