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

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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...
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 | 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)
| 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         |
| 2012 | 248          | Cefotaxime    | 1.2   | NA    | 36         |
| 2012 | 248          | Ceftriaxone   | 2.5   | NA    | 36         |
| 2012 | 248          | Cefuroxime    | 0.8   | NA    | 36         |
| 2012 | 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 reported diminished susceptibility (increased MIC) to penicillin (0.25 to 0.75 µg/mL) in 10 (5%) isolates, a study in India 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 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. The authors proposed that decreased β-lactam susceptibility was geographically widespread in strains with common *emm* gene subtypes. Coincidentally, Vannice et al 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 *emm*43.4 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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