

Research letters

suppression and/or tissue cell sequestration, which somewhat delayed the diagnosis. Studies have shown that the syndrome takes between 1 and 8 weeks to develop; in this case the patient became unwell within a matter of hours. The rapidity of the onset of the patient's symptoms mimics the IgE-mediated reaction seen in anaphylaxis; however, the negative mast cell tryptase result precludes this diagnosis.

In summary, we describe a novel, acute severe manifestation of DRESS syndrome caused by administration of a β -lactam antibiotic. The further administration of a β -lactam antibiotic to treat a presumptive neutropenic sepsis may have exacerbated the patient's condition and, had the early recognition of a possible DRESS syndrome not been made, could easily have resulted in a case report with a less favourable outcome. A case, nearly, of 'killing with kindness' through protocol-driven antimicrobial prescribing, in this case for presumed neutropenic sepsis. This case may question in part perhaps the broad philosophy of protocol-driven prescribing and emphasizes the need for better education regarding the presentation of acute sepsis and its medical mimics, and the existence of non-anaphylactic acute, severe drug reactions.

The patient has been told to avoid all β -lactam drugs in the future and that the condition may recur in conjunction with administration of other classes of drugs.

The patient's consent for publication of this case report has been obtained.

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Imipenem underdosing as a cause of persistent neutropenic fever?

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Sir,

Clinical trials with the recommended 2 g daily dose (500 mg four times a day) of imipenem in febrile neutropenia have reported success rates of 60–80%.¹ Causes of persistent neutropenic fever often remain unexplained, which results in multiple investigations and empirical modifications of antimicrobial therapy.² The pharmacodynamic parameter predicting the *in vivo* antibacterial efficacy of β -lactam antibiotics is the proportion of the dosing interval during which plasma concentrations are above the MIC for the causative pathogen ($T_{>MIC}$). For carbapenems, $T_{>MIC}$ during 50–60% of the dosing interval is required to achieve bactericidal activity in neutropenic experimental animal models.³ In life-threatening infections, such as febrile neutropenia, success rates were significantly higher with $T_{>MIC}$ during 75–100% of the dosing interval.⁴ Based on these observations, some experts have recommended maintaining the trough antibiotic concentrations above the MIC, e.g. by extending the drug infusion time or by administering the drug with a continuous infusion.^{3,5}

We retrospectively assessed the association between imipenem plasma concentrations and response to antibacterial therapy in 29 neutropenic patients (79% acute leukaemias; 86% males; median age 58 years, range 27–78) with persistent fever for ≥ 3 days: 14 microbiologically documented infections (MDIs; 48%); 9 clinically documented infections (CDIs; 31%); and 6 fever of unknown origin (FUO; 21%). Imipenem was prescribed at the recommended dose for febrile neutropenia adjusted to the

renal function (median 2 g/day, range 1–4; divided in four infusions over 30 min every 6 h). Results of imipenem plasma trough concentrations measured during persistent fever by a validated HPLC-UV method were obtained at a median of 6 days after start of therapy (range 3–11). Imipenem trough concentrations above 1 mg/L [MIC_{90} for the most frequent pathogens of febrile neutropenia according to the susceptibility data from the European Committee on Antimicrobial Susceptibility Testing (EUCAST); <http://www.eucast.org>] were targeted.

Median imipenem trough concentrations were 0.9 mg/L (range 0.25–5). A cause of persistent fever was documented in 16/29 (55%) episodes (6 resistant bacteria, 8 probable/possible mycoses and 2 non-infectious aetiologies). In 13/29 (45%) episodes (4 MDIs, 5 CDIs and 4 FUO) the cause of persistent fever (median duration 6 days, range 3–16) remained unknown. Imipenem concentrations were interpreted as low according to the above criteria in eight (62%) of them (median 0.6 mg/L, range 0.25–1). Imipenem underdosing was considered the probable cause of failure in three cases (no documented alternative cause and clinical improvement within 3 days after imipenem dose adjustment in the absence of any concomitant intervention): the clinical characteristics are summarized in Table 1. In the five remaining cases, the role of imipenem underdosing in the unexplained persistence of fever could not be assessed because of concomitant interventions in addition to imipenem dose adjustment (empirical antifungal therapy and/or vancomycin therapy, three cases), change of antibacterial therapy (one case) or spontaneous resolution of fever in the absence of any intervention (one case).

In febrile neutropenic patients, variations in the pharmacokinetics of β -lactam antibiotics, such as an increase in the volume of distribution and/or renal clearance, have been frequently reported. These modifications result in lower plasma concentrations when compared with healthy subjects.^{6,7} We observed a high proportion of insufficient imipenem plasma concentrations in febrile neutropenic patients with persistent fever receiving the recommended 2 g daily dose. The analysis of clinical data suggests that imipenem underdosing was the probable cause of failure in a subgroup of patients not responding to therapy.

The persistence of fever despite broad-spectrum antibacterial therapy is observed in one-third of febrile neutropenic episodes. According to the Infectious Diseases Society of America guidelines, reassessment of empirical antibacterial therapy is recommended after 3–5 days of persistent fever; as resistant bacterial infections or invasive mycoses are suspected, an extensive diagnostic work-up, empirical modifications of antibacterial therapy and/or addition of antifungal therapy have to be considered.² In the majority of cases the cause of persistent fever cannot be identified and the utility of such interventions remains unknown. Although changes in pharmacokinetic parameters are frequently observed in these patients, inappropriate antibiotic dosing is usually not considered among the possible causes of failure. The measurement of antibiotic plasma concentrations by HPLC (or bioassay, as a simple alternative in hospitals without a clinical pharmacology service) is non-invasive and inexpensive, and might be easily added to the clinical, microbiological and radiological reassessment of response to empirical antibacterial therapy recommended during the time window including 3–5 days of persistent neutropenic fever. Documentation of low antibiotic blood levels in the absence of another cause of failure may contribute to optimizing individual management by avoiding

Table 1. Clinical characteristics of neutropenic patients with persistent fever attributed to imipenem underdosing

| Sex (M/F)/age (years)/weight (kg)/creatinine clearance (mL/min) | Aetiology of febrile neutropenia | Imipenem dosing schedule | Imipenem trough blood concentration ^a | Assessment of response to imipenem therapy at time of obtention of trough concentrations: duration of fever/clinical course | Modification of imipenem dosing schedule | Days to resolution of fever after imipenem dose adjustment |
|-----------------------------------------------------------------|----------------------------------|--------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------|
| M/48/61/92 | CDI (neutropenic enterocolitis) | 0.5 g qid | 1 mg/L | 3 days/persistent fever and enterocolitis | increase infusion time from 30 to 120 min | 1 |
| M/51/67/75 | FUO | 0.5 g qid | <0.25 mg/L | 4 days/persistent fever | 100% increase: 1 g qid | 3 |
| M/69/99/51 | FUO | 0.5 g tid | 0.7 mg/L | 6 days/persistent fever | 33% increase: 0.5 g qid | 1 |

M, male; F, female; qid, four times a day; tid, three times a day.

^aHPLC-UV method validated according to international guidelines (analytical range 0.25–200 mg/L, intra-/inter-assay accuracy and precision >95% and <5%, respectively).⁸

unnecessary and expensive investigations and empirical modifications of therapy. Prospective pharmacodynamic investigations are needed to confirm the utility of measuring antibiotic plasma concentrations in persistent febrile neutropenia, which would justify its implementation in clinical management.

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Inadvertent non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy in dual HIV-1/2 and HIV-2 seropositive West Africans: a retrospective study

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Sir,
HIV-2 or dual HIV-1/2 infection makes up between 4% and 24% of all HIV infections in West Africa, and dual infection ~12% of all infections in Ghana.¹ HIV-2 infection progresses to AIDS more slowly than HIV-1; however, dual infection appears to progress at a rate similar to that of HIV-1.² Antiretroviral therapy (ART) has been widely available in Ghana since 2003, with good initial results.³ Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART is first-line therapy. In many centres HIV testing has not routinely been type-specific, so patients infected with HIV-2 have started ART including NNRTIs that are ineffective against HIV-2.

To analyse the impact of NNRTI-based ART in dual HIV-1/2 or HIV-2 seropositive individuals in terms of clinical outcomes, surrogate markers or resistance mutations, we conducted a retrospective study of patients attending a large HIV clinic in Ghana where type-specific HIV testing was not routine. The study was approved by the Committee on Human Research Publications and Ethics at KNUST, Kumasi. Patients were tested for HIV-2 seropositivity using the ImmunoComb HIV-1&2 Biospot test (Organics, Yavne, Israel). Response to NNRTI-based ART, efavirenz/nevirapine with two nucleoside reverse transcriptase inhibitors (NRTIs), was compared in 57 dual HIV-1/2 seropositive, 16 HIV-2 seropositive and 197 HIV-1 seropositive patients who had completed at least 12 months of ART. Clinical and laboratory data were collected retrospectively at 6 monthly intervals. Changes in patient weight, total CD4 count and HIV viral load a minimum of 3 months after starting ART were compared. Mean values for (normally distributed) laboratory data were compared using *t*-tests and χ^2 tests for categorical data.

Baseline characteristics (pre-ART) and responses to ART are shown in Table 1. There were significantly more females in the HIV-2-infected groups. Increases in mean CD4 count at 6 and/or 12 months after starting ART were significantly lower in HIV-2 seropositive compared with HIV-1 and dual seropositive patients, despite starting from higher CD4 counts. Weight gain was also lower in this group. Samples were available to quantify HIV-2 and/or HIV-1 viral loads in a proportion of patients (HIV-2, 63%; dual seropositive, 56%; HIV-1, 22%) after a median of 14 months of ART. Whilst in the majority of dual seropositive and HIV-1 seropositive patients HIV-1 \pm HIV-2 viral loads were suppressed on ART, only 19% of the HIV-2 seropositive patients achieved undetectable HIV-2 viral loads. There was little difference in the rates of AIDS-defining pathology between groups. Only one death was recorded, in a HIV-2 seropositive patient; however, a number of patients were lost to follow-up after the first year of ART. In samples from seven