File S1

Definitions

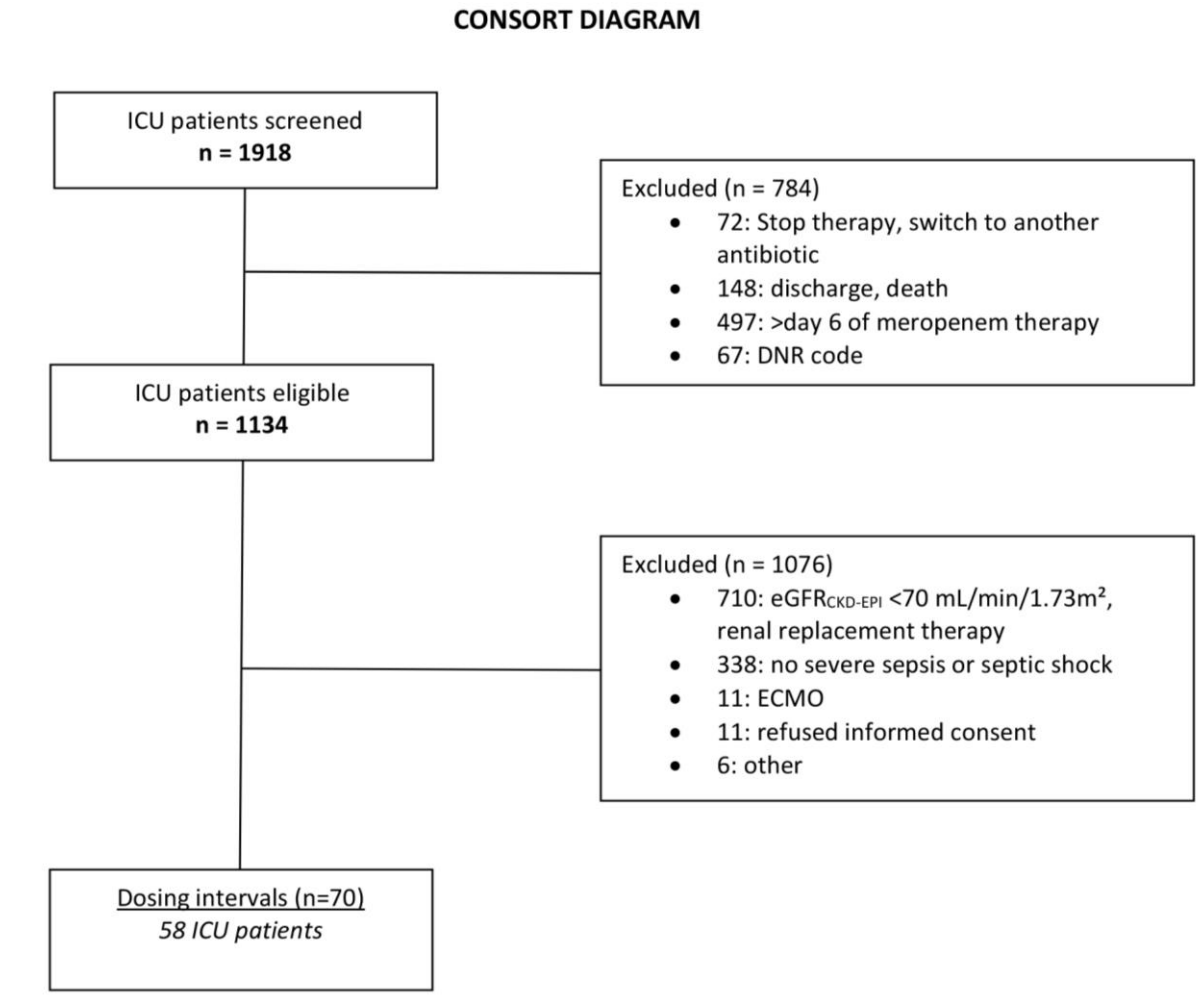
Sepsis was defined as a documented or suspected infection complicated by at least two of the following criteria: leukocytosis (total white blood cell count >12x10^9/L), leucopenia (total white blood cells <4x10^9/L), increased C-Reactive protein plasma concentration (>15 mg/L), abnormal body temperature (<36 or >38.3°C), tachypnea (>20/min) or mechanical ventilation with adjusted respiratory rate, significant edema or a positive fluid balance (>20mL/kg/24h) and tachycardia (>90/min). Severe sepsis was defined as sepsis complicated with organ dysfunction. Organ dysfunction was defined by at least one of the following criteria: respiratory distress (PaO2/FiO2 <300), oliguria (urinary output <0.5 mL/kg.h for at least 2 hours with adequate fluid treatment (30 ml/kg crystalloid)), increased serum creatinine concentrations (>0.5 mg/dL relative to the baseline or >2 mg/dL), prolonged prothrombin time (INR >1.5), thrombocytopenia (platelet count <100x109/L), hyperbilirubinemia (total bilirubin concentration >4mg/dL) and elevated serum lactate concentration (>1.6 mmol/L). Septic shock was defined as severe sepsis complicated with hypotension despite adequate fluid resuscitation: systolic blood pressure <90 mmHg, a decrease in systolic blood pressure of >40 mmHg in relative to the baseline, diastolic blood pressure <70 mm Hg or need for vasopressor therapy [11, 12].

File S2

NONMEM control stream

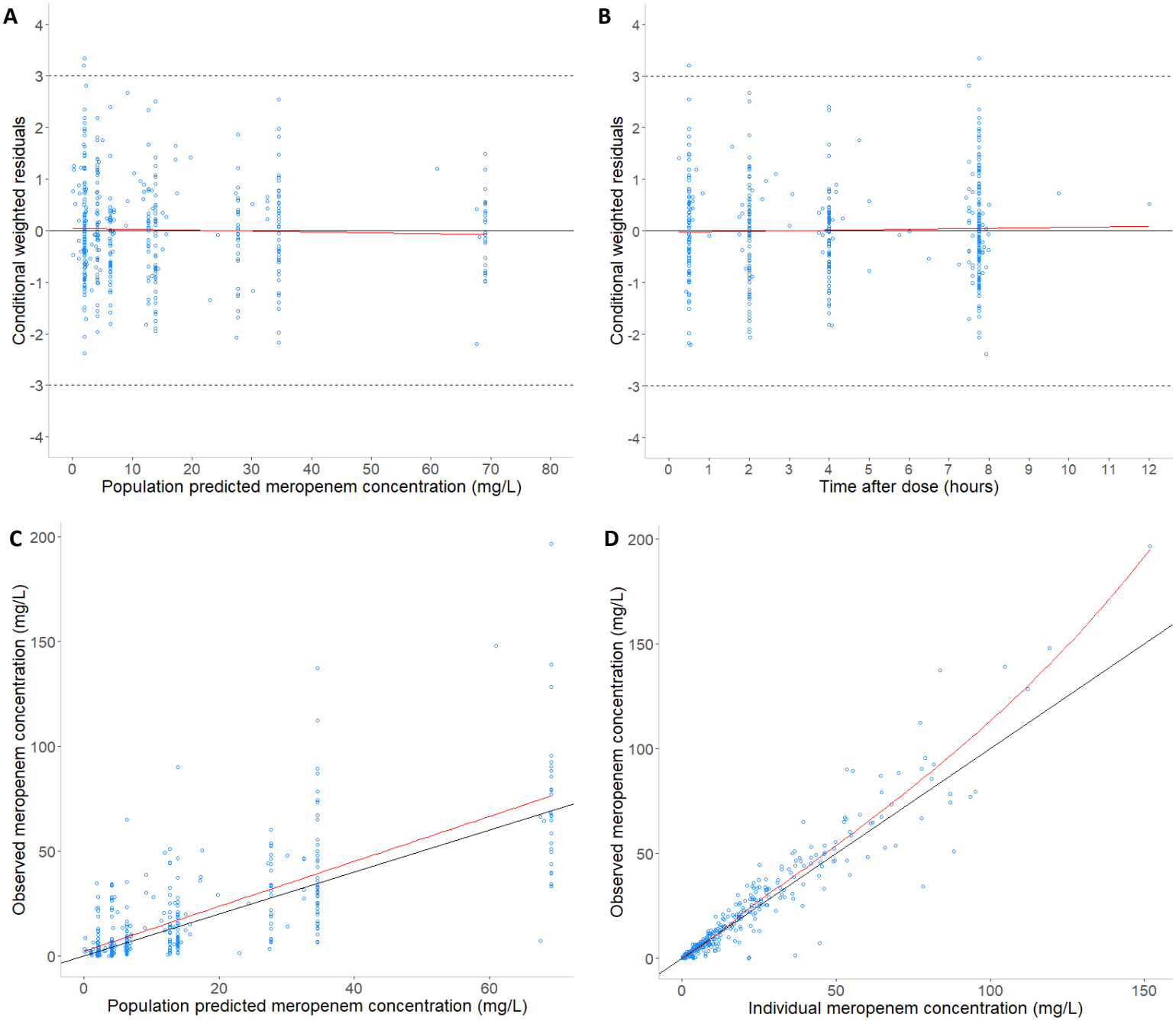
```
$PROBLEM Meropenem popPK modelling
$INPUT
        ID              ; patient identifier
        OCC             ; dosing occasion
        TAD             ; time after dose, in hours
        TIME            ; time, in hours
        EVENT
        DV              ; dependent variable, in mg/L
        EVID            ; event identifier: 1 is dosing event, 0 is observation event
        MDV             ; missing data value
        AMT             ; amount of L-AmB administered in mg
        RATE            ; infusion rate, in mg/hour
        SEX             ;1=male, 2=Female
        AGE
        BW
        NDOSE
        CG
$DATA DSCOV.csv IGNORE=@
$SUBROUTINES ADVAN13 TOL=9
$MODEL
        NCOMPARTMENTS=2
        COMP= (CENTRAL, DEFDOSE)
        COMP=(PERIPH)
$PK
        CLCG = ((CG/111.7) **THETA (5))
        CLCOV=CLCG
        TVCL=THETA (1)
        TVCL = CLCOV*TVCL
        TVV1=THETA (2)
        TVQ=THETA (3)
        TVV2=THETA (4)
        CL=TVCL*EXP (ETA (1))
        V1=TVV1*EXP(ETA(2))
        Q=TVQ
        V2=TVV2*EXP(ETA(3))
        KE=CL/V1
        K12=Q/V1
        K21=Q/V2
        S1=V1
        S2=V2
$DES
        DADT(1)= -KE*A(1) +K21*A(2) -K12*A(1)
        DADT(2)=        -K21*A(2) +K12*A(1)
$ERROR
        IPRED=F
        W=SQRT(SIGMA(1,1)*IPRED**2 + SIGMA(2,2))
        Y=IPRED * (1+EPS(1))+ EPS(2)
        IRES=DV-IPRED
        IWRES=IRES/W
$THETA
(0, 13.7)                       ; CL
(0,25.5)                ; V1
(0,8.13)                        ; Q
(0,12.4)                ; V2
(0,0.637)               ; CLCG

$OMEGA
        BLOCK (2)
        0.288                   ; IIV on CL
        0.185   0.281           ; IIV on V1
$OMEGA
        0.441                   ; IIV on V2
$SIGMA
        0.147                   ; prop err
        0.0925                  ; add err
$ESTIMATION METHOD=1 INTERACTION MAXEVAL=9999 NSIG=3 SIGL=9 PRINT=1 POSTHOC NOABORT
$COVARIANCE PRINT=E
```

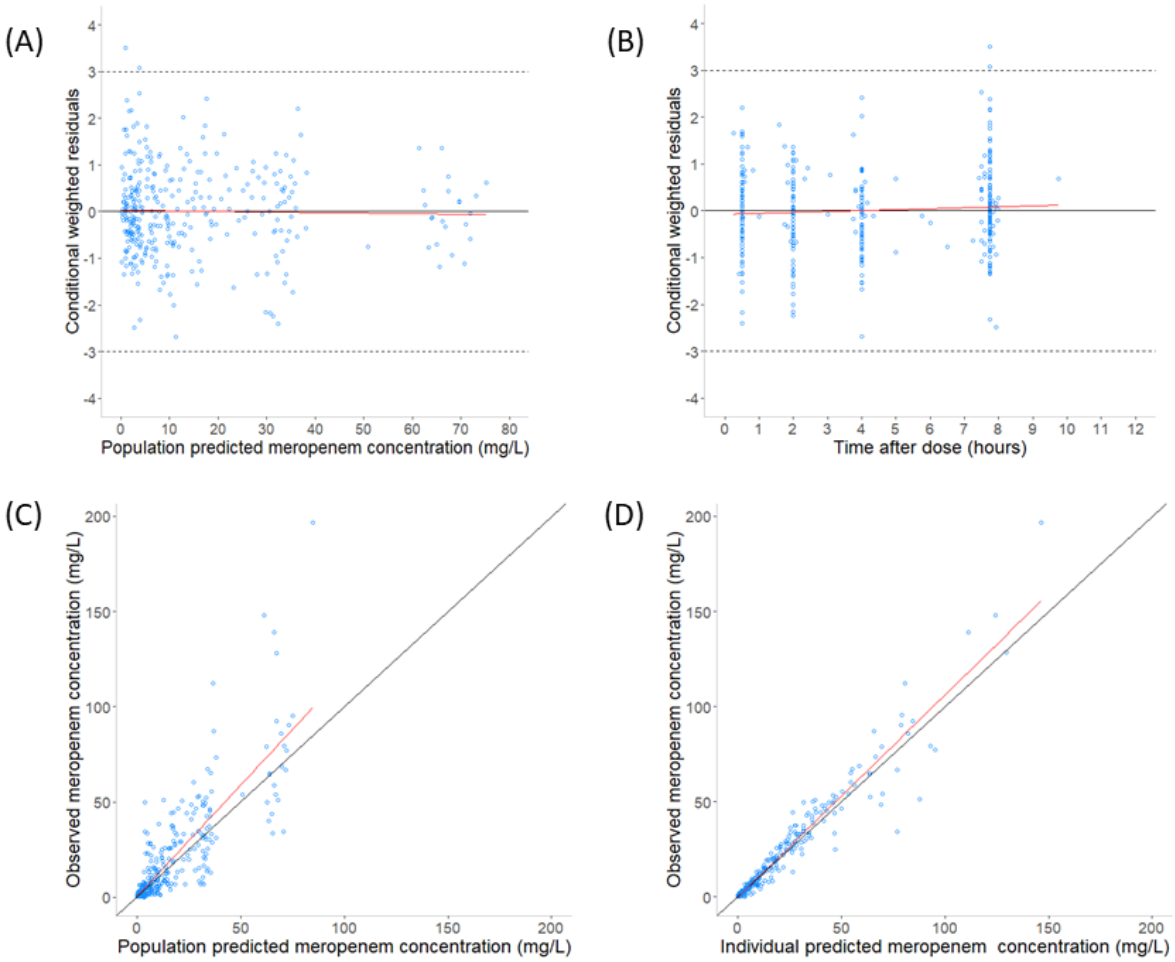


ICU = intensive care unit; DNR = do not resuscitate; ECMO = extracorporeal membrane oxygenation; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation

Supplementary Figure 1. Study flow diagram.



Supplementary Figure 2. Base model goodness-of-fit plots. (A) Conditional weighted residuals (CWRES) versus population predicted (PRED); (B) CWRES versus time after dose; (C) observed versus PRED meropenem concentration; (D) observed versus individual predicted meropenem concentration. Solid black lines in panels A -D: line of identity; solid red lines: linear regression lines.



Supplementary Figure 3. Final model goodness-of-fit plots. (A) Conditional weighted residuals (CWRES) versus population predicted (PRED); (B) CWRES versus time after dose; (C) observed versus PRED meropenem concentration; (D) observed versus individual predicted meropenem concentration. Solid black lines in panels A -D: line of identity; solid red lines: linear regression lines.