Supplementary material

Table S1: Gentamicin analytical techniques

	LDL (mg/L)	Precision		
		within-run (%CV)	total (%CV)	measured at
St George's	0.4	5.0	6.4	2.3 mg/L
Liverpool	0.3	1.0	2.9	3.4 mg/L
Oxford	0.17	5.59	6.27	1.52 mg/L
Coventry	0.24	5.2	6.7	1.6 mg/L
Portsmouth	0.13	3.8	5.3	2.1 mg/L

LDL is the lowest detectable level; CV is coefficient of variation

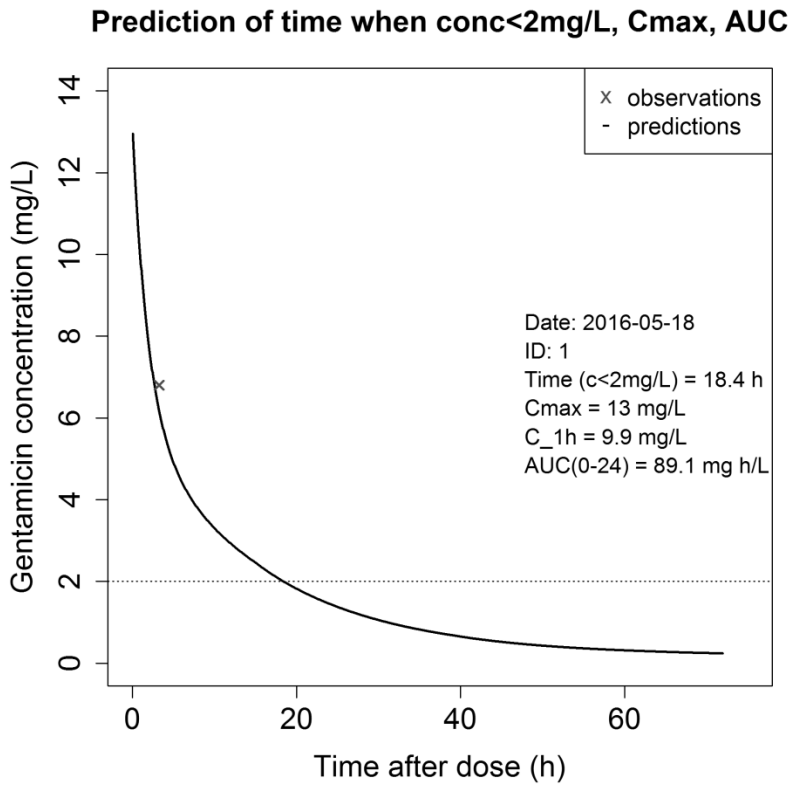

Figure S1: An example of the neoGent output.

Supplementary material: R code for predicting the time when plasma concentration of gentamicin goes below 2 mg/L, peak concentration, and AUC(0-24)

```
########################################
### R script for the neoGent software ###
###    developed by Eva Germovsek     ###
###              2016                 ###
########################################
#
#clean workspace
rm(list=ls())
#
#set working directory
setwd("C:/neoGent/RShell")
#
##### read in a .csv file (from e.g. hospital)
## information needed (with order and names of the columns):
#      ID,GA(days),GIRL(1=female),DATE(DD/MM/YYYY),TIME(HH:MM),PNA(days),
#      WT(g),CREAT(umol/L),RATE(dose/infusion duration,mg/h),AMT(mg),DV(mg/L),
#      OCC(occasion is a dose with subsequent gentamicin samples taken)
# e.g.
# ID  GA    GIRL  DATE        TIME  PNA   WT  CREAT RATE AMT DV  OCC
# 1   226    1    03/09/2013  12:00  1   1770  59   240   8  0    1
# 1   226    1    05/09/2013  00:15  3   1710  59   240   8  0    1
# 1   226    1    05/09/2013  10:11  3   1710  59   0     0  3.4  1
# 1   226    1    06/09/2013  12:29  4   1710  50   240   8  0    2
# 1   226    1    06/09/2013  15:45  4   1710  50   0     0  6.8  2
#
data1 <- read.csv("Patient_data.csv",head=T,skip=0)
#
#########################################################################
#################### Change the datafile ################################
#########################################################################
#
## change date and time to time in decimal hours
colnames(data1)[5]<-"TIMEX"
data1$DT <- do.call(paste,c(data1[c("DATE","TIMEX")],sep=" "))
data1$DT <- as.POSIXct(strptime(data1$DT,format="%d/%m/%Y %H:%M",
      tz="UTC"))
TIME2 <- NA
data1$TIME2<-data1$DT[1]
data1$TIME <- as.numeric(difftime(data1$DT,data1$TIME2,units="hours"))
data1<-data1[,-c(4,5,13,14)]
last<-nrow(data1)
lastT<-data1$TIME[last]
lastdT<-max(data1$TIME[data1$AMT!=0])
lastD<-which(data1$TIME==lastdT)
#
## extend the data frame (5000 additional rows)
data2<-data.frame(
 ID=rep(data1$ID[1],5000),
 GA=rep(data1$GA[1],5000),
 GIRL=rep(data1$GIRL[1],5000),
 PNA=NA,
 WT=NA,
 CREAT=NA,
 RATE=0,
```

```
 AMT=0,
 DV=0,
 OCC=NA,
 TIME=seq((lastdT+0.05),lastT+200,0.05)[1:5000]
 )
## exclude time after dose >72h
# (dosing interval would not be >3 days)
data2<-data2[data2$TIME<(lastdT+72),]
#
## remove rows where TIME=NA
# (since TIME only to 72hrs, some rows TIME=NA)
data2<-data2[complete.cases(data2$TIME),]
#
data<-rbind(data1,data2)
## order by time
data<-data[order(data$TIME),]
#
## interpolate/carry forward WT, CREAT
data$WT[lastD:last]<-data1$WT[lastD]
data$WT[(last+1):nrow(data)]<-data1$WT[last]
data$CREAT[lastD:last]<-data1$CREAT[lastD]
data$CREAT[(last+1):nrow(data)]<-data1$CREAT[last]
#
## EVID
# if AMT-> EVID=1
# if DV-> EVID=0
# if extra dummy time point-> EVID=2
#
for(i in 1:nrow(data)){
       if(data$AMT[i]!=0) data$EVID[i]<-1
       if(data$DV[i]!=0) data$EVID[i]<-0
       if((data$AMT[i]==0)&(data$DV[i]==0)) data$EVID[i]<-2
}
#
## PNA
# if t>12 -> +1 day PNA
# if t>36 -> +1 day PNA
# if t>60 -> +1 day PNA
#
for(i in (lastD+1):nrow(data)){
 if(data$TIME[i]<(lastT+12)) data$PNA[i]<-data1$PNA[lastD]
 if((data$TIME[i]>=(lastT+12))&(data$TIME[i]<(lastT+36)))
       data$PNA[i]<-data1$PNA[lastD]+1
 if((data$TIME[i]>=(lastT+36))&(data$TIME[i]<(lastT+60)))
       data$PNA[i]<-data1$PNA[lastD]+2
 if(data$TIME[i]>=(lastT+60)) data$PNA[i]<-data1$PNA[lastD]+3
}
#
## PMA
data$PMA <- (data$GA+data$PNA)/7
#
## TCREA
# formula:Cuzzolin et al (Pediatr Nephrol.2006);
# Rudd et al (Arch Dis Child.1983)
data$TCREA <- (data$PMA*(-2.8488)+166.48)
#
## OCC
data$OCC[data$EVID==2]<-data1$OCC[lastD]
#
```

```
## MDV = missing data value
data$MDV[data$EVID==0]<-0
data$MDV[data$EVID!=0]<-1
#
## rearrange the order of the columns
data <- data.frame(data["ID"],data["GA"],data["GIRL"],data["TIME"],
       data["PNA"],data["PMA"],data["WT"],data["CREAT"],data["TCREA"],
       data["RATE"],data["AMT"],data["DV"],data["EVID"],data["OCC"],
       data["MDV"])
#
## write .csv file
write.csv(data,file="Patient_data-NM.csv",quote=FALSE,row.names=FALSE)
#
#
######################################################################
######################### Run NONMEM #################################
######################################################################
cmd<-paste("nmfe73 neoGent.mod neoGent.lst")
shell(cmd)
#
#
######################################################################
############# Read the results from NONMEM back into R #############
######################################################################
nGtab0<-read.table(file="nG_tab",head=TRUE,skip=1)
#
#only look at the last dosing interval
nGtab<-nGtab0[(nGtab0$OCC>=nGtab0$OCC[lastD]),]
#
# locate the row where CP(plasma conc) goes below 2mg/L first
dtime<-0
dtime[1]<-1
for(i in 2:nrow(nGtab)){
       if((nGtab$TLE2[i]!=0) & (nGtab$TLE2[i-1]==0))
              dtime[i]<-100
       else
       dtime[i]<-1
}
nGtab$dtime <- dtime
below2 <- nGtab[nGtab$dtime==100,]
below2 <- below2[,c("ID","TLE2","CP")]
below2$CP<-round(below2$CP,2)
below2$TLE2<-round(below2$TLE2,1)
name<-below2$ID
time<-below2$TLE2
conc<-below2$CP
fortable<-below2
#
## get Cmax
cmax<-round(max(nGtab$CP),1)
tmax<-nGtab$TAD[nGtab$CP==max(nGtab$CP)]
fortable$Cmax<-cmax
#
## get C_1h (i.e. gentamicin concentration at 1h post dose)
c1h<-round(nGtab$CP[nGtab$TAD==1],1)
fortable$C_1h<-c1h
#
## get AUC
# exclude amount rows
```

```
dataauc<-nGtab[!nGtab$EVID==1,]
# trapezoidal rule function
trap.rule <- function(x,y) sum(diff(x)*(y[-1]+y[-length(y)]))/2
# calculate AUC(0-24)
dataauc<-dataauc[dataauc$TAD<=24,]
AUC <- round(trap.rule(dataauc$TAD,dataauc$CP),1)
fortable$AUC<-AUC
#
names(fortable) <- c("SubjectID","Time(h)c<2mg/L","Trough(mg/L)",
       "Cmax(mg/L)","C_1h(mg/L)","AUC(0-24)(mg h/L)")
#
#
##########################################################################
################### Generate output ######################################
##########################################################################
#
datestamp<-Sys.Date()
#
######### a table
write.csv(fortable,file=paste("Below_2mgL,Cmax,AUC_","ID",name,"_",
       datestamp,".csv",sep=""),quote=F,row.names=F)
#
########## a plot
#remove dosing rows
nGtab1<-nGtab[nGtab$EVID==2,]   # predictions
nGtab2<-nGtab[nGtab$EVID==0,]   # observations
#
pdf(paste("Below_2mgL_","ID",name,"_",datestamp,".pdf",sep=""))
par(mar=c(5,5,4,2))
plot(nGtab1$TAD,nGtab1$CP,      # predictions
 main="Prediction of time when conc<2mg/L, Cmax, AUC",
 xlab="Time after dose (h)",
 ylab="Gentamicin concentration (mg/L)",
 cex.lab=1.5,cex.axis=1.5,cex.main=1.5,
 xlim=c(0,75),
 ylim=c(0,14),
 type="n",
 )
lines(nGtab1$TAD,nGtab1$CP,col="black",lwd=2)
abline(h=2,lty=3)
par(new=T)
plot(nGtab2$TAD,nGtab2$DV,      # observations
 col="red",
 pch=4,
 lwd=2,
 axes=F,
 xlab="",ylab="",
 xlim=c(0,75),
 ylim=c(0,14),
 )
par(new=F)
# put a legend in the top right corner
legend("topright",
cex = 1.2,
       legend = c("observations","predictions"),
       col = c("red","black"),
       pch = c("x","-"),
        )
# put a legend - central, right
```

```
legend(43,9,cex = 1.1,bty = "n",legend = paste("Date:",datestamp),)
legend(43,8.3,cex = 1.1,bty = "n",legend = paste("ID:",name),)
legend(43,7.6,cex = 1.1,bty = "n",legend = paste("Time (c<2mg/L) =",time,"h"),)
legend(43,6.9,cex = 1.1,bty = "n",legend = paste("Cmax =",cmax,"mg/L"),)
legend(43,6.2,cex = 1.1,bty = "n",legend = paste("C_1h =",c1h,"mg/L"),)
legend(43,5.5,cex = 1.1,bty = "n",legend = paste("AUC(0-24) =",AUC,"mg h/L"),)
dev.off()
############################## end code ###################################
```

Supplementary material: NONMEM control file for the final gentamicin model

```
$PROBLEM neoGent model Germovsek 2016
$INPUT ID GA GIRL TIME PNA PMA WT CREA TCRE RATE AMT DV EVID OCC MDV
;GA (days), PNA (days), PMA (weeks)
;GIRL: 0=male, 1=female
;TIME (hrs, time after the first dose)
;RATE (mg/h), AMT (mg), DV=genta conc (mg/L)
;EVID: 0=DV measurement, 1=dose given, 2=dummy time point
;WT (g)
;CREAT (umol/L)
;TCREA = typical SCr for PMA [Cuzzolin 2006 and Rudd 1983]
;OCC=a dose with a subsequent level reported
;
$DATA Patient_data-NM.csv IGNORE=@
$SUBROUTINE ADVAN6 TOL=6
;
$MODEL
COMP=(CENTRAL)
COMP=(PERIPH1)
COMP=(PERIPH2)
COMP=(COVCMT1)           ; PNA time-var. covariate compartment
COMP=(COVCMT2)           ; CREATININE t-v. cov. compartment
;
$PK
; Three-comp model
; -------- Parameterisation for time-varying covariates ----------------------
IF(NEWIND.NE.2)OTIM1=0
IF(NEWIND.NE.2)OCOV1=0
IF(NEWIND.NE.2)OTIM2=0
IF(NEWIND.NE.2)OCOV2=0
;
WTKG = WT/1000
T50  = 55.4
HILL = 3.33
MF   = PMA**HILL/(PMA**HILL+T50**HILL)
;
SECR = CREA
IF(SECR.LE.0) SECR = TCRE      ; when SCr is NA=-99, it is the typical SCr
;
P50  = THETA(8)  ; postnatal age when 50% of adult's clearance is reached
;
CRPWR = THETA(7)  ; power exponent on the creatinine function
;
; -------- Inter-occasion variability code -----------------------------------
BOVC = 0
IF(OCC.EQ.1)  BOVC = ETA(7)
IF(OCC.EQ.2)  BOVC = ETA(8)
IF(OCC.EQ.3)  BOVC = ETA(9)
IF(OCC.EQ.4)  BOVC = ETA(10)
IF(OCC.EQ.5)  BOVC = ETA(11)
```

```
IF(OCC.EQ.6)  BOVC = ETA(12)
IF(OCC.EQ.7)  BOVC = ETA(13)
IF(OCC.EQ.8)  BOVC = ETA(14)
IF(OCC.EQ.9)  BOVC = ETA(15)
IF(OCC.EQ.10) BOVC = ETA(16)
IF(OCC.EQ.11) BOVC = ETA(17)
IF(OCC.EQ.12) BOVC = ETA(18)
IF(OCC.EQ.13) BOVC = ETA(19)
IF(OCC.EQ.14) BOVC = ETA(20)
IF(OCC.EQ.15) BOVC = ETA(21)
IF(OCC.EQ.16) BOVC = ETA(22)
IF(OCC.EQ.17) BOVC = ETA(23)
IF(OCC.EQ.18) BOVC = ETA(24)
IF(OCC.EQ.19) BOVC = ETA(25)
IF(OCC.EQ.20) BOVC = ETA(26)
IF(OCC.EQ.21) BOVC = ETA(27)
IF(OCC.EQ.22) BOVC = ETA(28)
;
TVCL = THETA(1)*MF*(WTKG/70)**(0.632)   ; typical value of CL
TVV1 = THETA(2)*(WTKG/70)               ; typical value of V1
TVQ  = THETA(3)*(WTKG/70)**(0.75)       ; ty. value of inter-compartmental CL
TVV2 = THETA(4)*(WTKG/70)               ; ty. value of V2
TVQ2 = THETA(5)*(WTKG/70)**(0.75)       ; ty value of CL3
TVV3 = THETA(6)*(WTKG/70)               ; ty value of V3
;
CL   = TVCL*EXP(ETA(1)+BOVC)            ; individual value of CL
V1   = TVV1*EXP(ETA(2))                 ; individual value of V1
Q    = TVQ*EXP(ETA(3))                  ; individual value of Q
V2   = TVV2*EXP(ETA(4))                 ; individual value of V2
Q2   = TVQ2*EXP(ETA(5))                 ; individual value of Q2
V3   = TVV3*EXP(ETA(6))                 ; individual value of V3
;
K    = CL/V1                            ; rate constants
K12  = Q/V1
K13  = Q2/V1
K21  = Q/V2
K31  = Q2/V3
;
; -------- Code to calculate time after dose ---------------------------------
IF(EVID.EQ.1) TM=TIME
IF(EVID.EQ.1) TAD=0
IF(EVID.NE.1) TAD=TIME-TM
;
; -------- Parameterisation for time-varying covariates ----------------------
SL1 = 0
IF(TIME.GT.OTIM1) SL1 = (PNA-OCOV1)/(TIME-OTIM1)
A_0(4) = PNA
;
SL2 = 0
IF(TIME.GT.OTIM2) SL2 = (SECR-OCOV2)/(TIME-OTIM2)
A_0(5) = SECR
```

```
;
; -------- Differential equations -------------------------------------------
$DES
DADT(4)= SL1
TCOV1 = A(4)
;
DADT(5)= SL2
TCOV2 = A(5)
;
PNAF = TCOV1/(P50+TCOV1)
OF = (TCOV2/TCRE)**CRPWR
DADT(1) = A(3)*K31+A(2)*K21-A(1)*(K*PNAF*OF+K12+K13)
DADT(2) = A(1)*K12-A(2)*K21
DADT(3) = A(1)*K13-A(3)*K31
;
$ERROR
CP=A(1)/V1
IF (CP.LE.2) TLE2=TAD
; -------- Statistical model ------------------------------------------------
Y = CP*(1+EPS(1)) + EPS(2)
;
OCOV1 = PNA
OTIM1 = TIME
;
OCOV2 = SECR
OTIM2 = TIME
;
$THETA  6.20684 FIX       ; 1. TVCL
$THETA  26.5004 FIX       ; 2. TVV1
$THETA  2.15099 FIX       ; 3. TVQ
$THETA  21.151 FIX        ; 4. TVV2
$THETA  0.270697 FIX      ; 5. TVQ2
$THETA  147.893 FIX       ; 6. TVV3
$THETA  -0.129934 FIX     ; 7. power exponent on creatinine
$THETA  1.70302 FIX       ; 8. PNA50

$OMEGA  BLOCK(2)
 0.175278                 ; IIV_CL
 0.115896 0.112362 FIX    ; COvariance IIV_CL-IIV_V; IIV_V
$OMEGA  0  FIX            ; IIV_Q
$OMEGA  0.131759 FIX      ; IIV_V2
$OMEGA  0  FIX            ; IIV_Q2
$OMEGA  0.177214 FIX      ; IIV_V3

$OMEGA  BLOCK(1) 0.0140684 FIX  ; 7. IOV_CL
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
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$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME

$SIGMA  0.036033 FIX  ; PROP res error
$SIGMA  0.0164023 FIX ; ADD res error

$ESTIMATION METHOD=1 INTER MAXEVAL=0 PRINT=1      ; estimation method

$TABLE ID TIME GA PMA AMT TAD TLE2 CP OCC EVID   NOPRINT ONEHEADER FILE=nG_tab
```