The Antimicrobial Susceptibility of *Bacillus anthracis* Isolated from Human Cases: A Review of the Turkish Literature

İnsan Olgularından İzole Edilen *Bacillus anthracis* Suşlarının Antimikrobiyal Duyarlılıkları: Türkiye Literatürünün Gözden Geçirilmesi

Gökhan METAN, MD,[a]
Mehmet DOĞANAY, MD[a]

[a]Department of Infectious Diseases and Clinical Microbiology, Erciyes University Faculty of Medicine, Kayseri

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Yazışma Adresi/*Correspondence:*
Gökhan METAN, MD
Erciyes University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Kayseri, TÜRKİYE/TURKEY
gokhanmetan@gmail.com

ABSTRACT Anthrax is still an endemic disease in central parts of the world including Turkey. The aim of this study was to assess the local therapeutic options by reviewing the articles published in Turkey about the antibiotic susceptibility of *Bacillus anthracis.* A total of 138 clinical isolates from human cases were evaluated in 5 studies from 1990 to 2007. All isolates tested against penicillin G were susceptible. None of the strains produced beta-lactamase. Doxcycline, tetracycline, erythromycin, aminoglycosides and ciprofloxacin were highly active against all strains. According to the results of this analysis, penicillin G is still a reliable option for the treatment of naturally acquired human anthrax in Turkey.

Key Words: Anthrax; anti-infective agents

ÖZET Şarbon Türkiyenin de içinde bulunduğu dünyanın çeşitli bölgelerinde halen endemiktir. Bu yazının amacı, Türkiye'de *Bacillus anthracis*'in antibiyotik duyarlılığı konusunda yapılan çalışmaların değerlendirilmesi ve tedavi alternatiflerinin sunulmasıdır. Literatür taraması sonucu 1990-2007 yılları arasında insan olgularından soyutlanan toplam 138 klinik izolatı değerlendiren 5 çalışmaya ulaşıldı. Penisilin G için test edilen tüm izolatlar bu ajana duyarlı idi. İzolatların hiçbiri beta-laktamaz üretmiyordu. Doksisiklin, tetrasiklin, eritromisin, aminoglikozidler ve siprofloksasin tüm izolatlara karşı yüksek düzeyde aktif idi. Bu analizin sonuçlarına göre Türkiye'de doğal yoldan oluşan insan şarbonunda penisilin G halen güvenilir bir seçenektir.

Anahtar Kelimeler: Şarbon; antimikrobiyal ajanlar

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Bacillus anthracis is the causative agent of anthrax which is an endemic zoonosis in some parts of the world. Despite the hard efforts for the control of the spread of *B. anthracis*, human anthrax is still endemic in some parts of Turkey. A total of 2510 cases were reported to the Turkish Ministry of Health between 2000-2006 (http://www.saglik.gov.tr/TR/istatistik/ 2006/tablo34.htm).

Due to effective control programs human anthrax is very rare in industrialized countries and currently human anthrax cases occur mostly in agricultural regions of the world where anthrax in animals is still prevalent. Penicillin has been the drug of choice for treatment with rare clinical failure and the interest on the antimicrobial susceptibility profile of *B. anthracis* is small. However, after the 'anthrax letter' events of October and November

2001 in the United States of America (USA), the antimicrobial susceptibility of *B. anthracis* became an important issue based on the concern of bioterrorism attack with an antibiotic resistant strain.[1]

Lightfoot et al reported the first article about the antimicrobial susceptibility of *B. anthracis* and Doğanay and Aydın followed them.[2,3] There are several studies concerning the antibiotic susceptibility of *B. anthracis* in Turkey but there are no systematic reviews to guide the treatment of human anthrax based on local epidemiological data. In this study, the international articles published in Turkey about the antibiotic susceptibiliy of *B. anthracis* were reviewed to assess local therapeutic options.

Studies that evaluated antimicrobial susceptibility patterns among human clinical isolates of *B. anthracis* in Turkey from 1990 to 2007 were identified through the literature search of international and Turkish MEDLINE (www.turkishmedline.com and http://medline.pleksus.com.tr) databases. The search terms were anthrax, *B. anthracis*, susceptibility and Turkey (the terms 'anthrax, *B. anthracis*, sensitivity, Türkiye' were used for Turkish MEDLINE). The references of the articles were also searched when necessary. Only full text articles were included in this study. The susceptibility of penicillin G, doxycycline and ciprofloxacin were interpreted according to the breakpoint for *B. anthracis* suggested by the Clinical Laboratory Standards Institute (CLSI).[4]

We were able to identify 5 studies that evaluated the antimicrobial susceptibility of *B. anthracis* from 1990 to 2007. The antimicrobial susceptibilities were determined by agar dilution in 2, both agar dilution and disk diffusion in one, Sceptor (Becton Dickinson Diagnostic Instrument Systems, Towson, MD) automated system in one and disk diffusion in one study.[3,5-8] Beta-lactamase production of the strains was detected by acidimetric method or nitrocefin in 2 studies.[3,7]

A total of 138 clinical isolates from human cases were evaluated. The isolates were collected from central and eastern regions of Turkey where anthrax is an endemic disease. All of the 104 isolates tested against penicillin G were susceptible.[3,5,7,8] Beta-lactamase production was tested for 50 isolates and all were negative.[3,7] Doxycycline, tetracycline, erythromycin and ciprofloxacin were highly active against all strains. Although the minimal inhibitory concentration (MIC) of cefazolin was low, cefuroxime, ceftriaxone, cefotaxime and ceftazidime had higher MICs. The results of the studies were summarized in Table 1. Penicillin G susceptibility was evaluated according to the breakpoint of the CLSI for three studies.[3,5,7] Ciprofloxacin susceptibility was assessed in 2 studies[5] and doxycyline in one study.[3,5] Although CLSI provided standards for the susceptibility of *B. anthracis* after the publication of those studies, the results of the studies that used dilution methods were concordant with CLSI cut off values for penicilin G, doxycycline and ciprofloxacin (Table 2).

CLSI suggested broth dilution as a reference method for antimicrobial susceptibility of *B. anhtracis* recently. All studies except one used a dilution method.[3,5-7] Agar dilution, broth microdilution, E-test agar gradient method and automated systems were used in different studies.[1,9-13] Breakpoints for staphylococci were used in some studies carried out before CLSI provided values for *B. anthracis*.[9-11] The results of the Turkish studies interpreted according to the breakpoints of the CLSI for *B. anthracis* seemed to be in agreement with previous reports. The susceptibilities of penicillin G, doxycycline and ciprofloxacin, drugs that are recommended as first line agents for the treatment of *B. anthracis* infections in different studies were summarized in Table 2.

B. anthracis isolates are susceptible against a wide range of antibiotics. However, the rate of penicillin resistance reached 11.5% in a French study that tested 96 isolates of *B. anthracis*. Although, 28 isolates were from animal sources and 67 were from the environment, humans become infected from animal and environmental sources; thus the susceptibilities of these isolates are significant for assessing treatment options.[9] The other studies performed out of Turkey also reported penicillin as a highly active agent against *B. anthracis* strains isolated from naturally acquired human anthrax cases.[1,2,10-13] In our analysis, all strains were isolated

TABLE 1: Comparison of reports on antibiotic susceptibility of *B. anthracis* stains isolated from human cases in Turkey.

Antibiotic	Study and reference number	Test method of the strains	Number breakpoints	CLSI MIC (mg/L)			MIC (mg/L)			Interpretation of susceptibility according to DD, (n)			Interpretation of susceptibility according to CLSI breakpoints*, (n)		
				S**	I	R	Range	50%	90%	S	I	R	S	I	R
Penicillin G	Doğanay and Aydın[3]	AD	22	≤0.12	-	≥0.25	0.015-0.03	0.015	0.015	22	0		22	0	0
	Esel et al[5]	AD	40	≤0.12		≥0.25	0.016-0.013	0.016	0.016				40	0	0
	Öncül et al[8]	DD	14							14	0	0			
	Bakıcı et al[7]	SAS	28	≤0.12	-	≥0.25			≤0.03				28	0	0
Doxycycline	Esel et al[5]	AD	40	≤0.5	-	-	≤0.016-0.03	≤0.016	0.03				40	0	0
Ciprofloxacin	Doğanay and Aydın[3]	AD	22	≤0.5	-	-	0.03-0.06	0.03	0.06	22	0	0	22	0	0
	Bakıcı et al[7]	SAS	28	≤0.5	-	-			≤ 1				NA	NA	NA
	Esel et al[5]	AD	40	≤0.5	-	-	0.008-0.12	0.03	0.06				40	0	0
	Öncül et al[8]	DD	14							14	0	0			
Ofloxacin	Doğanay and Aydın[3]	AD	22				0.03-0.06	0.06	0.06	22	0	0			
Levofloxacin	Esel et al[5]	AD	40				0.016-0.12	0.06	0.12						
Gatifloxacin	Esel et al[5]	AD	40				0.016-0.06	0.03	0.06						
Ampicillin	Doğanay and Aydın[3]	AD	22				0.03-0.125	0.03	0.03	22	0	0			
Ampicillin-sulbactam	Doğanay and Aydın[3]	AD	22				0.015-0.03	0.015	0.015	22	0	0			
Amoxicillin	Doğanay and Aydın[3]	AD	22				0.015-0.03	0.015	0.015						
Amoxicillin-clavulanic acid	Doğanay and Aydın[3]	AD	22				0.015-0.015	0.015	0.015	22	0	0			
Piperacillin	Doğanay and Aydın[3]	AD	22				0.125-0.5	0.25	0.5	22	0	0			
Piperacillin/tazobactam	Bakıcı et al[7]	SAS	28						≤2 /4						
Mezlocillin	Doğanay and Aydın[3]	AD	22				0.015-0.06	0.06	0.06	22	0	0			
Cefazolin	Doğanay and Aydın[3]	AD	22				0.015-0.03	0.015	0.015						
Cephalothin	Doğanay and Aydın[3]	DD	22							22	0	0			
	Bakıcı et al[7]	SAS	28						≤ 8						
Cephradine	Doğanay and Aydın[3]	DD	22							22	0	0			
Cefoxitin	Öncül et al[8]	DD	14							14	0	0			
Cefadroxil	Öncül et al[8]	DD	14							14	0	0			
Cefuroxime	Doğanay and Aydın[3]	AD	22				16-64	64	64	1	2	19			
	Öncül et al[8]	DD	14							14	0	0			
Cefotaxime	Doğanay and Aydın[3]	AD	22				8-32	32	32	1	3	18			
	Öncül et al[8]	DD	14							10	0	4			
Ceftizoxime	Doğanay and Aydın[3]	AD	22				16-64	32	32	1	3	18			

Ceftriaxone	Doğanay and Aydın[3]	AD	22	16-32	16	32	2	11	9
	Bakıcı et al[7]	SAS	28			32			
Ceftazidime	Doğanay and Aydın[3]	AD	22	128-256	128	128	1	0	21
Cefoperazone	Doğanay and Aydın[3]	AD	22	0.5-4	2	4	22	0	0
Cefepime	Bakıcı et al[7]	SAS	28			>16			
Aztreonam	Doğanay and Aydın[3]	AD	22	>128	>128	>28	0	0	22
Erythromycin	Doğanay and Aydın[3]	DD	22				22	0	0
	Öncül et al[8]	DD	14				14	0	0
	Bakıcı et al[7]	SAS	28			≤0.5			
	Sümerkan et al[6]	AD	34	0.025-1	0.5	1			
Azithromycin	Sümerkan et al[6]	AD	34	0.5-4	1	4			
Clarithromycin	Sümerkan et al[6]	AD	34	0.03-0.25	0.06	0.12			
	Bakıcı et al[7]	SAS	28			≤2			
Roxithromycin	Sümerkan et al[6]	AD	34	0.06-0.25	0.25	0.25			
Clindamycin	Doğanay and Aydın[3]	AD	22	0.5-1	1	1	21	1	0
	Bakıcı et al[7]	SAS	28			0.5			
Tetracycline	Doğanay and Aydın[3]	DD	22				22	0	0
	Öncül et al[8]	DD	14				12	0	2
	Bakıcı et al[7]	SAS	28			<4			
Trimethoprim-	Doğanay and Aydın[3]	AD	22	1.6/8-3.2/16	3.2/16	3.2/16	22	0	0
sulfamethoxazole	Bakıcı et al[7]	SAS	28			2/38			
Chloramphenicol	Doğanay and Aydın[3]	AD	22	1-2	2	2	22	0	0
	Bakıcı et al[7]	SAS	28			16			
	Öncül et al[8]	DD	14				11	0	3
Gentamicin	Doğanay and Aydın[3]	AD	22	0.03-0.25	0.06	0.125	22	0	0
	Bakıcı et al[7]	SAS	28			≤ 4			
Streptomycin	Doğanay and Aydın[3]	AD	22	1-4	2	4			
Amikacin	Doğanay and Aydın[3]	AD	22	0.03-0.06	0.03	0.06	22	0	0
Netilmicin	Doğanay and Aydın[3]	AD	22	0.015-0.125	0.06	0.125	22	0	0
Tobramycin	Doğanay and Aydın[3]	AD	22	0.25-1	0.25	1	22	0	0
Vancomycin	Doğanay and Aydın[3]	AD	22	0.25-1	1	1	21	1	0
	Bakıcı et al[7]	SAS	28			≤ 2			
Teicoplanin	Bakıcı et al[7]	SAS	28			≤8			
Imipenem	Bakıcı et al[7]	SAS	28			≤ 4			
	Öncül et al[8]	DD	14				14	0	0
Meropenem	Bakıcı et al[7]	SAS	28			≤4			

CLSI: Clinical Laboratories Standards Institute; MIC: Minimum inhibitory concentration; S: Susceptible;
I: Intermediately susceptible; R: Resistant; AD: Agar dilution; DD: Disk diffusion; SAS: Sceptor® automated system (Becton Dickinson Diagnostic Instrument Systems, Towson, MD), NA: Not applicable.
* The breakpoints for *B. anthracis* were provided only for penicillin G, doxycycline and ciprofloxacin.
**Only susceptible breakpoints were established for these drugs.

TABLE 2: The in vitro activity of penicillin G, doxycyline and ciprofloxacin against *B. anthracis* strains reported in different studies.

Antibiotic	The study and reference number	Test method of the strains	Number of strains,	CLSI MIC breakpoints, (mg/L)			MIC (mg/L)			Interpretation of susceptibility according to CLSI breakpoints, n	
				S**	I	R	Range	50%	90%	S	R
Penicilin G	Lightfoot et al[2]	Agar dilution	70	≤0.12	-	≥0.25	0.015-64	0.06	0.125	68	2
	Doğanay and Aydın[3]	Agar dilution	22	≤0.12	-	≥0.25	0.015-0.03	0.015	0.015	22	0
	Çoker et al[11]	E-test	25	≤0.12	-	≥0.25	<0.016-0.5	0.042	0.236	22	3
	Mohammed et al[0]	Broth microdilution	65	≤0.12	-	≥0.25	≤0.016-128	≤0.06	≤0.06	63	2
	Cavallo et al[9]	Agar dilution	96	≤0.12	-	≥0.25	0.125-16	0.125	8	85	11
	Esel et al[5]	Agar dilution	40	≤0.12	-	≥0.25	0.016-0.013	0.016	0.016	40	0
	Bakıcı et al[7]	Sceptor aut sys	28	≤0.12	-	≥0.25	≤0.03	≤0.03	≤0.03	28	0
	Turnbull et al[1]	E-test	74	≤0.12	-	≥0.25	<0.016->32	<0.016	0.023	72	2
	Maho et al[12]	Sensitre aut sys	12	≤0.12	-	≥0.25	<0.12	<0.12	<0.12	12	0
	Luna et al[13]	E-test, Sensitre aut sys	18	≤0.12	-	≥0.25	0.008–0.032	0.016	0.032	18	0
Doxycyline	Çoker et al[11]	E-test	25	≤0.5	-	-	0.094-0.38	0.23	0.34	25	0
	Cavallo et al[9]	Agar dilution	96	≤0.5	-	-	0.125-0.25	0.125	0.25	96	0
	Esel et al[5]	Agar dilution	40	≤0.5	-	-	≤0.016-0.03	≤ 0.016	0.03	40	0
Ciprofloxacin	Lightfoot et al[2]	Agar dilution	70	≤0.5	-	-	0.03-0.06	0.06	0.06	70	0
	Doğanay and Aydın[3]	Agar dilution	22	≤0.5	-	-	0.03-0.06	0.03	0.06	22	0
	Çoker et al[11]	E-test	25	≤0.5	-	-	0.032-0.38	0.094	0.094	25	0
	Mohammed et al[10]	Broth microdilution	65	≤0.5	-	-	0.03-0.12	0.06	0.06	65	0
	Cavallo et al[9]	Agar dilution	96	≤0.5	-	-	0.03-0.5	0.06	0.5	96	0
	Esel et al[5]	Agar dilution	40	≤0.5	-	-	0.008-0.12	0.03	0.06	40	0
	Turnbull et al[1]	E-test	76	≤0.5	-	-	0.032-0.094	0.125	0.125	76	0
	Maho et al[12]	Sensitre aut sys	12	≤0.5	-	-	<0.25	<0.25	<0.25	12	0
	Luna et al[13]	E-test, Sensitre aut sys	18	≤0.5	-	-	0.023-0.064	0.047	0.064	18	0

CLSI: Clinical Laboratories Standards Institute; MIC: Minimum inhibitory concentration; S: Susceptible; I: Intermediately susceptible; R: Resistant; AD: Agar dilution; Sceptor aut sys: Sceptor® automated system (Becton Dickinson Diagnostic Instrument Systems, Towson, MD), Sensitre aut sys: Sensitre automated system (TREK Diagnostic Systems, Cleveland, OH, USA).
*Only susceptible breakpoints were established for these drugs.

from naturally acquired human anthrax cases. There was no penicillin resistance in Turkish studies. Penicillin G is the first choice of treatment without any clinical failure in recent cutaneous anthrax case series in Turkey.[8,14,15] The strains were also sensitive to ampicillin or amoxicillin with a MIC range of 0.015-0.03 mg/L. They could be used as oral treatment options.

Lightfoot et al reported that beta-lactamase production in three out of 70 *B. anthracis* isolates.[2] However, Coker et al detected no beta-lactamase in 3 penicillin resistant *B. anthracis* isolates.[3] A MEDLINE search revealed only 2 reports concerning the beta-lactamase production of *B. anthracis* in Turkey. None of the tested strains showed beta-lactamase. CLSI does not recommend examination for beta-lactamase production in routine laboratory setting. Inducible beta-lactamase production after exposure to subinhibitory concentration of flucloxacillin in *B. anthracis* strains was reported.[2] Inducible beta-lactamases among *B. anthracis* isolates were also reported during anthrax events in the USA.[16] Appropriate dosing of penicillin G could play an important role to solve such problems.

Ciprofloxacin has become an important alternative for the treatment of anthrax after bioterrorism attack in 2001.[16] The development of reduced susceptibility of *B. anthracis* to ofloxacin followed by sequential subculture in sub inhibitory concentrations was demonstrated.[17] A variant strain of *B. anthracis* resistant to ampicillin (MIC 512 mg/L), rifampicin (MIC 128 mg/L), doxycyline (MIC 64 mg/L), chloramphenicol (MIC 64 mg/L), macrolides and lincomycin (MIC 128 mg/L) has already been derived in laboratory conditions by Russian investigators.[18] Quinolones could be reserved for specific conditions to avoid the development of drug resistance. Doxycycline, erythromycin, clindamycin and cefazolin are promising treatment options with low MICs where penicillin use is not available.

Although CLSI did not provide breakpoints for second and 3rd generation cephalosporines, the MICs of cefuroxime, cefotaxime, ceftriaxone and ceftazidime were high in the studies reported from Turkey. Similar results were reported for cefuroxime, cefotaxime[1] and ceftriaxone in other studies.[1,2,9-11] Those agents should not be used for the treatment of anthrax.

Penicillin and streptomycin synergy was reported for systemic anthrax.[1] Gentamicin, streptomycin, amikacin, netilmicin and tobramycin had good in vitro activity against *B. anthracis*. The addition of an aminoglycoside as a 2nd drug in cases with systemic involvement could be a reasonable idea. A combination of penicillin G and streptomycin is recommended particularly for the treatment of gastrointestinal anthrax in the current guideline of the World Health Organization.[19]

In conclusion, penicillin is still a reliable option for the treatment of naturally acquired human anthrax in Turkey. A combination of penicillin G and other antibiotics active against *B. anthracis* may be recommended in gastrointestinal, pulmonary and central nervous system anthrax. Continuous surveillance of resistance to certain antibiotics that are commonly used in the treatment of human anthrax would help to choose the appropriate antibiotic regimen.

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