Transparency declarations

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References


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Decreasing prevalence of levofloxacin-resistant Streptococcus pneumoniae in Hong Kong, 2001 to 2007


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Sir,

Streptococcus pneumoniae is the most common identifiable cause of community-acquired pneumonia. With the rise in resistance to penicillin and macrolides, other classes of antibiotics, notably the newer fluoroquinolones, are increasingly being used for the empirical treatment of pneumonia. As observed for other antibiotics, fluoroquinolone resistance has emerged in S. pneumoniae among sporadic isolates as well as in the major epidemic clones.1 Our previous work documented the rapid emergence of pneumococcal resistance to the fluoroquinolones in Hong Kong since the late 1990s.2,3

This study assessed the recent epidemiology of levofloxacin-resistant S. pneumoniae (LRSP) using the database of a clinical microbiology laboratory in Hong Kong. This laboratory provides service to a network of five hospitals, including one acute care university teaching hospital (HKW1) with 1400 beds and all the clinical disciplines and four chronic care hospitals (HKW2, HKW3, HKW4 and HKW5) with 110–524 beds. HKW4 only admits children. The hospital network is estimated to provide clinical service to a population of approximately 1 million. The data on S. pneumoniae from 2001 to 2007 were extracted, and duplicate isolates were removed by the initial isolate per patient method, irrespective of susceptibility and specimen source. Only the first isolate from each patient was included during the whole surveillance period. During this period, all isolates were routinely tested for their susceptibility to penicillin (oxacillin), erythromycin, co-trimoxazole, chloramphenicol and levofloxacin by the disc diffusion method. Penicillin MICs were determined by Etest (AB Biodisk, Solna, Sweden). All results were interpreted according to the CLSI.4 Strains were identified as S. pneumoniae by Gram stain, colony morphology, optochin susceptibility and bile solubility.3,5

There were a total of 2290 S. pneumoniae isolates during the 7 year period, and the selection criteria identified 1680 isolates for analysis. These included 203 isolates from outpatients and 1477 from inpatients. All isolates were obtained from clinical samples submitted for investigation. The specimen sources were respiratory (n=1466), blood (n=139), wound (n=61) and other body fluid (n=14). Overall, 11% of these isolates had reduced susceptibility to levofloxacin; 15 (0.9%) were intermediate (equivalent MIC breakpoint, 4 mg/L) and 169 (10.1%) were resistant (equivalent MIC breakpoint, >8 mg/L). Most LRSP exhibited co-resistance to penicillin (MIC>0.06 mg/L, 97.6%), co-trimoxazole (93.5%), chloramphenicol (92.3%) and erythromycin (97%). The 169 LRSP isolates were obtained from sputum (n=148), blood (n=13), tracheal aspirate (n=4), bronchoalveolar lavage (n=3) and pleural fluid (n=1). All patients with LRSP were adults (aged >17 years). The great majority of patients with LRSP were elderly; 87.6% were 64 years and 72.1% were >74 years.

During the study period, there were fluctuations in the annual proportion of LRSP. The proportions of LRSP by year were 11.7% (39/334) for 2001, 12.9% (40/311) for 2002, 8.7% (19/218) for 2003, 12.2% (24/196) for 2004, 10.3% (18/174) for 2005, 7.8% (18/232) for 2006 and 5.1% (11/215) for 2007.
(P=0.02, for 2001–07). Rates of resistance to levofloxacin were 6.3% (80/1268) for HKW1, 64.4% (29/45) for HKW2, 30.8% (40/130) for HKW3 and 8.8% (20/226) for HKW5. No LRSP was found in HKW4. Isolates from inpatients were significantly more likely to be LRSP than those from outpatients (11.4% versus 0.5%, P<0.001). The frequency of LRSP among isolates from the chronic care hospitals was also higher than that from the acute hospital (21.6% versus 6.3%, P<0.001). When the levofloxacin susceptibility rates were examined by age groups, susceptibility to levofloxacin declined with increasing age in hospital inpatients (linear regression, R^2=0.838, P=0.01), but not in outpatients (Figure 1).

In Hong Kong, studies from 1998 to 2000 revealed that the emergence of fluoroquinolone resistance was attributed to the spread of variants related to the Spain23F-1 clone, nosocomial transmission and suboptimal use of fluoroquinolones involving ofloxacin and ciprofloxacin among elderly patients with chronic lung diseases.3,5 In 2003, a local survey of over 200 consecutive patients hospitalized for acute exacerbation of chronic chest diseases showed that the suboptimal use of fluoroquinolones in which small doses (100–200 mg) of ofloxacin and levofloxacin were administered twice or thrice daily was still prevalent (P. L. Ho, unpublished results). Thereafter, action was taken to remove ofloxacin from the drug formulary of the major hospitals, and the small-dose levofloxacin preparations (100 mg tablet) were replaced by the standard 250 mg tablet. Although ofloxacin remains registered in Hong Kong, its usage has declined significantly since 2003. This and the greater emphasis on hospital hygiene following the severe acute respiratory disease outbreak have probably contributed to the decline of LRSP from 12.2% in 2004 to 5.1% in 2007. In the present study, the isolates were obtained from a single hospital laboratory whilst those reported in our previous work were obtained from multiple laboratories located in widely separate areas of Hong Kong.3 Hence, whether the observed decline is territory-wide remains uncertain. Nonetheless, our data demonstrate that fluoroquinolone resistance in S. pneumoniae is declining among community isolates, despite its persistence in institutional settings. It also highlights the importance of using the fluoroquinolones properly with the correct drug choice, as well as the right dose and duration. In particular, ciprofloxacin should not be used in the respiratory tract. Although we were unable to collect the LRSP isolates for typing, their homogeneous resistance profiles strongly suggest that the isolates were clonally related. In our locality, universal immunization of children with the heptavalent pneumococcal conjugate vaccine will be implemented in 2009. Given that in 1995–2001 our LRSP isolates were of the vaccine serotypes,3,6 it will be interesting to follow-up the effect of this on the LRSP epidemiology.

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**References**


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Mecillinam: a low-risk antimicrobial agent for induction of Clostridium difficile infection in an in vitro human gut model

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Sir,

Clostridium difficile infection (CDI) is a major cause of diarrhoea among the hospitalized elderly and a significant financial burden upon healthcare systems worldwide.1 Incidence continues to increase, particularly following the emergence of hypervirulent C. difficile PCR ribotype 027 (NAP1/BI).2 CDI is thought to arise as a result of depletion of the colonic microflora and colonization resistance by broad-spectrum antibiotics,3 allowing C. difficile germination, proliferation and toxin production. Antimicrobials differ markedly in their propensity to induce CDI both in vitro and in vivo. Piperacillin/tazobactam has a broad spectrum of activity but is considered low risk for CDI induction. In contrast, third-generation cephalosporins are relatively high risk for CDI but have narrower spectra of activity.4

Mecillinam is an amidino-penicillin β-lactam agent, used mainly for the treatment of urinary tract infections. It is principally active against Enterobacteriaceae, but is poorly active against Gram-positive bacteria. Few data exist on the propensity of mecillinam to induce CDI in vivo.5 We examined the effect of mecillinam on two epidemic C. difficile strains (PCR ribotypes 001 and 027) and the indigenous gut microflora using a triple-stage chemostat human gut model. We have previously used the gut model to investigate both antimicrobial induction of and therapeutic interventions for CDI,5 and results correlate well with clinical observations. However, although this is a reproducible model of CDI, it cannot simulate secretory or immunological events, which may be important in C. difficile pathogenesis.

The model was prepared and inoculated, and C. difficile total counts, spores and toxin titres and gut bacterial populations were monitored as described previously. Gut bacterial populations were allowed to equilibrate (14 days), whereupon ~107 cfu of C. difficile spores was added. No further interventions were made for 7 days. A further ~103 cfu of C. difficile spores was added and mecillinam instillation commenced (1 mg/L mecillinam twice-daily for 7 days) to reflect published faecal concentrations.5 No further interventions were made. Mecillinam concentrations were determined by large-plate bioassay using Escherichia coli ATCC 25922 as described previously.4 MICs of mecillinam for 60 C. difficile isolates were measured using a reference agar dilution method (CLSI) for anaerobe susceptibility testing.

In the absence of mecillinam, gut bacterial populations remained stable, with no evidence of C. difficile spore germination, proliferation or cytotoxin production in either experiment, as reported previously (Figure 1a and b).5 Similarly, C. difficile spores remained quiescent during and after mecillinam instillation (Figure 1a). Behaviours of both C. difficile ribotypes were similar, demonstrating no detectable cytotoxin (PCR ribotype 027 or ≤2 relative units (RU) (PCR ribotype 001) following the dosing period (Figure 1a, period C). We consider the latter low cytotoxin titres to be of doubtful significance given the absence of sustained C. difficile proliferation in an epidemic strain with a recognized propensity to induce CDI in vivo.5 Prior gut model experiments have indicated that subinhibitory

![Figure 1](https://example.com/figure1.png)

Figure 1. Mean (±SE) (a) C. difficile total counts and spore counts (log10 cfu/mL) and cytotoxin titres (log10 RU) and (b) indigenous gut microflora (log10 cfu/mL) in vessel 3 of the C. difficile ribotype 027 gut model. Vertical lines indicate the final day of each experimental time period.