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Causative pathogens and antibiotic resistance in diabetic foot infections: A prospective multi-center study

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ABSTRACT

Aim: Clinical practice guidelines for the management of diabetic foot infections developed by the Infectious Diseases Society of America (IDSA) are commonly used worldwide. The issue of whether or not these guidelines need to be adjusted for local circumstances, however, has seldom been assessed in large prospective trials.
Methods: The Turk-DAY trial was a prospective, multi-center study in which infectious disease specialists from centers across Turkey were invited to participate (NCT02026830).
Results: A total of 35 centers throughout Turkey enrolled patients in the trial. Overall, investigators collected a total of 522 specimens from infected diabetic foot wounds for culture from 447 individual patients. Among all isolates, 36.4% were gram-positive organisms, with *Staphylococcus aureus* the most common among these (11.4%). Gram-negative organisms constituted 60.2% of all the isolates, and the most commonly isolated gram-negative was *Escherichia coli* (15%). The sensitivity rates of the isolated species were remarkably low for several antimicrobials used in the mild infection group.
Conclusions: Based on our findings, several of the antimicrobials frequently used for empirical treatment, including some also recommended in the IDSA guidelines, would not be optimal for treating diabetic foot infections in Turkey. Although the IDSA guideline recommendations may be helpful to guide empiric antimicrobial therapy of DFIs, they should be adjusted to local conditions.

1. Introduction

Infection of the foot in persons with diabetes is a growing problem worldwide and causes substantial morbidity and increased mortality (Gariani et al., 2014; Raspovic & Wukich, 2014; Sinwar, 2015). Clinical practice guidelines for the management of diabetic foot infections (DFI) developed by the Infectious Diseases Society of America (IDSA) have been cited in over 1400 publications and are commonly used worldwide. The IDSA recommendations on selection of a regimen for empiric antimicrobial therapy of DFIs are based on the severity of the infection, but to our knowledge the validity of these recommendations have not previously been addressed. Specifically, the issue of whether or not these guidelines need to be adjusted for local circumstances has not been assessed in a prospective trial.

We designed the Turk-DAY (Turkish Diabetic Foot Management Study Group) study after noting that several previously published studies from Asia and Africa revealed findings that contrasted with those from studies that were largely conducted in western countries (Hatipoglu et al., 2014; Turhan et al., 2013; Ramakant et al., 2011; Tiwari et al., 2012; Djahmi et al., 2013; Zenelaj et al., 2014; Citron et al., 2007; Raja, 2007; Ozer et al., 2010; Al Benwan et al., 2012; Mendes et al., 2012). Because the majority of these non-western studies were retrospective (Raja, 2007; Saltoglu et al., 2015) and/or from a single center (Hatipoglu et al., 2014; Djahmi et al., 2013; Ozer et al., 2010; Al Benwan et al., 2012), we believe that they require confirmation by multicenter prospective trials.

The aims of the Turk-DAY Study were three-fold: (1) to confirm or refute previous findings on the microbiological profile of DFIs in Turkey; (2) to compare the bacteriological profile and resistance patterns of pathogens isolated in patients with mild, compared to moderate-to-severe DFIs; (3) to review the implications of the results of our microbiological findings with regard to the antibiotic recommendations in the IDSA guidelines. We believe that these data may be useful both for clinicians in Turkey and for researchers involved in developing local guidelines in other countries for the empirical antimicrobial treatment of DFIs.

2. Materials and Methods

The Turk-DAY trial was a prospective, multi-center study in which infectious disease specialists from centers across Turkey who were involved in the treatment of DFIs were invited to participate. We provided each participating center a comprehensive DFI flow chart on which were requested the investigators to provide initial and follow-up data for all enrolled patients. We decided on a three-month period for patient enrollment. The local ethical committee approved the study protocol and investigators obtained written informed consent from all patients prior to enrollment. The clinicaltrials.gov registration number for this study is NCT02026830.

Among patients with diabetes who presented with a foot problem, we instructed investigators to enroll only those with a clinically infected wound. DFI was defined by criteria consistent with the IDSA 2012 guideline (Lipsky et al., 2012), i.e., by the presence of at least two signs or symptoms of inflammation. To grade infection severity we used the infection part of the PEDIS classification developed by the International Working Group on the Diabetic Foot (IWGDF) (Schaper, 2004). The IDSA guideline uses a similar classification scheme of infection severity, describing PEDIS infection grade I as uninfected, PEDIS infection grade II as mildly infected, PEDIS infection grade III as moderately infected, and PEDIS infection grade IV as severely infected. For practical reasons, and based on antibiotic recommendations in the IDSA guideline, we then classified infection severity into just two categories, i.e., mild and moderate-to-severe. Investigators obtained specimens from all infected wounds for microbiological analysis. The type of specimens and methods by which they were obtained for culture (swab, deep tissue, purulent aspirate, bone, blood) varied among the centers. Centers used standard clinical laboratory methods to isolate and identify microorganisms.

We used SPSS version 15.0 (SPSS Inc., Chicago, IL) statistical software to analyze the results. We calculated the percentage of each isolate by dividing the number of that particular isolate by the total number of all bacteria. We assessed antibiotic sensitivities for all aerobic gram-positive and gram–negative bacteria. We also specifically calculated the percentage of each isolate and their antibiotic sensitivities for infections in the mild and the moderate-to-severe subgroups. We analyzed the distribution of isolates between patients with versus those without peripheral arterial disease, and between patients who had and did not have a history of recent prior antibiotic using the chi-square test, designating a p value < 0.05 as statistically significant.