Alterations of penicillin-binding proteins 1A, 2B and 2X of streptococcus pneumoniae linked to penic

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ABSTRACT

Background: Streptococcus pneumoniae is an important pathogen that can cause disease. There are mainly two concerns worldwide: (1) Escalating antimicrobial resistance, especially resistance to penicillin and extended-spectrum cephalosporins. (2) Serotype 19A has been shown increasingly emerged apparently due to the widely use of 7-valent pneumococcal conjugate vaccine (PCV7). Methods: A total of 82 clinical isolates (part I 80 isolates and part II 2 isolates) collected from Chang Gung Children ’ s Hospital were subjected to (1) antimicrobial susceptibility testing and penicillin-binding protein gene sequencing. (2) To antimicrobial susceptibility testing, multilocus sequence typing (MLST) and sequence analysis of the flanking regions upstream and downstream respectively pbp1a and pbp2x . Results: (1) Six amino acid mutations closed to the C-terminus of PBP1A were found associated with penicillin nonsusceptibility in S. pneumonia and 10 amino acid mutations closed to the N-terminal were shown associated with ceftriaxone nonsusceptibility. Based on the PBP2B sequence analysis, 12 amino acid alterations due to mutation were found associated with ceftriaxone nonsusceptibility in S. pneumoniae. These mutations were around the active binding site N427. On PBP2X not only ceftriaxone but also penicillin nonsusceptibility exhibited common amino acid mutations when MIC of ceftriaxone and penicillin < 0.19 μl/mg, it seems the mutations started earlier when compared to the PBP1A and 2B mutations. (2) Although serotype 19A and 14 have common mutations they belong to different sequence type (ST), serotype 19A is ST320 while serotype 14 is ST876. Sequencing analysis of pbp2x and pbp1a showed sequences upstream of pbp2x and downstream of pbp1a were homologues. Conclusions: This study provides evidence that (1) mutations in the PBP1A C-terminal region are specifically associated with penicillin nonsusceptibility and in N-terminal region associated with ceftriaxone nonsusceptibility. Mutation in PBP2B is responsible for ceftriaxone nonsusceptibility in S. pneumoniae. In PBP2X, mutations are common for both penicillin nonsusceptible and ceftriaxone nonsusceptible isolates, suggesting that these mutations developed early in the evolution of S. pneumoniae to become β-lactam antibiotic resistant. (2) Serotype 19A ST320 and serotype 14 ST876 have common mutations in pbp1a and pbp2x due to antibiotic selective pressure.

Keywords : Streptococcus pneumonia、penicillin-binding proteins、C-terminal、N-terminal

Table of Contents

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