until analysis. Cytokine qualification was performed with an enzyme-linked immunosorbent assay (ELISA) kit for TNFα and IL-6 (Quantikine®; R&D Systems, Minneapolis, MN). Analyses were performed in a blind fashion. Measurements were performed at time 0 just before starting therapy as well as at 4, 8, 12, 16, 24, 48 and 72 h and 5, 7 and 14 days after starting the antibiotic.

Five patients were randomised to receive daptomycin at a dose of 4 mg/kg daily and in another five patients (controls) received vancomycin 30 mg/kg daily or oxacillin 2 g every 4 h, at the prescribing physician's discretion. Treatment duration was 7–14 days with intravenous drug, not changing to oral therapy. Clinical response was defined as previously published [3]. To assess cytokine trends over time, each cytokine was assessed by a linear logistic regression, considering a *P*-value of <0.05 as statistically significant, showing value linearity over time as a percentage of the initial value.

All infections occurred in the lower limbs, comprising six cases in the right lower limb and four cases in the left lower limb. Infection occurred in six men with a mean age of 46.8 years [standard deviation (S.D.) 12.3 years] and in four women with a mean age of 49.7 years (S.D. 8.42 years). There was no skin culture as patients did not have lesions for adequate material collection. All patients progressed favourably according to the investigators' criteria. There were no serious adverse events with the prescribed drugs.

IL-6 graphics for daptomycin indicate a single trend of a decrease among initial samples with patient progress (Fig. 1A), whilst the control patients' graphics show only an initial decrease followed by an increase after 24 h and a later decrease (Fig. 1B). However, the regression analysis for both groups indicates different results. The drop over time for IL-6 in the daptomycin group was shown to be significant ($P = 0.02$), whilst in control group there was no significant drop ($P = 0.17$).

TNFα graphics did not show any decreasing trends for either group. In the TNFα regression analysis there were no significant changes for either group, either in analyses regarding only initial time points or for the total analysis time.

Serum levels are an opportunity to assess the effects that antibiotics may have on cytokine expression, but they are not always related to tissue expression. *Staphylococcus* has different IL-6 production patterns compared with *Streptococcus* [4]. It is possible that the lack of difference between groups treated with either daptomycin or with control drug may have been due to different aetiologies and less IL-6 expression, not allowing a more precise assessment. The *S. aureus* wall thickness may influence IL-6 production, i.e. the higher the amount of antigens, the higher the IL-6-producing gene expression [5].

The TNFα serum levels were not useful to assess the cellulitis course in patients from this sample. In patients using daptomycin, there was a significant drop in IL-6, which was not seen in the control group, confirming previous animal model studies.

This study is registered at ClinicalTrials.gov [Identifier: NCT01626560].

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Competing interests

FFT and JLR received grants from MSD, Pfizer, Novartis, Sanofi-Aventis and AstraZeneca. All other authors declare no competing interests.

Ethical approval

This study was approved by the Ethical Committee of is FEPAR (Faculdade Evangélica de Medicina do Parana, Curitiba, Parana, Brazil) [register CAAE – 0191.0.081.000-11]. All patients signed an informed consent before inclusion.

References

[1] Grandgirard D, Oberson K, Bühlmann A, Gäumann R, Leib SL. Attenuation of cerebrospinal fluid inflammation by the nonbacteriolytic antibiotic daptomycin versus that by ceftriaxone in experimental pneumococcal meningitis. Antimicrob Agents Chemother 2010;54:1323–6.
[2] Ambrosch A, Halevy D, Fwity B, Brin T, Lobmann R. Effect of daptomycin on local interleukin-6, matrix metalloproteinase-9, and metallopeptidase inhibitor 1 in patients with MRSA-infected diabetic foot. Int J Low Extrem Wounds 2013;12:100–5.
[3] Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI; Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004;38:1673–81.
[4] Kragsbjerg P, Söderquist B, Holmberg H, Vikerfors T, Danielsson D. Production of tumor necrosis factor-α and interleukin-6 in whole blood stimulated by live Gram-negative and Gram-positive bacteria. Clin Microbiol Infect 1998;4:129–34.
[5] Schmitz FJ, Verhoef J, Hadding U, Heinz HP, Jones ME. Reduction in cytokine release from human monocytes by modifications in cell wall structure of *Staphylococcus aureus* induced by subinhibitory concentrations of oxacillin. J Med Microbiol 1998;47:533–41.

Felipe F. Tuon [a,b,*]
[a] *Division of Infectious Diseases, Hospital Universitário Evangélico de Curitiba, Paraná, Curitiba, PR, Brazil*
[b] *Division of Infectious Diseases, Hospital de Clinicas da UFPR, Curitiba, PR, Brazil*

Jaime L. Rocha
[a] *Division of Microbiology, Frischmann Aisengart/DASA Medicina Diagnóstica, Curitiba, PR, Brazil*

Hugo Manuel Morales
School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, PR, Brazil

Marcus Henrique Sakumoto
Karisa Farias Miksza
Division of Infectious Diseases, Hospital Universitário Evangélico de Curitiba, Paraná, Curitiba, PR, Brazil

Roberto Pecoit-Filho
School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, PR, Brazil

* Corresponding author. Present address: Hospital Universitário Evangélico de Curitiba, Alameda Augusto Stellfeld, 1908 – Bigorrilho, Curitiba, Paraná 80730-150, Brazil. Tel.: +55 41 3240 5055.
E-mail address: flptuon@gmail.com (F.F. Tuon)

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Emerging role of doxycycline in vector-borne diseases

Sir,

Vector-borne diseases, particularly emerging diseases such as chikungunya and zika, are currently of high concern in Latin America given the current epidemics [1]. These are in addition to the long-standing situation of dengue in this region. Other tropical

diseases such as malaria and enteric fever as well as zoonoses such as leptospirosis and rickettsial infection are also common threats.

Curiously and fortunately, doxycycline is an effective therapeutic and/or prophylactic drug for these infections. Doxycycline has been highlighted in therapy against these pathogens, not only for its mechanism of action as an antibiotic but it has also been recognised as having an immunomodulatory role [2]. Recently, these effects of doxycycline were thoroughly studied in vitro against dengue virus (DENV) replication, where the virus titre decreased significantly ($P < 0.001$) after treatment with 60 μM and 80 μM doses, levels lower than its 50% cytotoxic concentration (CC_{50} = 100 μM). It showed serotype-specific inhibition, with a higher rate of success against DENV2 and DENV4 compared with other serotypes. These results are explained by dengue serine protease inhibition by doxycycline and its affect in blocking the conformational change of E, an envelope protein responsible for activating membrane fusion necessary for virus entry into host cells and its spread [2].

The immunomodulatory role of doxycycline against DENV has been the subject of other important research conducted by Autonomous University of Yucatan (Mérida, Mexico) [3]. The authors added doxycycline to DENV standard supportive management in one-half of a sample of patients diagnosed with dengue haemorrhagic fever, resulting in a 46% reduction in mortality [13/116 (11.2%) vs. 24/115 (20.9%)] [3]. Patients received 100 mg every 12 h for 7 days and samples were obtained at 0, 3, 5 and 7 days and were tested for levels of tumour necrosis factor (TNF) and interleukin (IL)-6. Addition of doxycycline also resulted in a significant and progressive decrease in both cytokines, and their levels in patients who died were significantly higher compared with those who survived in both treatment groups [3].

These cytokines that are increased in DENV infection are involved in the onset and regulation of coagulation and fibrinolysis, and very high levels, according to the coagulation degree, may result in considerable fibrin formation leading to multiorgan failure and ultimately to death [4].

Studies have shown the role of cytokines in dengue infection. Suharti et al. reported that TNF was associated with D-dimer levels, an activation marker of fibrinolysis, whilst IL-6 was significantly associated with coagulation and fibrinolysis markers [4]; both of these are affected directly by the anti-inflammatory action of doxycycline [5].

More recently, a study found that doxycycline showed higher inhibition of viral infectivity and entry of chikungunya virus (CHIKV) into Vero cells compared with ribavirin [5]. In contrast, however, ribavirin showed higher inhibition against viral replication in target cells compared with doxycycline. Assays using mice as an animal model revealed that doxycycline plus ribavirin effectively inhibited CHIKV replication and attenuated its infectivity in vivo. Further experimental and clinical studies are warranted to investigate their potential application for clinical intervention of chikungunya disease, but the available evidence is promising [5].

In conclusion, fever in the returning traveller has become a high risk for patients and a not easy challenge for clinicians. Lack of knowledge about these pathogens, which are very uncommon in non-tropical settings, in the diagnosis clinicians make daily in their own countries, plus the similarity in symptoms, has led to inadequate therapies and unexpected complications. With malaria being the most common diagnosis, it is important to highlight its easy means of diagnosis through blood films compared with the others entities that require serological tests that are not always available. The immunomodulatory role of doxycycline offers the possibility of unifying the management of fever in the returning traveller, using it like an empirical treatment before the diagnosis has been made, either because of a lack of input or diagnostic doubts.

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Competing interests

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References

[1] Alfaro-Toloza P, Clouet-Huerta DE, Rodríguez-Morales AJ. Chikungunya, the emerging migratory rheumatism. Lancet Infect Dis 2015;15:510–2.
[2] Rothan HA, Mohamed Z, Paydar M, Rahman NA, Yusof R. Inhibitory effect of doxycycline against dengue virus replication in vitro. Arch Virol 2014;159:711–8.
[3] Fredeking TM, Zavala-Castro JE, Gonzalez-Martinez P, Moguel-Rodríguez W, Sanchez EC, Foster MJ, et al. Dengue patients treated with doxycycline showed lower mortality associated to a reduction in IL-6 and TNF levels. Recent Pat Antiinfect Drug Discov 2015;10:51–8.
[4] Suharti C, van Gorp EC, Setiati TE, Dolmans WM, Djokomoeljanto RJ, Hack CE, et al. The role of cytokines in activation of coagulation and fibrinolysis in dengue shock syndrome. Thromb Haemost 2002;87:42–6.
[5] Rothan HA, Bahrani H, Mohamed Z, Teoh TC, Shankar EM, Rahman NA, et al. A combination of doxycycline and ribavirin alleviated chikungunya infection. PLoS ONE 2015;10:e0126360.

María Paula Olivera
Faculty of Medicine, Universidad Militar Nueva Granada, Bogotá, Colombia

Álvaro A. Faccini-Martínez [a,b,c,d]
[a] *Servicios y Asesorías en Infectología (SAI), Bogotá, Colombia*
[b] *Grupo de Enfermedades Tropicales e Infecciosas (GETI), Universidad Militar Nueva Granada, Bogotá, Colombia*
[c] *Faculty of Medicine, Universidad de La Sabana, Bogotá, Colombia*
[d] *Working Group on Zoonoses, International Society for Chemotherapy, Aberdeen, UK*

Carlos E. Pérez-Díaz [a,b,c]
[a] *Servicios y Asesorías en Infectología (SAI), Bogotá, Colombia*
[b] *Infectious Diseases Department, Clínica de Marly, Bogotá, Colombia*
[c] *Infectious Diseases Department, Hospital Universitario de la Samaritana, Bogotá, Colombia*

Alfonso J. Rodriguez-Morales [a,b,*]
[a] *Public Health and Infection Research and Incubator Group, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Risaralda, Colombia*
[b] *Working Group on Zoonoses, International Society for Chemotherapy, Aberdeen, UK*

[*] Corresponding author at: Public Health and Infection Research and Incubator Group, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Risaralda, Colombia. Tel.: +57 300 884 7448.
E-mail address: arodriguezm@utp.edu.co (A.J. Rodriguez-Morales)

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