Codon 91 Gyrase A Testing Is Necessary and Sufficient to Predict Ciprofloxacin Susceptibility in Neisseria gonorrhoeae

To the Editor—We read with great interest the article by Grad et al [1]. We agree with their conclusion that gyrA (gyrA) genotype testing of Neisseria gonorrhoeae is a valuable means of resistance testing; however, we believe that gyrA testing, specifically of codon 91, is both necessary and sufficient for predicting susceptibility to ciprofloxacin. There have been 11 studies (N=4777 specimens) comparing real-time polymerase chain reaction (RT-PCR) genotype results with conventional antimicrobial susceptibility testing methods, all of which have demonstrated high sensitivity and specificity (93.8%–100% and 93.2%–100%, respectively). Positive and negative predictive values were similarly impressive (94.4%–100% and 87.5%–100%, respectively). Furthermore, 4 studies found that mutation at codon 91 of the gyrA gene as determined by RT-PCR was 100% specific for N. gonorrhoeae compared with other Neisseria species [2–5].

Other mutations have been shown to contribute to ciprofloxacin resistance, but previous studies have shown that other mutations in general occur in conjunction with a mutation in the gyrA gene [6, 7].

In addition, it is estimated that approximately 80% of N. gonorrhoeae infections in the United States are susceptible to ciprofloxacin [8]. Those 2 facts support the implementation of gyrA genotype testing to promote the use of targeted ciprofloxacin therapy. That may in turn reduce overuse of ceftriaxone. A recent article showed that treatment may be a major driver of ceftriaxone resistance in Neisseria gonorrhoeae [9], which has been called one of the top 3 urgent threats to public health by the Centers for Disease Control and Prevention [10].

We developed a rapid codon 91 gyrA genotypic assay using RT-PCR techniques [6], and we verified the assay in accordance with Clinical Laboratory Improvement Amendments [2]. UCLA Health introduced that assay into routine clinical practice for all N. gonorrhoeae–positive specimens in November 2015. Further studies are underway to characterize the impact of that implementation.

Notes

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References


Reply to Allan-Blitz and Klausner

To the Editor—We thank Allan-Blitz and Klausner [1] for the citations to their group’s work in this area and to the efforts underway to test diagnostics for quinolone resistance in Neisseria gonorrhoeae. Although our study investigated the genetic basis of resistance and assessed the positive and negative predictive values of specific mutations for resistance in the set of samples we analyzed [2], we take no position on the suitability of particular diagnostics. We note, however, that the US Food and Drug Administration has published guidance for antimicrobial susceptibility test systems [3]. The lower end of the range in negative predictive value cited by Allan-Blitz and Klausner (87.5%) is considerably lower than the 99% we observed.

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possibly owing to sampling from a different gonococcal population, in which alternative mechanisms of resistance may exist. This emphasizes the importance of establishing rates of major and very major discrepancy [3], as well as regularly monitoring the circulating gonococcal lineages to ensure the diagnostic test characteristics accurately reflect the distribution of resistance mechanisms in gonococci, which may vary over time and by geographic and demographic groups.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of General Medical Sciences or the National Institutes of Health.

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References


Antiviral Activity of the Combination of Interferon and Ribavirin Against Chikungunya Virus: Are the Results Conclusive?

To the Editor—We agree with Gallegos and colleagues [1] that chikungunya virus (CHIKV) is a significant public health problem today, and that effective antiviral agents are urgently needed to treat severe cases of CHIKV fever. On the basis of their results, the authors suggest that ribavirin (RBV) and interferon (IFN) α2a are effective, when used in combination, against CHIKV replication in Vero cells, and that such combination represents a promising therapeutic strategy against the infection [1]. Although these findings are interesting and meaningful, we are concerned about some shortcomings in the experimental design, which might lead to misleading conclusions.

First, the evaluation of the antiviral activity performed to support the development of an “investigational” product requires to test at least the effect of an increasing multiplicity of infection (MOI) and, whenever possible, the antiviral activity in different cellular lines, giving priority to human cells (which are more likely to reflect in vivo condition). Gallegos et al. [1] have analyzed the potency of the IFNα against CHIKV by using a very low MOI (e.g., 0.0001 plaque-forming units/cell), we found that the antiviral activity of IFNs against CHIKV strains significantly decreased by increasing the MOI (Table 1). Furthermore, the authors estimated the antiviral activity of IFNα2a against CHIKV in Vero cells only. This is a nonhuman primate cell line that lacks an intact type I IFN signaling [9]. In relation to that, we found that the antiviral activity of IFNα, IFNβ, and IFNω against both strains of CHIKV is different in Hep-2, a human cell line, compared to that recorded in Vero cells (Table 1). Perhaps more importantly, the antiviral activity of RBV seems to be naturally limited in many cell types, including the Vero cell line (personal observations, [10]), thus indicating the importance of using multiple cell lines of different origin when antiviral activity and potency are studied for new and/or established drugs in vitro.

Lastly, Gallegos et al. evaluated the anti-CHIKV activity of only one type I IFN preparation (e.g., IFNα2a), not addressing/discussing at all the issue of the different commercially available