BÖLÜM 19

GLİKOPEPTİDLERE DİRENÇ MEKANİZMALARI

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Giriş

Antimikrobiyal direnç (AMD) ciddi bir küresel halk sağlığı sorunudur. Direkt ve dolaylı yollar ile 2019 yılında yaklaşık olarak beş milyon ölüme sebep olmuştur (1). Ekonomik Kalkınma ve İşbirliği Örgütü (*Organisation for Economic Co-operation and Development,* OECD) Ülkeleri arasında, 2020 yılı için, her bin kişiye düşen günlük sistemik antibiyotik tüketim miktarı en yüksek olan üçüncü ülkenin, Yunanistan (28.1) ve Şili'den (24.7) sonra, Türkiye (24.4) olduğu rapor edilmiştir (2). Akılcı olmayan, aşırı antibiyotik kullanımı AMD ile sonuçlanmaktadır. Yayılımındaki istikrarlı artış devam ederse, AMD'in, 2050'den önce yılda 10 milyon insan ölümüne sebep olacağı tahmin edilmektedir (1). Dünya Sağlık Örgütü'nün (DSÖ) insan sağlığını tehdit eden, AMD'i olan öncelikli patojenler listesindeki 12 bakteriden ikisi yüksek öncelikli patojenler alt grubunda yerini alan vankomisine dirençli *Enterococcus faecium* ve vankomisine dirençli veya orta duyarlı *Staphylococcus aereus*'tur (3). Bu etkenlerin sebep olduğu enfeksiyonlar aynı zamanda ciddi bir ekonomik yüke yol açmaktadır. Örneğin tahminlere göre bu etkenlerin sebep olduğu maliyet Amerika Birleşik Devletler'inde (ABD) yıllık 4.6 milyar dolardır (4).

Toprak kökenli *Actinomycetes* bakterilerinden elde edilen glikopeptid antibiyotikler (GPA'lar; vankomisin, teikoplanin) hayatı tehtid eden, çoklu ilaç direnci (ÇİD) bulunan *S. aureus*, *Enterococcus spp* ve *Clostridioides difficile* gibi patojenlerin etken olduğu enfeksiyonların tedavisinde son çare ilaçlar olarak kabul edilirler. GPA'lar, Gram pozitif bakterilerde peptidoglikan (PG) öncülerinin d-a-

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MİK > 2 mg/L, CLSI kriterlerine göre MİK ≥ 4 mg/L ise vankomisine dirençli kabul edilir (8, 9). Avrupa ve ABD'de vankomisin ile kür oranlarının şimdiden %93-100'den % 82-88'e düştüğü bildirilmektedir. Vankomisin *C. difficile* izolatlarında PG prekürsörünün (UDP-N-acetylmuramyl pentapeptid) d-Ala-d-Ala subünitesine bağlanarak etki gösterir. Vankomisine direnç PG biyosentezi için gereken proteinlerin mutasyonu ile hedef yapının değişmesi, biyofilm formasyonu ve spor oluşturması ile ilişkili olduğu tespit edilmiştir. Biyofilmi olan bir patojenik bakterinin antibiyotiklere direnci (protektif bariyer oluşturması, bakterinin dormant formda olması ve beraberindeki bakterilerle gen alışverişinde bulunabilmesi sebebi ile) planktonik bakterilere göre 10-1000 kat artmaktadır (41-43).

C. innocuum intrinsik vankomisin direnci olan, bağışıklık sistemi baskılanmış hastalarda nadiren patojen olabilen intestinal mikrobiyatanın bir üyesidir. Diyare, bakteriyemi, osteomiyelit, peritonit, ampiyem, yumuşak doku enfeksiyonları ve intraabdominal abse gibi enfeksiyonlarda bildirilmiştir. Nadiren spor oluşturması, Gram değişken boyanması, atipik koloni morfolojisi ve değişken antibiyotik duyarlılığı ile laboratuvar tanısı atlanabilmektedir. Bilinen toksin geni bulunmamaktadır. Genellikle piperasilin-tazobaktam, metranidazol ve klindamisin ile tedavi edilmektedir. Ancak prognozu yine de kötüdür, mortalite oranının %33'tür (44-46).

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