Linear regressions were near ideal, with the exception of the one-compartment WIN4 model.

## Discussion

### Continuous administration

The advantage of continuous administration of vancomycin is a lower risk of nephrotoxicity, despite aiming for a higher therapeutic range. As described by Flannery et al.'s (5) meta-analysis of critically ill patients, the odds of acute kidney injury declined by 50% compared to intermittent administration. However, continuous administration of vancomycin is rarely used in our area, and if so, only in intensive care units (ICU), as it is preferable to use a central line due to possible endothelial cell toxicity (5). The disadvantages are: one intravenous access is permanently occupied, the patient's movement is restricted, and, from the clinical point of view, in the case of underdosing the plasma levels remain insufficient for the entire duration of the dosing interval.

### Model selection

The Mw\Pharm DOS version offers two models for continuous vancomycin administration, while the Windows version offers several models for the prediction of vancomycin kinetics. With paediatric models excluded, four WIN models remained available for the prediction of continuous vancomycin administration in adults. According to the MW\Pharm manual (12) and manufacturer personal information (13), the source of population-based data for the DOS2 and WIN models was a study performed by Rodvold et al. (14). Patients in the reference group, compared to our patient group, were younger (55 ± 16 yrs vs. 66 ± 12 yrs), their body weight was slightly higher (88 ± 21 kg vs. 85 ± 16 kg), and had lower renal function (serum creatinine 1.4 ± 0.8 mg/dL, i.e. 123.8 μmol/L ± 70.7 μmol/L vs. 112 ± 70 μmol/L).

Because of the high correlation between fluorescence polarization immunoassay (FPIA) and LC-MS/MS analytical techniques, where linear regression models are near ideal (8), the choice of analytical method for model estimation (i.e. FPIA) is not expected to have been responsible for any significant differences in model outcomes.

As models are usually based on a different reference population than the population that is being examined, their potential differences must be considered to avoid inaccurate prediction and insufficient therapy.

Four WIN models and two DOS models for prediction of vancomycin concentration during continuous administration were compared with the values measured. The results presented show that vancomycin concentrations predicted by all models were statistically different from the values measured. %PE in two-compartment models (DOS1, DOS2, WIN1-WIN3) varied from –7.4 to –3.2%, which could be considered as clinically insignificant. The %PE values produced by DOS1 and by other models were in high correlation with linear regression line (near ideal). This means that the large bias produced by unexpected outlier values was caused either by sampling error or unstable condition of a critically ill patient, something not possible to be predicted by any model, as seen in Add Fig. 1 and Add Fig. 2.

Even though only an error of 8% for the one-compartment model has been described in the literature (15), the WIN4 one-compartment model produced a %PE of –21%, which makes it unsuitable for TDM of vancomycin under continuous administration.

As a different (higher) therapeutic range is used for continuous administration, it might

**Fig. 6.** *Comparison of %PE produced by (A) WIN1 and DOS1 model, (B) WIN2 and DOS1 model, (C) WIN3 and DOS1 model, (D) WIN4 and DOS1, (E) DOS1 and DOS2. The full line represents linear regression, while the dashed line is the line of identity (y = x). R = Pearson's R, P < 0.0001*