Comment on Guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK

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Keywords: Staphylococcus spp., antibiotic policy, empirical treatment

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Sir,

In the Guidelines for prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK,1 the Joint Working Party states for empirical treatment that 'The prevalence level at which flucloxacillin or other penicillinase-stable penicillins, in a patient group, becomes no longer the drug of choice is debatable, but 10% resistance has been used as a guide for avoiding the use of empirical gentamicin in Gram-negative infection and we would recommend the same threshold is used when contemplating treatment of staphylococcal infections with isoxazolylpenicillins or cephalosporins. This threshold may be adjusted depending on the apparent severity of infection.'

This threshold (of 10%) ignores the evidence that β-lactam drugs are more effective than glycopeptides for infections caused by methicillin-susceptible S. aureus (MSSA) in the eradication of infection, prevention of recurrence and prevention of death.2–7 Moreover, it was impossible to show an advantage of glycopeptide appropriate empirical treatment over inappropriate treatment.8 The 10% threshold means that in order to offer appropriate treatment (vancomycin) to 10 patients with severe infections caused by MRSA, 90 people with severe infections caused by MSSA will be given less effective treatment (vancomycin and not cloxacillin).

To try and take this factor into account, we have looked at 429 patients with S. aureus bacteraemia included in the Beilinson Bacteremia Database.9,10 The fatality rate in patients given inappropriate empirical antibiotic treatment was 38% (69 of 183), versus 24% (57 of 246) in patients given appropriate treatment, P = 0.007. The multivariable-adjusted odds ratio was 1.8 [95% confidence interval (CI) 1.2–2.7].9 In patients with MSSA bacteraemia, the fatality rate was 28% (47 of 166) in patients treated with vancomycin versus 8% (4 of 48) in patients given cloxacin, P = 0.004, univariate odds ratio of 4.3 (95% CI 1.5–12.8). The multivariable-adjusted odds ratio was larger than the univariate ones.

If indeed the advantage of cloxacillin over vancomycin as empirical treatment is at least as large as that of appropriate versus inappropriate treatment, the threshold of the baseline susceptibility to methicillin for preferring vancomycin over cloxacillin in a patient suspected of harbouring a severe infection with S. aureus should be ~50% rather than ~10%.

Transparency declarations

We have no conflicts of interest to declare.

References


Comment on: Suboptimal CD4 gains in HIV-infected patients receiving didanosine plus tenofovir

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Keywords: pharmacokinetics, pharmacodynamics, drug interactions

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Sir,

Barreiro and Soriano present an interesting hypothesis for what seems to be a paradoxical depletion of CD4+ cells in the face of virological suppression when the combination of didanosine and tenofovir is used. The central tenet of their hypothesis is the inhibition of purine nucleoside phosphorylase (PNP) by tenofovir or its metabolites such that an accumulation of deoxyribonucleotides, particularly dGTP, leads to a specific T-lymphocytopenia. This situation is akin to congenital immunodeficiency disorders caused by deficiency in PNP activity. We reported a similar hypothesis earlier and are encouraged to see that the issue has not been forgotten. In our report, we also linked the pharmacology of PNP inhibition to the poor antiviral response to triple nucleoside reverse transcriptase inhibitor (NRTI) therapies that included tenofovir and other purine analogue NRTIs. We reasoned that poor antiviral potency would be a natural consequence of raised dGTP and dATP levels with which purine analogue NRTIs compete for potency. We further postulated that poor antiviral inhibition to the poor antiviral response to triple nucleoside reverse transcriptase inhibitor (NRTI) therapies that included tenofovir and other purine analogue NRTIs might be related. One mechanism for the poor antiviral response to the NRTI combination was a low genetic barrier reaching with one adenosine analogue leaving little additional effect from the second adenosine analogue. Finally, another hypothesis for the triple NRTI failures is a low genetic barrier resistance whereby the individual components select for similar mutations creating a synergic selection of specific mutations such as M184V or K65R.

In summary, it is important to understand the pharmacological mechanism(s) for these undesirable patient responses so that rational strategies can be devised to manage these problems clinically and to avoid similar problems in the future. These needs also underscore the importance of translational research to bridge bench-top findings to the clinical setting.

Transparency declarations

P. L. A. has received research grant support from Bristol-Myers Squibb and GlaxoSmithKline. T. N. K. is an employee of Tibotec, Inc.

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