

Systematic Review of Clinical PK-PD Studies of Antibacterials

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Background

- *It has been suggested that there are problems with current clinical PK-PD studies:*
 - Small size (<100 patients)
 - Mixed pathogens
 - Mixed sites of infection
 - Free drug not measured
 - Few designed with a primary pharmacodynamic end point in mind
 - May be a bias in the literature towards reporting positive results
 - cIAI and some SSTI studies may be confounded by surgery
 - Uncertainty over how results should be analysed, especially role of CART

Objectives of this systematic review

- To identify and describe the characteristics of clinical PK-PD studies of antibacterials and antifungals performed since 1980
- To assess the strengths and limitations of the clinical PK-PD studies
- To determine the essential characteristics of a high quality PK-PD study, to aid the design of future studies



Criteria for considering studies for this review

- RCTs or cohort studies (including participants from one arm of RCTs)
- Participants with a bacterial or fungal infection, being treated with an antibiotic or antifungal
- Pharmacokinetic parameters calculated for individuals
- Pathogen MICs to the therapy drug determined
- Clinical or microbiological cure or some other relevant outcome assessed
- A pharmacodynamic index (i.e. AUC/MIC) is related to the outcome

Systematic search and screen

- Medline, Embase, Web of Science and Biosis were systematically searched
- Search strategy based on combining terms for PK-PD parameters AND antifungals/antibacterials AND treatment outcome
- No restrictions on language or publication status
 - 9,828 records identified; 6082 after de-duplication
- Titles and abstracts of identified records screened. Clearly irrelevant records excluded
- Full publications of remaining records obtained and assessed for eligibility
 - >100 papers included

Data extraction

- Data extracted on:
 - Funding
 - Number of study participants
 - Source of these patients (clinical trials, retrospective or prospective cohorts)
 - Infection and infecting organisms
 - Antibiotic treatment and concurrent antibiotic treatment
 - Outcome measure, including timing of measurement
 - The number of patients without the outcome (i.e. treatment failures)
 - How PK parameters were derived
 - How MICs were determined
 - Average PDI values for the population
 - How the relationship between PDI and outcome was examined (statistical analyses performed) and if a power calculation was performed
 - Covariates analyses for association

Overview of included studies

- Due to the number of studies identified, an overview of the studies of aminoglycosides (12 studies) and beta-lactams (13 studies) that explicitly reported that they measured serum concentrations of antibiotics will be presented
- Aminoglycosides
 - Studies on aminoglycosides involved between 13 and 236 participants, although only two studies had >100 participants
 - Only one study reported industry funding, although the majority of studies did not report a funding source
- Beta-lactams
 - Studies on beta-lactams involved between 20 and 526 participants, with five studies with >100 participants
 - Seven studies reported industry funding

Aminoglycoside studies

| First Author, Year | Industry funded | Number of patients | Antibiotic |
|---------------------|-----------------|--------------------|--|
| Pajot (2015) | No | 39 | Amikacin (given in combination with imipenem) |
| Duszynska (2013) | No* | 63 | Amikacin |
| Heintz (2011) | NR | 33 | Amikacin, gentamicin, streptomycin or tobramycin |
| Burkhart (2006) | No | 33 | Tobramycin |
| Sato (2006) | NR | 174 | Arbekacin |
| Mouton (2005) | NR | 13 | Tobramycin |
| Zelenitsky (2003) | NR | 20+16* | Gentamicin, tobramycin or ciprofloxacin* |
| Smith (2001) | NR | 23 | Tobramycin |
| Tod (1999) | NR | 81 | Isepamicin |
| Kashuba (1999) | Yes | 78 | Gentamicin or tobramycin |
| Moore (1987) | NR | 236 | Gentamicin, tobramycin, or amikacin |
| Deziel-Evans (1986) | NR | 45 | Amikacin, tobramycin, gentamicin) |

*PK parameters for aminoglycosides and ciprofloxacin analysed together

Beta-lactam studies

| First Author, Year | Industry funded | Number of patients | Antibiotic |
|-------------------------|-----------------|--------------------|---|
| Bhavnani (2015) | Yes | 526 | Ceftaroline fosamil |
| Pajot (2015) | No | 39 | Imipenem (given in combination with amikacin) |
| Muller (2014) | Yes | 243-251* | Ceftobiprole |
| Bhavnani (2013) | Yes | 124 | Ceftaroline fosamil |
| Muller (2013) | Yes | 154 | Ceftazidime |
| Narawadeeniamhun (2012) | No | 28 | Cefoperazone/sulbactam |
| Zhou (2011) | No | 45 | Meropenem |
| Kimko (2009) | Yes | 309 | Ceftobiprole |
| Li (2005) | Yes | 94 | piperacillin/ tazobactam |
| Sadaba (2004) | NR | 87 | Ceftriaxone, cefepime or piperacillin |
| Tam (2002) | Yes | 20 | Cefepime |
| Smith (2001) | NR | 68 | Aztreonam |
| Munzenberger (1993) | NR | 20 | Ceftazidime |

*Number of patients in different analyses varied

Selection bias

- There may be patient characteristics that affect the availability of PK parameters and MICs for pathogens and which affect outcomes
- None of the identified studies compared baseline features and outcomes between patients included in the PK-PD analysis and other eligible patients
- *Studies should compare features and outcomes of patients included in the PK-PD analysis (because there is data for PK parameters and MICs for pathogens) and other eligible patients (same infection, same pathogen, same antibiotic but for some reason do not have PK data or MICs of pathogens) to ensure that there are no significant differences*

Homogeneity of population- Aminoglycosides

| First Author, Year | Type of Infection | Single infection | Single pathogen |
|---------------------------|------------------------------|-------------------------|------------------------|
| Pajot (2015) | Pulmonary/ Respiratory Tract | Yes | No |
| Duszynska (2013) | Bloodstream | No | No |
| Heintz (2011) | Bloodstream | No | No |
| Burkhart (2006) | Pulmonary/ Respiratory Tract | Yes | Yes |
| Sato (2006) | Multiple | No | Yes |
| Mouton (2005) | Pulmonary/ Respiratory Tract | Yes | Yes |
| Zelenitsky (2003) | Multiple | No | Yes |
| Smith (2001) | Multiple | No | No |
| Tod (1999) | Pulmonary/ Respiratory Tract | Yes | No |
| Kashuba (1999) | Pulmonary/ Respiratory Tract | Yes | No |
| Moore (1987) | Multiple | No | No |
| Deziel-Evans (1986) | Multiple | No | No |

NB Bloodstream infections included septicæmia and bacteraemia but were not considered a single type of infection. Pulmonary/respiratory tract infections included pneumonia, LRTIs and pulmonary infections and were considered a single type of infection. Skin and skin structure infections were not considered a single type of infection. Intra-abdominal infections were not considered a single type of infection.

Homogeneity of population- Beta-lactams

| First Author, Year | Type of Infection | Single infection | Single pathogen |
|-------------------------|------------------------------------|------------------|-----------------|
| Bhavnani (2015) | Skin and skin structure infections | No | Yes/No* |
| Pajot (2015) | Pulmonary/ Respiratory Tract | Yes | No |
| Muller (2014) | Pulmonary/ Respiratory Tract | Yes | No |
| Bhavnani (2013) | Pulmonary/ Respiratory Tract | Yes | No |
| Muller (2013) | Pulmonary/ Respiratory Tract | Yes | No |
| Narawadeeniamhun (2012) | Pulmonary/ Respiratory Tract | Yes** | No |
| Zhou (2011) | Pulmonary/ Respiratory Tract | Yes | No |
| Kimko (2009) | Skin and skin structure infections | No | No |
| McKinnon (2008) | Multiple | No | No |
| Li (2005) | Intra-abdominal infections | No | No |
| Sadaba (2004) | Multiple | No | No |
| Tam (2002) | Multiple | No | No |
| Smith (2001) | Multiple | No | No |
| Munzenberger (1993) | Pulmonary/ Respiratory Tract | Yes | Yes*** |

*A separate PK-PD analysis was performed for the subgroup of patients with *S. aureus* isolated at baseline (n=423) **Some patients had co-infections, although PK-PD analysis was only performed for the pulmonary/respiratory tract infection ***Although *P. aeruginosa* was considered the major respiratory isolate, *Pseudomonas cepacia* or *Staphylococcus aureus* was also isolated from 11 of the 20 patients

Homogeneity of population

- Few studies were performed on patients with one infection caused by a single pathogen
 - 2 aminoglycoside studies
 - 1 beta-lactam study
- Grouping multiple infections and pathogens may obscure potential relationships between PDI and outcome
- *Studies should try and ensure that the population is as homogeneous as possible*



Sample size and power calculations

- 10/12 aminoglycoside studies and 8/13 beta-lactam studies had fewer than 100 participants
- Failure rates ranged from 8% to 43% in the aminoglycoside papers and 4.3% to 57% in the beta-lactam papers
- Few studies perform a sample size calculation
- Without a range of PDI exposures and a range of outcomes PDI-outcome relationships may be obscured
- *Power calculations should be performed, the precise methods need further discussion*

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Determination of PDIs- Aminoglycosides

| First Author, Year | Concurrent antibiotics | Number of blood samples taken per patient who had samples taken | Proportion of patients with blood samples | Free concentrations measured? | Protein binding adjusted for? |
|---------------------|------------------------|---|---|-------------------------------|-------------------------------|
| Pajot (2015) | Yes | 5 | 100% | No | Yes |
| Duszynska (2013) | Yes | ≥1 | 100% | No | No |
| Heintz (2011) | Yes | 1 | 100% | No | No |
| Burkhart (2006) | Yes | 7 or 8 | 100% | No | No |
| Sato (2006) | No/Yes* | ≥1 | 100% | No | No** |
| Mouton (2005) | Yes | 15 | 100% | No | Yes |
| Zelenitsky (2003) | Yes | 2 | 100% | No | Yes |
| Smith (2001) | Yes | ~8 | 70% | No | No |
| Tod (1999) | Yes | 1-18 | 100% | No | No |
| Kashuba (1999) | Yes | ≥3 | 100% | No | No |
| Moore (1987) | Yes | 2 on alternate days during therapy | 100% | No | No |
| Deziel-Evans (1986) | NR | ≥1 | 100% | No | No |

*Analysis split according to whether patients received monotherapy or combination therapy **the PDIs were calculated on the basis of the total concentrations of arbekacin because the protein binding rate of arbekacin is reportedly as low as 3 to 12%

Determination of PDIs- Beta-lactams

| First Author, Year | Concurrent antibiotics | Number of blood samples taken per patient who had samples taken | Proportion of patients with blood samples measured? | Free concentrations measured? | Protein binding adjusted for? |
|---------------------------|-------------------------------|--|--|--------------------------------------|--------------------------------------|
| Bhavnani (2015) | No | ≤4-5 | 20% | No | Yes |
| Pajot (2015) | Yes | 6 | 100% | No | Yes |
| Muller (2014) | Yes | ≥1 | Unclear | No | Yes |
| Bhavnani (2013) | No | 4 | 23% | No | Yes |
| Muller (2013) | Yes | ≥1 | 49% | No | Yes |
| Narawadeeniamhun (2012) | Yes | 4 | 100% | No | Yes |
| Zhou (2011) | Unclear | 10 | 100% | No | No |
| Kimko (2009) | Unclear | NR | NR | No | Yes |
| Li (2005) | NR | 3-5 | Unclear | No | Yes |
| Sadaba (2004) | Yes | 3-4 | 100% | No | Yes |
| Tam (2002) | Yes | 3 | 100% | No | Yes |
| Smith (2001) | Yes | 8 | 35% | No | No |
| Munzenberger (1993) | No | 9 | 100% | No | No |

Determination of PDIs

- To determine whether there is an association between PDI and outcome PDIs need to be measured accurately
- Many studies allowed concurrent antibiotics
- No study measured free (unbound) concentrations
- Many studies did adjust for protein binding. However, is adjusting for protein binding using a flat rate appropriate, as protein binding may vary?



Determination of PDIs

- *If free concentrations of antibiotics are important, then they should be measured rather than adjusting for protein binding using a flat rate to allow for the fact that protein binding may vary*
- *MICs of baseline pathogens only should be considered*



Outcomes- Aminoglycosides

| First Author, Year | Outcome (s) | Outcome timing |
|---------------------|--|---|
| Pajot (2015) | Microbiological success. Secondary outcomes: 28 day mortality; SOFA score>3 at day 7; duration of mechanical ventilation from day 1; and total duration of mechanical ventilation during ICU stay. | During therapy (day 3)(microbiological success); Secondary outcomes: 28 day mortality; SOFA score>3 at day 7; duration of mechanical ventilation from day 1; and total duration of mechanical ventilation during ICU stay. |
| Duszynska (2013) | Clinical efficacy; microbiological response; development of acute kidney injury | Clinical efficacy and microbiological response: End of therapy (day 7- amikacin administered for a maximum of 5 to 7 days); Acute kidney injury: Any time during amikacin therapy until 72 hours after drug discontinuation). |
| Heintz (2011) | All cause 30-day mortality | 30-days |
| Burkhart (2006) | Proportional improvement in forced expiratory volume in 1s (FEV1 % pred.) expressed as a percentage of the predicted normal values for age, sex and height; change in inflammatory parameters (CRP, leukocyte count and IgG) | End of therapy |
| Sato (2006) | Clinical cure/improvement | End of therapy |
| Mouton (2005) | Relative improvement in: Forced expiratory volume (FEV); Forced vital capacity (FVC). (FEV on day 0-FEV1 on day 9, 10 or 11) divided by FEV1 on day 0 | During therapy (day 9, 10 or 11) |
| Zelensitsky (2003) | Clinical response | Until discharge or for 30 days, whichever was less |
| Smith (2001) | Clinical cure | Not reported |
| Tod (1999) | Clinical efficacy | 7 days after end of therapy |
| Kashuba (1999) | Time to temperature resolution; Time to leukocyte count resolution | During therapy (day 7 chosen to determine breakpoints) |
| Moore (1987) | Clinical response | Not reported |
| Deziel-Evans (1986) | Therapeutic cure (negative cultures or the disappearance of clinical or radiologic signs of infection) | Not reported |

Outcomes- Beta-lactams

| First Author, Year | Outcome (s) | Outcome timing |
|-------------------------|---|--|
| Bhavnani (2015) | Clinical response; microbiological response | Test of cure (day 8 to 14-15) |
| Pajot (2015) | Microbiological success. Secondary outcomes: 28 day mortality; SOFA score >3 at day 7; duration of mechanical ventilation from day 1; and total duration of mechanical ventilation during ICU stay. | During therapy (day 3)(microbiological success) |
| Muller (2014) | Microbiological cure; Clinical cure | End of therapy (microbiological cure) and Test of cure (clinical cure) |
| Bhavnani (2013) | Clinical response; Microbiological response | Test of cure (8 to 15 days post therapy) |
| Muller (2013) | Microbiological eradication; Clinical cure | End of therapy or test of cure |
| Narawadeeniamhun (2012) | Clinical response; Microbiological response | End of treatment |
| Zhou (2011) | Clinical response, Bacteriological response | 1 week after meropenem withdrawal (clinical response); 1 day after cessation of treatment (bacteriological response) |
| Kimko (2009) | Clinical cure | Test of cure: 7 to 14 days after end of therapy |
| Li (2005) | Clinical response; microbiological response | NR |
| Sadaba (2004) | Clinical recovery, Bacterial response | NR |
| Tam (2002) | Microbiological success | End of therapy or discharge, whichever was earlier |
| Smith (2001) | Clinical cure | NR |
| Munzenberger (1993) | Clinical outcomes (Brasfield score, pulmonary function score, clinical score, general score) | Day 2, 7 (during treatment) and 14 (end of treatment) |

Outcomes

- Outcomes analysed generally included clinical response and microbiological response
 - Of the 12 studies, 3 aminoglycoside studies assessed microbiological response and 9 studies assessed some form of clinical response. Only one study did not report either of these outcomes (30-day mortality, Heintz et al.)
 - Of the 13 studies, 10 beta-lactam studies assessed microbiological response and 11 beta-lactam studies assessed clinical response
- The timing of outcome assessment varied, with some studies assessing outcomes at the end of therapy, and other studies assessing outcomes at the test of cure (where reported)
- ***There should be a standardised outcome that all papers should report (for example microbiological cure at the end of therapy?)***

Covariates analysed- aminoglycosides

| First Author, Year | Covariates (in addition to PDIs) |
|---------------------|--|
| Pajot (2015) | None (no multivariate analysis performed) |
| Duszynska (2013) | None (no multivariate analysis performed) |
| Heintz (2011) | None |
| Burkhart (2006) | Unclear, but ICU admission, diabetes, and lactose-negative gram negative rod all significantly associated with outcome in multivariate analysis |
| Sato (2006) | Sex, combination therapy, disease type, use of antifungals, age, body weight, creatinine clearance, MIC, pharmacokinetic parameters (Cmax, Cmin, AUC0-24, cumulative AUC, first Cmax) |
| Mouton (2005) | Age* |
| Zelensitsky (2003) | Patient demographics, medical history, clinical status, antibiotic therapy |
| Smith (2001) | Treatment group, site of infection, organism, sensitivity, MIC, PK parameters (AUC24, Cmax, Cmin) |
| Tod (1999) | Severity scores, age, combination with a glycopeptide, etc. |
| Kashuba (1999) | Age, sex, weight, presence of shock, presence of comorbid conditions, estimated prognosis, intensive care unit admission, laboratory test results, fluid intake and output, albumin and nutritional status, organism culture and organism susceptibility data, concurrent pharmacotherapy, concurrent antibiotic therapy, type and duration of aminoglycoside therapy, total aminoglycoside dose, aminoglycoside dose/total and ideal body weight. |
| Moore (1987) | age, sex, life expectancy, shock, initial leukocyte count, diabetes, initial temperature, initial systolic BP, initial creatinine clearance, initial blood urea nitrogen, renal function decline, infection site, antibiotic, organism, maximal peak, mean peak, maximal trough, mean trough, maximal geometric mean, mean geometric mean, MIC |
| Deziel-Evans (1986) | None |

Covariates analysed- beta-lactams

| First Author, Year | Covariates (in addition to PDIs) |
|---------------------------|--|
| Bhavnani (2015) | Age, BMI, disease severity score, MIC and weight |
| Pajot (2015) | None (no multivariate analysis performed) |
| Muller (2014) | Volume of distribution at steady state, APACHE II score, age, sex, body weight, BMI, height, albumin, white-blood-cell count, creatinine clearance, creatinine, CRP, systemic inflammatory response syndrome, combination therapy with an antipseudomonal antibiotic, infection-type (VAP/non-VAP) |
| Bhavnani (2013) | None |
| Muller (2013) | Unclear |
| Narawadeeniamhun (2012) | None (no multivariate analysis performed) |
| Zhou (2011) | Unclear |
| Kimko (2009) | None |
| Li (2005) | None |
| Sadaba (2004) | Treatment duration, surgery, and concomitant antibiotics |
| Tam (2002) | Not explicitly reported. Baseline APACHE II score, MIC analysed |
| Smith (2001) | Treatment group, site of infection, organism, sensitivity, MIC, PK parameters (AUC ₂₄ , C _{max} , C _{min}) |
| Munzenberger (1993) | None |

Confounding

- Confounding clinical factors may explain the association between response and PDIs
- Potential confounders may vary with infection
- *There should be a standardised list of covariates that should be looked at to see if they are associated with outcome*
 - *For example severity of illness*
 - *Presence of co-morbidities*



Statistical analyses: Aminoglycosides

| First Author, Year | Methods used to look at relationship between PDI and outcome |
|---------------------------|---|
| Pajot (2015) | Non-parametric Wilcoxon, Spearman correlation coefficient or Fisher exact test; ROC curve analysis; CART |
| Duszynska (2013) | Chi-square, Fisher's exact test, Student's t test, or Mann-Whitney U test |
| Heintz (2011) | Fisher exact test; multivariate regression analysis |
| Burkhart (2006) | Correlation. FEV1 (%) versus Cmax/MIC and FEV1 (%) versus AUC24/MIC were fitted using a log linear model |
| Sato (2006) | Univariate logistic regression; multivariate logistic regression |
| Mouton (2005) | Hill equation (Emax model). Non parametric correlations. |
| Zelensitsky (2003) | Univariate analyses (students t-test, Mann-Whitney U, Pearson chi-squared or Fisher's exact test); multivariate logistic regression; CART; ROC curve analysis |
| Smith (2001) | CART; logistic regression; nonlinear regression analyses with Hill-type functions; Kruskal-Wallis nonparametric analysis of variance |
| Tod (1999) | Mann-Whitney test; multivariate logistic regression |
| Kashuba (1999) | Univariate Cox proportional model; multivariate Cox proportional model; CART; logistic regression |
| Moore (1987) | Univariate statistic analyses with the non-parametric Wilcoxon rank-sums test; multiple logistic regression |
| Deziel-Evans (1986) | Point-biserial correlation coefficient |

Statistical analyses: Beta-lactams

| First Author, Year | Methods used to look at relationship between PDI and outcome |
|-------------------------|--|
| Bhavnani (2015) | CART; univariate analyses (Pearson chi square test or Fisher's exact test, logistic regression); multivariable logistic regression |
| Pajot (2015) | Non-parametric Wilcoxon, Spearman correlation coefficient or Fisher exact test; ROC curve analysis; CART |
| Muller (2014) | CART, Fisher's exact test, multiple logistic regression |
| Bhavnani (2013) | CART; univariate analyses (Pearson chi square test or Fisher's exact test, logistic regression) |
| Muller (2013) | CART, Fisher exact test, logistic regression, multivariate logistic regression, Emax model |
| Narawadeeniamhun (2012) | λ^2 test or Fisher exact test |
| Zhou (2011) | t-tests, Mann-Whitney U-test, Chi-squared test. Binary logistic regression. ROC curves |
| Kimko (2009) | Univariable (Pearson's chi-squared), CART, logistic regression |
| Li (2005) | CART, Fisher's exact test |
| Sadaba (2004) | χ^2 , ANOVA test, Fisher's Exact Test, non-parametrical tests (Mann-Whitney U-test or Kruskal-Wallis test), multivariate analysis |
| Tam (2002) | CART, Fisher's exact test, univariate logistic regression |
| Smith (2001) | CART; logistic regression; nonlinear regression analyses with Hill-type functions; Kruskal-Wallis nonparametric analysis of variance |
| Munzenberger (1993) | Pearson product-moment correlation coefficient |

Statistical analysis

- Multiple regression (e.g. logistic regression or proportional hazards regression) is commonly used to identify PDI parameters that predict response.
- Power calculations could be performed for the logistic regression, though are seldom reported.
- Specific regression models are usually assumed
- An attractive alternative may be flexible approaches, such as fractional polynomials or spline-based methods, to characterize the relationship between PD parameters and response probabilities.



Statistical analysis

- CART analysis is a data-mining technique that selects a cut-point (threshold) in the distribution of the predictor.
- The threshold is selected by trying out all breakpoints in the predictor and choosing the one that fulfils a pre-specified criterion (which is rarely reported in these studies).
- It is not clear to us that a CART breakpoint will be clinically useful.
 - Prespecifying important response rates (reaching some consensus in the field on what these might be) and determining PD parameters that predict these might be a more meaningful approach.
- Data-determined thresholds are very specific to the data set in hand. Validation studies are required to evaluate thresholds, though are seldom undertaken.
- *The use of larger sample sizes and cross-validation would help in this regard.*

Statistical analysis

- *All PK-PD studies should plot PDI vs. probability of outcome or amount of improvement so that individuals can determine their own breakpoints depending on what probability of cure they think is appropriate for their patients*
- *There should be a pre-defined statistical analysis plan.*

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Statistical analyses: PDI vs outcome plotted in some form

Aminoglycosides

| First Author, Year | PDI vs. outcome plotted? |
|---------------------|--------------------------|
| Pajot (2015) | Yes |
| Duszynska (2013) | Yes |
| Heintz (2011) | Yes |
| Burkhart (2006) | Yes |
| Sato (2006) | Yes |
| Mouton (2005) | Yes |
| Zelensitsky (2003) | Yes |
| Smith (2001) | Yes |
| Tod (1999) | No |
| Kashuba (1999) | Yes |
| Moore (1987) | Yes |
| Deziel-Evans (1986) | No* |

Beta-lactams

| First Author, Year | PDI vs. outcome plotted? |
|-------------------------|--------------------------|
| Bhavnani (2015) | Yes |
| Pajot (2015) | Yes |
| Muller (2014) | Yes |
| Bhavnani (2013) | No |
| Muller (2013) | Yes |
| Narawadeeniamhun (2012) | No |
| Zhou (2011) | No |
| Kimko (2009) | Yes |
| Li (2005) | No |
| Sadaba (2004) | No |
| Tam (2002) | Yes |
| Smith (2001) | Yes |
| Munzenberger (1993) | No |

NB studies which plotted the distribution of PDIs with success/failure also included.

*Although not plotted, this study presented a table detailing the relation between cure and values for pharmacokinetic indices

Recommendations

- *Studies should compare features and outcomes of patients included in the PK-PD analysis (because there is data for PK parameters and MICs for pathogens) and other eligible patients (same infection, same pathogen, same antibiotic but for some reason do not have PK data or MICs of pathogens) to ensure that there are no significant differences*
- *Studies should try and ensure that the population is as homogeneous as possible*
- *Power calculations should be performed*
- *If free concentrations of antibiotics are important, then they should be measured rather than adjusting for protein binding using a flat rate to allow for the fact that protein binding may vary*
- *MICs of baseline pathogens should be considered*
- *There should be a standardised outcome that all papers should report (for example microbiological cure at the end of therapy?)*

Recommendations

- *There should be a standardised list of covariates that should be assessed to see if they are associated with outcome*
 - *For example severity of illness at diagnosis*
 - *Presence of co-morbidities*
- *All PK-PD studies should plot PDI vs. probability of outcome or amount of improvement so that individuals can determine their own breakpoints depending on what probability of cure they think is appropriate for their patients*
- *There should be a pre-defined statistical analysis plan*
- *The most appropriate way of statistically analysing the relationship between PDIs and outcomes needs to be further investigated*