Effects of Antibiotics on the Expression of Toxin Genes and their Regulators in *Streptococcus pyogenes*

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**ABSTRACT**

Background: *Streptococcus pyogenes*, also known as group A streptococcus (GAS) or “the flesh-eating bacteria”, is a Gram positive human pathogen that causes many diseases, ranging in severity from mild infections such as pharyngitis to life-threatening necrotizing fasciitis/myositis and streptococcal toxic shock syndrome (1). Although GAS remains susceptible to penicillin, this beta-lactam antibiotic (a cell wall-synthesis inhibitor) is not efficacious in treating severe GAS myonecrosis, whereas treatment with clindamycin (a lincomycin that inhibits protein synthesis) is 80-100% protective. We have previously demonstrated that sub-inhibitory concentrations of the beta-lactam antibiotic, nafcillin, increases and prolongs extracellular protein production in *Staphylococcus aureus*, another Gram positive pathogen (2). The present study seeks to examine the effects of sub-inhibitory antibiotics on GAS toxin gene transcription and to determine the effects of antibiotics on gene expression, bacteria were cultured in the presence of sub-inhibitory concentrations of antibiotics (i.e., 0.5 x MIC) until the late-log phase of growth (4 h). Expression of toxin genes and global gene regulators were examined by northern analysis and reverse transcriptase (RT)-PCR.

**RESULTS**

We utilized a clinical isolate of GAS associated with fatal infection, bacteria were cultured in the presence of sub-inhibitory concentrations of antibiotics (i.e., 0.5 x MIC) until the late-log phase of growth (4 h). Expression of toxin genes and global gene regulators were examined by northern analysis and reverse transcriptase (RT)-PCR. Cldamycin increased the expression of the genes coding for two exotoxins, namely streptolysin O (SLO) and streptoplasmin, in GAS strain 88-003. It also increased expression of two global toxin gene regulators, *cra* and *mga*. By contrast, 0.5 x MIC of nafcillin decreased the expression of these genes. The effects of penicillin at 0.5 x MIC were similar to that of nafcillin, except that penicillin caused a slight increase in *cra* expression. Conclusions: Despite its well known ability to prevent translation of bacterial mRNA into exotoxins, cldamycin at sub-inhibitory doses augments toxin gene transcription in GAS. The effects of beta lactam antibiotics on toxin gene regulation appears to be species-, and perhaps, strain-specific.

**CONCLUSIONS**

1. In contrast to *S. aureus* (reviewed in reference 2), sub-inhibitory concentrations of nafcillin decreased toxin gene expression in GAS 88-003. Thus, the effects of beta lactam antibiotics on toxin gene regulation appears to be species-, and perhaps, strain-specific.

2. Sub-inhibitory concentrations of clindamycin significantly upregulated toxin gene transcription, though additional studies such as western blot analysis need to be performed to verify the absence of toxin production by clindamycin-treated GAS strain 88-003.

3. The question remains as to whether the observed increase in toxin gene expression is due to direct effects on the toxin genes themselves, or whether it follows upregulation of toxin gene regulators. Future studies to address this could utilize isogenic CsrR- and/or Mga-deficient GAS strains.

**REFERENCES**


