

BÖLÜM 3

YOĞUN BAKIM ÜNİTELERİNDE ÇOKLU İLACA DİRENÇLİ GRAM NEGATİF BAKTERİLER, DİRENÇ MEKANİZMALARI VE YENİ TEDAVİ SEÇENEKLERİ

Abdullah Umut PEKOK¹

Gram Negatif Bakterilerde Çoklu İlaça Direncin Ortaya Çıkışı

Gram negatif bakterilerde direnç gelişimi dört mekanizma ile olmaktadır:

- İnaktivasyon
- hedef modifikasyonu
- permeabilite azalması-kaybı
- efluks pompaları

Günümüzde tek tek direnç mekanizmalarından daha fazla, çoklu ilaca direnç gelişiminin mekanizmaları önem taşımaktadır.

Çoklu ilaca direnç gelişimi bakterilerin başlıca iki özelliği ile ilişkilidir (1):

- Diğer mikroorganizmalardan kaynaklanabilecek direnç determinantlarının bakteriye ulaşması ve eksprese olması.
- Edinsel mekanizmalarla eksprese edilen direnç düzeyini arttırabilecek intrinsik mekanizmaların devreye sokulabilmesi.

Bakterinin canlılığını sürdürmesi için esas olan periplazmik aralığın kontrolüdür ve bakteri bunu spesifik ve nonspesifik mekanizmalarla gerçekleştirir (1).

Nonspesifik mekanizmalar (Porin ve efluks pompaları): Pek çok çözünen madde bakteri hücresi içine porin adı verilen protein kanalları kullanarak girer (2). Porinler arasında farklılıklar söz konusudur ve bazı porinlerden madde daha hızlı geçer. Porinlerden geçiş hızı dış membran permeabilitesinin belirleyicisidir.

¹ Dr. Öğr. Üyesi, İstanbul Aydın Üniversitesi Tıp Fakültesi, VM Medical Park Pendik Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji, Umut.pekok@yahoo.com

KAYNAKLAR

1. Rice LB: Emerging issues in the management of infections caused by multidrug-resistant gram-negative bacteria, *Clev Clin J Med* 2007;74(Suppl 4):S12-20.
2. Nikaido H: Molecular basis of bacterial outer membrane permeability revisited, *Microbiol Mol Biol Rev* 2003;67(4):593-656.
3. Livermore DM: Interplay of impermeability and chromosomal beta-lactamase activity in imipenem-resistant *Pseudomonas aeruginosa*, *Antimicrob Agents Chemother* 1992;36(9):2046-8.
4. Webber MA, Piddock LJ: The importance of efflux pumps in bacterial antibiotic resistance, *J Antimicrob Chemother* 2003;51(1):9-11.
5. Murakami S, Nakashima R, Yamashita E, Yamaguchi A: Crystal structure of bacterial multidrug efflux transporter AcrB, *Nature* 2002;419:(6907)587-93.
6. Haeggman S, Lofdahl S, Paaauw A, Verhoef J, Brisse S: Diversity and evolution of the class A chromosomal beta-lactamase gene in *Klebsiella pneumoniae*, *Antimicrob Agents Chemother* 2004;48(7):2400-8.
7. Bradford PA: Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat, *Clin Microbiol Rev* 2001;14(4):933-51.
8. Hernández-Allés S, Alberti S, Alvarez D et al: Porin expression in clinical isolates of *Klebsiella pneumoniae*, *Microbiology* 1999;145(Pt 3):673-9.
9. Essack SY, Hall LM, Pillay DG, McFadyen ML, Livermore DM: Complexity and diversity of *Klebsiella pneumoniae* strains with extended-spectrum beta-lactamases isolated in 1994 and 1996 at a teaching hospital in Durban, South Africa, *Antimicrob Agents Chemother* 2001;45(1):88-95.
10. Rice LB, Carias LL, Bonomo RA, Shlaes DM: Molecular genetics of resistance to both ceftazidime and beta-lactam-beta-lactamase inhibitor combinations in *Klebsiella pneumoniae* and in vivo response to beta-lactam therapy, *J Infect Dis* 1996;173(1):151-8.
11. Schiappa DA, Hayden MK, Matushek MG et al: Ceftazidime resistant *Klebsiella pneumoniae* and *Escherichia coli* bloodstream infection: a case-control and molecular epidemiologic investigation, *J Infect Dis* 1996;174(3):529-36.
12. Bratu S, Mooty M, Nichani S et al: Emergence of KPC-possessing *Klebsiella pneumoniae* in Brooklyn, New York: epidemiology and recommendations for detection, *Antimicrob Agents Chemother* 2005;49(7):3018-20.
13. Babini GS, Livermore DM: Antimicrobial resistance amongst *Klebsiella* spp. collected from intensive care units in Southern and Western Europe in 1997-1998, *J Antimicrob Chemother* 2000;45(2):183-9.
14. Bratu S, Tolaney P, Karumudi U et al: Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents, *J Antimicrob Chemother* 2005;56(1):128-32.
15. Stover CK, Pham XQ, Erwin AL et al: Complete genome sequence of *Pseudomonas aeruginosa* PA01, an opportunistic pathogen, *Nature* 2000;406(6799):959-64.
16. Nordmann P, Poirel L: Emerging carbapenemases in Gram-negative aerobes, *Clin Microbiol Infect* 2002;8(6):321-31.
17. Dubois V, Arpin C, Melon M et al: Nosocomial outbreak due to a multiresistant strain of *Pseudomonas aeruginosa* P12: efficacy of cefepime-amikacin therapy and analysis of beta-lactam resistance, *J Clin Microbiol* 2001;39(6):2072-8.
18. Carmeli Y, Troillet N, Eliopoulos GM, Samore MH: Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents, *Antimicrob Agents Chemother* 1999;43(6):1379-82.
19. Mussi MA, Limansky AS, Viale AM: Acquisition of resistance to carbapenems in multidrug-resistant clinical strains of *Acinetobacter baumannii*: natural insertional inactivation of a gene encoding a member of a novel family of beta-barrel outer membrane proteins, *Antimicrob Agents Chemother* 2005;49:1432-40.
20. Chau SL, Chu YW, Houang ET: Novel resistance-nodulation-cell division efflux system AdeDE in *Acinetobacter* genomic DNA group 3, *Antimicrob Agents Chemother* 2004;48(10):4054-55.

Yoğun Bakım Ünitelerinde Çoklu İlaça Dirençli Gram Negatif Bakteriler, Direnç Mekanizmaları ve Yeni Tedavi Seçenekleri

21. Heritier C, Poirel L, Fournier PE, Claverie JM, Raoult D, Nordmann P: Characterization of the naturally occurring oxacillinase of *Acinetobacter baumannii*, *Antimicrob Agents Chemother* 2005;49(10):4174-79.
22. Fournier PE, Richet H: The epidemiology and control of *Acinetobacter baumannii* in health care facilities, *Clin Infect Dis* 2006;42(5):692-9.
23. Go ES, Urban C, Burns J et al: Clinical and molecular epidemiology of *Acinetobacter* infections sensitive only to polymyxin B and sulbactam, *Lancet* 1994;344(8933):1329-32.
24. Landman D, Quale JM, Mayorga D et al: Citywide clonal outbreak of multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Brooklyn, NY: the preantibiotic era has returned, *Arch Intern Med* 2002;162(13):1515-20.
25. Sobieszczyk ME, Furuya EY, Hay CM et al: Combination therapy with polymyxin B for the treatment of multidrug-resistant gram-negative respiratory tract infections, *J Antimicrob Chemother* 2004;54(2):566-9.
26. Garnacho-Montero J, Ortiz-Leyba C, JimenezJimenez FJ et al: Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP, *Clin Infect Dis* 2003;36(9):1111-8.
27. Markou N, Apostolakis H, Koumoudiou C et al: Intravenous colistin in the treatment of sepsis from multidrug-resistant Gram-negative bacilli in critically ill patients, *Crit Care* 2003;7(5):R78-83.
28. Kasiakou SK, Michalopoulos, Soteriades ES, Samonis G, Sermaides GJ, Falagas ME: Combination therapy with intravenous colistin for management of infections due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis, *Antimicrob Agents Chemother* 2005;49(8):3136-46.
29. Tam VH, Schilling AN, Vo G et al: Pharmacodynamics of polymyxin B against *Pseudomonas aeruginosa*, *Antimicrob Agents Chemother* 2005;49(9):3624-30.
30. Falcone, M., & Paterson, D. 2016. *JAC*, 71(10)
31. Zhanel, George G. 2014. *Drugs* 74.1
32. Bassetti M, et al. *Curr Opin Infect Dis* 2017; 177-88
33. Aparico DB, et al. Potency of meropenem-vaborbactam in lung surfactant. *Antimicrobial agents and Chemotherapy* 2018; 62(1): 1702-17.
34. Castanheira M, et al. *Antimicrobial Agents and Chemotherapy* 2017; 61(9):e00567-17
35. Lob SH, et al. *Antimicrobial Agents and Chemotherapy* 2017; 61(6):e 02209-16.
36. Sader H, et al. WCK 5222 (Cefepime-Zidebactam) Antimicrobial Activity against Clinical Isolates of Gram-Negative organism producing clinically relevant beta-lactamases. *J Antimicrob Chemother* doi: 10.1093/jac/dkx050
37. Frampton J E. *Drugs*, 2013, 73.10
38. Very LM, Nicolas DP. *Expert Opinion on Investigational Drugs*. 2018; 27:4:325-38.
39. Bassetti M et al. 2019 *Front. Med*