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COMMENTARY

Is There Emergence of β-Lactam Antibiotic-Resistant *Streptococcus pyogenes* in China?

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Dingle Yu[1,2,*]
Yuejie Zheng[2,*]
Yonghong Yang[1,2]

[1]Laboratory of Microbiology and Immunology, Beijing Children's Hospital Affiliated to Capital Medical University, Beijing, People's Republic of China; [2]Department of Respiratory, Shenzhen Children's Hospital, Shenzhen, People's Republic of China

*These authors contributed equally to this work

Abstract: *Streptococcus pyogenes* is regarded as susceptible to β-lactam antibiotics. The guidelines of the Clinical and Laboratory Standards Institute (CLSI) are widely recognized and have long-recommended penicillin for treatment of *S. pyogenes* infections. There is no CLSI guideline for the treatment of *S. pyogenes* infections that have intermediate susceptibility or resistance to penicillin. However, there have been several reports of *S. pyogenes* isolates that are nonsusceptible or even resistant to β-lactam antibiotics, mostly from Chinese journals. The purpose of this commentary is to show data from the literature which suggests the presence of *S. pyogenes* isolates that are not susceptible to β-lactam antibiotics and whether these strains are really nonsusceptible to β-lactam antibiotics and the presence of mutation in the *pbp2x* gene requires further research and confirmation.

Keywords: *Streptococcus pyogenes*, GAS, β-lactam, antibiotic resistance, China

Introduction

Streptococcus pyogenes, also called group A *Streptococcus* (GAS), is a major human pathogen that can cause a broad spectrum of acute infections. Traditionally, *S. pyogenes* was regarded as susceptible to β-lactam antibiotics, including penicillins and cephalosporins. Thus, penicillin is administered as a first-line antibiotic, and macrolides are an alternative option.[1] However, there have been several reports of the emergence of *S. pyogenes* isolates with resistance to β-lactam antibiotics or reduced susceptibility to penicillin. These findings require confirmation. What is the actual situation? We will address this issue by reviewing the literature.

Search Strategy and Selection Criteria

Data for this review were identified by searches of MEDLINE, Current Contents, PubMed, Wanfang, and references from relevant articles using the search terms "antibiotic", "resistance", "surveillance", "*Streptococcus pyogenes*" and "group A *streptococci*". Abstracts and reports from meetings were included only when they related directly to previously published work. Only articles published in the English language between 1995 and 2019 were included. Moreover, the references of all identified articles were searched for further articles. Finally, the search was restricted to manuscripts that were published in China up to May 2020.

Reports of *S. pyogenes* That is Nonsusceptible to β-Lactam Antibiotics

There have been several reports of the emergence of *S. pyogenes* isolates that are nonsusceptible or even resistant to β-lactam antibiotics, most of which were

Correspondence: Yonghong Yang
Email yyh628628@sina.com

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Table 1 Publications Reporting the Percentages of Resistance (R) and Intermediate Susceptibility (I) to β-Lactam Antibiotics in Isolates of *Streptococcus pyogenes* in China

Year	Strain Number	Antibiotics	R (%)	I (%)	References
2002	33	Ampicillin	10.0		[7]
2006	334	Penicillin	NA	NA	[8]
2006	17	Cefotaxime	11.1	NA	[9]
2006	17	Ceftriaxone	17.6	NA	[9]
2007	308	Ceftriaxone	2.7	NA	[10]
2007	308	Penicillin	0.3	NA	[10]
2008	328	Cefotaxime	3.4	NA	[11]
2008	328	Ceftriaxone	2.6	NA	[11]
2008	328	Penicillin	0.3	NA	[11]
2008	491	Cefotaxime	4.1	NA	[12]
2008	491	Ceftriaxone	2.9	NA	[12]
2008	491	Penicillin	0.2	NA	[12]
2008	487	Ceftriaxone	2.9	NA	[13]
2008	487	Penicillin	0.7	NA	[13]
2008	61	Cefotaxime	19.7	NA	[14]
2008	51	Ceftriaxone	13.7	NA	[14]
2008	33	Cefuroxime	12.1	NA	[14]
2008	202	Ampicillin	6.9	0	[15]
2008	88	Cefazolin	2.3	NA	[15]
2008	210	Cefuroxime	1.4	NA	[15]
2008	29	Cefotaxime	3.4	0	[16]
2008	29	Ceftriaxone	6.9	0	[16]
2008	52	Penicillin	7.7	0	[16]
2008	18	Cefazolin	5.6	0	[17]
2008	30	Cefotaxime	13.3	0	[17]
2008	53	Ceftriaxone	11.3	0	[17]
2008	19	Cefuroxime	5.3	NA	[17]
2009	491	Cefotaxime	4.1	NA	[18]
2009	491	Ceftriaxone	2.9	NA	[18]
2009	491	Penicillin	0.2	NA	[18]
2009	423	Cefotaxime	0.8	NA	[19]
2009	423	Ceftriaxone	1.5	NA	[19]
2009	423	Penicillin	0.2	NA	[19]
2009	426	Ceftriaxone	2.0	NA	[20]
2010	122	Ampicillin	NA	NA	[21]
2010	122	Cefotaxime	NA	NA	[21]
2010	122	Ceftriaxone	NA	NA	[21]
2010	122	Penicillin	NA	NA	[21]
2010	250	Ceftriaxone	4.5	NA	[22]
2010	265	Cefotaxime	2.9	NA	[23]
2010	265	Ceftriaxone	3.7	NA	[23]
2010	265	Penicillin	0.4	NA	[23]
2010	12	Cefazolin	8.3	0	[24]
2010	68	Cefotaxime	14.7	5.9	[24]
2010	74	Ceftriaxone	9.5	5.4	[24]
2010	10	Cefuroxime	0	10.0	[24]
2011	253	Cefotaxime	6.1	NA	[25]
2011	253	Ceftriaxone	8.9	NA	[25]
2011	253	Cefuroxime	0.5	NA	[25]
2011	253	Penicillin	1.2	NA	[25]

(*Continued*)

Table 1 (Continued).

Year	Strain Number	Antibiotics	R (%)	I (%)	References
2011	239	Ceftriaxone	11.2	NA	26
2011	239	Penicillin	0.9	NA	26
2011	220	Ampicillin	65.0	NA	27
2011	383	Cefazolin	30.8	NA	27
2011	708	Cefepime	17.8	NA	27
2011	545	Cefotaxime	21.3	NA	27
2011	660	Ceftriaxone	31.8	NA	27
2011	407	Penicillin	18.7	NA	27
2012	584	Cefuroxime	0.2	NA	28
2012	34	Cefepime	3.3	NA	29
2012	34	Cefotaxime	3.7	NA	29
2012	209	Cefprozil	0.5	NA	30
2012	209	Ceftriaxone	3.5	NA	30
2012	209	Penicillin	1.5	NA	30
2012	29	Cefotaxime	10.3	NA	31
2012	41	Ceftriaxone	22.0	NA	31
2012	12	Cefuroxime	8.3	NA	31
2012	400	Penicillin	9.2	NA	32
2012	138	Cefotaxime	43.5	NA	33
2012	150	Ceftriaxone	42	NA	33
2012	39	Penicillin	35.9	NA	33
2012	32	Ampicillin	3.1	NA	34
2012	37	Cefotaxime	10.8	NA	34
2012	37	Ceftriaxone	5.4	NA	34
2012	50	Cefotaxime	54.0	4.0	35
2012	49	Ceftriaxone	42.9	12.2	35
2012	87	Penicillin	16.1	1.1	35
2013	248	Cefotaxime	1.2	NA	36
2013	248	Ceftriaxone	2.5	NA	36
2013	248	Cefuroxime	0.8	NA	36
2013	248	Penicillin	1.3	NA	36
2013	238	Cefotaxime	25.7	0	37
2013	238	Ceftriaxone	12.5	0	37
2014	558	Cefepime	3.5	NA	38
2014	558	Cefotaxime	0.6	NA	38
2014	558	Ceftriaxone	1.6	NA	38
2014	558	Cefuroxime	0.2	NA	38
2014	558	Penicillin	0.8	NA	38
2014	193	Cefotaxime	5.0	NA	39
2014	193	Ceftriaxone	2.4	NA	39
2014	193	Penicillin	2.9	NA	39
2014	13	Cefotaxime	15.4	0	40
2014	20	Penicillin	10.0	0	40
2015	456	Ceftriaxone	1.3	NA	41
2016	2551	Cefotaxime	0.1	NA	42
2016	2551	Ceftriaxone	0.1	NA	42
2016	2551	Penicillin	0.2	NA	42
2016	68	Penicillin	1.5	NA	43
2018	3589	Cefotaxime	0.2	NA	44
2018	3589	Ceftriaxone	2.5	NA	44
2018	3589	Penicillin	0.2	NA	44

Abbreviation: NA, no data.

published in Chinese journals between 2002 and 2018. Most of these reports were from the large Antimicrobial Surveillance Network (CHINET) in China and were published in Chinese Journals (Table 1). Our examination of the literature indicated only a few isolates of *S. pyogenes* outside of China were not susceptible to β-lactam antibiotics. A study in Mexico[2] reported diminished susceptibility (increased MIC) to penicillin (0.25 to 0.75 μg/mL) in 10 (5%) isolates, a study in India[3] identified 7 of 34 strains (20.6%) that were nonsusceptible to penicillin (MICs of 0.19 to 0.25 μg/mL), and a study in Japan[4] found 2 of 93 strains that were "resistant" to penicillin (MIC > 2.0 U/mL).

The standards of the Clinical and Laboratory Standards Institute (CLSI) are widely recognized, and its standard for treatment of *Streptococcus* infections with penicillin has not changed for many years. These standards consider an inhibition zone diameter of 24 mm or more or a MIC of 0.12 μg/mL or less as indicating susceptibility to penicillin, and by extension to other β-lactam antibiotics (ampicillin, amoxicillin, and cefaclor). The breakpoints for nonsusceptibility are slightly different for penicillin (MIC > 0.12 μg/mL), ampicillin (MIC > 0.25 μg/mL), and cefotaxime/ceftriaxone (MIC > 0.5 μg/mL). However, there is no specific CLSI standard for the use of penicillin for the treatment of patients who have isolates with intermediate susceptibility or resistance.

We read with great interest of a study that investigated 7025 genome sequences of *S. pyogenes* strains and identified 137 strains that had 37 nonsynonymous mutations in 36 codons in the *pbp2x* gene.[5] The authors proposed that decreased β-lactam susceptibility was geographically widespread in strains with common *emm* gene subtypes. Coincidentally, Vannice et al[6] also recently reported two nearly identical GAS isolates, each with the same rare mutation that led to elevated β-lactam MICs and an invasive infection. The two nearly identical clinical *S. pyogenes* isolates had the subtype *emm43.4* and a *pbp2x* missense mutation (T553K).

Conclusion

Traditionally, *S. pyogenes* was regarded as susceptible to β-lactam antibiotics. However, many publications, mostly from China (Table 1), have reported intermediate susceptibility or even resistance to β-lactam antibiotics, but without confirmation. Whether these strains are really nonsusceptible to β-lactam antibiotics, and whether they really have *pbp2x* mutations will require further research and confirmation.

Author Contributions

YY conceived the idea. DY and YZ were responsible for the concept and contributed to the manuscript. All authors reviewed and agreed with the final manuscript.

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

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