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Application of therapeutic drug monitoring to the treatment of bacterial central nervous system infection: a scoping review

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Background: Bacterial central nervous system (CNS) infection is challenging to treat and carries high risk of recurrence, morbidity, and mortality. Low CNS penetration of antibiotics may contribute to poor clinical outcomes from bacterial CNS infections. The current application of therapeutic drug monitoring (TDM) to management of bacterial CNS infection was reviewed.

Methods: Studies were included if they described adults treated for a suspected/confirmed bacterial CNS infection and had antibiotic drug concentration(s) determined that affected individual treatment.

Results: One-hundred-and-thirty-six citations were retrieved. Seventeen manuscripts were included describing management of 68 patients. TDM for vancomycin (58/68) and the beta-lactams (29/68) was most common. Timing of clinical sampling varied widely between studies and across different antibiotics. Methods for setting individual PK-PD targets, determining parameters and making treatment changes varied widely and were sometimes unclear.

Discussion: Despite increasing observational data showing low CNS penetration of various antibiotics, there are few clinical studies describing practical implementation of TDM in management of CNS infection. Lack of consensus around clinically relevant CSF PK-PD targets and protocols for dose-adjustment may contribute. Standardised investigation of TDM as a tool to improve treatment is required, especially as innovative drug concentration-sensing and PK-PD modelling technologies are emerging. Data generated at different centres offering TDM should be open access and aggregated to enrich understanding and optimize application.

Background

Evasion of the blood–brain barrier and multiplication of bacteria in the brain, spinal cord or meninges, can cause a diverse range of clinical conditions termed bacterial infections of the central nervous system (CNS). Community acquired meningitis and/or encephalitis most commonly occurs as a result of haematogenous spread,[1] whereas nosocomial bacterial meningitis (NBM) occurs following instrumentation, surgery or trauma to the CNS, and may complicate up to 22% of neurosurgical procedures.[2,3] These conditions carry a high risk of infection recurrence, morbidity (including neurological sequalae) and mortality.

Medical management is usually with systemic antimicrobial therapy. However, there is increasing concern that the penetration of commonly used antimicrobials into CSF and brain parenchyma may be inadequate.[4–6] Studies of vancomycin,[7] meropenem,[8,9] ceftazidime[9] and ceftriaxone[10] have shown that significant numbers of patients may not reach pharmacokinetic-pharmacodynamic

(PK-PD) targets in CSF, particularly when treating organisms with higher MICs. Additionally, there is likely significant inter- and intra-individual variation in blood and CSF antimicrobial concentration, with potential clinical covariates including comorbidities, concomitant medications, age, weight, renal replacement therapy, sepsis and vascular permeability, fluid balance and albumin status.[11] The management of bacterial CNS infection is also complicated by difficulties in obtaining samples for microbiological analysis, potential involvement of prosthetic material in NBM, and a high incidence of resistant organisms.[12] This group of patients are therefore highly likely to benefit from an individualized approach to antimicrobial treatment.

TDM is the practice of measuring a drug concentration with the intention of modifying the dose to achieve a set target, or to prompt some other change in clinical management. It is commonly used for drugs with a narrow therapeutic drug index, to assess the effect of a drug–drug interaction or when patients are at high risk of PK-PD variation. It may be especially useful for antimicrobials, due to a strong relationship between drug concentration and response and the lack of other immediate markers of efficacy. For TDM to work in practice, patients who may benefit must be identified, and relevant, appropriately timed samples obtained, handled, then analysed in a timely fashion using a validated drug concentration assay. Results should be interpreted in the knowledge of the sample collection time, drug dose and administration time, using a nomogram or PK-PD model to determine individual PD parameters. If a dose adjustment is made, the process can be repeated to ensure the modification was successful. Figure 1 outlines steps that are typically required to perform antimicrobial TDM and optimize antimicrobial dosing.

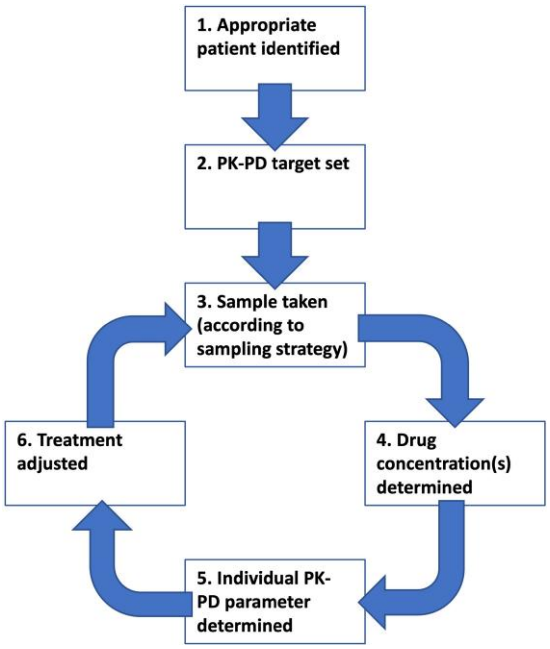

Figure 1. Typical steps used to perform antimicrobial TDM and optimize treatment. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Infectious Diseases Society of America (IDSA) guidelines include a recommendation for CSF TDM in individuals who are receiving intraventricular (ITV) administration of antimicrobials [target inhibitory quotient (trough concentration/MIC for agent of infecting organism) >10–20] [13] However, there is little such guidance for patients who are being treated systemically.

Objectives

The objective of this scoping review was to characterize the current application of TDM in the individual management of patients with bacterial CNS infection, including monitoring of blood and/or CSF compartments.

Methods

A literature search in Medline was conducted. The search strategy was constructed by P.A., R.W. and K.W. from combinations of medical subject headings and keywords (see Supplementary material 1, available as Supplementary data at *JAC* Online). Results were imported into Covidence software and deduplicated.[14] P.A. and R.W. examined citations at a title/abstract level for potential inclusion, then examined each study at a full-text level for inclusion. Discrepancies were resolved by discussion until consensus was reached. Studies for which eligibility could not be determined on the basis of the abstract were obtained in full for further assessment. Citation lists from these studies, as well as those from all review articles identified by the original search, were also reviewed.

Studies were included if they were listed before 21 February 2022 (no previous time limit set) and fulfilled the following criteria: (i) described one or more adult who was being treated for a suspected or confirmed bacterial infection of the CNS; (ii) there was determination of antimicrobial drug concentration from clinical specimen(s) and (iii) there was adjustment of individual treatment based on these results (or an active decision to maintain the same treatment). All types of clinical study design were eligible. Studies were excluded if they only included children or individuals being managed for mycobacterial infections or were not English language.

Data were collected from included studies according to a predetermined proforma designed by P.A., R.W. and K.W. This included 'clinical details' (diagnosis, culture and sensitivity results, antimicrobial treatments, doses), 'details of drug-level determination' (sample types and handling, sample timing in relation to drug administration, type of assay), 'PK-PD target and individual PD parameter determination' (target, nomogram or model used to assess PD parameter) and 'treatment adjustments' (changes to management, methods used for deciding dose adjustment, clinical outcome). The quality and risk of bias among papers was not formally assessed and quantified because this was a scoping review that did not have a specific predetermined measurable outcome.[15] For studies that described more than one case, data were collected on an individual patient basis where possible.

Results

Study characteristics

The database search retrieved 136 citations, of which 109 were excluded based on titles and abstracts. Twenty-seven full texts were therefore assessed for eligibility, of which 10 were included and 17 were excluded. The commonest reason for exclusion at full-text review was 'TDM used to observe only, no change to individual management, or no active decision to continue' (12/17).

Seven further studies were identified through review of citations and subsequently included. A consort diagram is shown in Supplementary material 2. In total, 12 case reports and five retrospective observational studies were included, which were published between 1981 and 2021. These described 68 patients who were being treated for suspected/confirmed bacterial CNS infection and in whom drug concentration determination was used to individualize treatment.

Clinical details

Where a specific clinical diagnosis was given, this was most commonly ventriculitis (36/51 cases) followed by meningitis (12/51, of which three were specified to be post-neurosurgical) and cerebral abscess (3/51). Causative organisms were identified in 18/68 cases, including coagulase negative *Staphylococci* (7/18), gram-negative bacilli (5/18, and *Staphylococcus aureus* (3/18). Antibiotic MICs were reported for infecting organisms in 12/18 cases. The reason for initiation of TDM was persistent CSF culture positivity in 3/68 cases, lack of clinical improvement in 2/68, MDR infection in 1/68 and suspected drug toxicity in 1/68. In 43/68 cases (described in three studies[16–18]), TDM was used because it is part of local standard-of-care and in 18/68 cases the reason for initiation of TDM was not stated. No studies included a control group of individuals who did not receive TDM.

Antibiotic TDM

Most studies described the management of individuals with CNS infections using CSF and/or blood TDM of vancomycin,[16,18–29] often alongside TDM of other co-administered antibiotics including meropenem,[16,18,27,29] piperacillin/tazobactam,[26] gentamicin,[21] levofloxacin[26] and ciprofloxacin.[26] Other studies described CSF and/or blood TDM of linezolid,[17,30] flucloxacillin,[31] colistin[32] and ceftazidime/avibactam.[33] Study methods, including those relating to drug-level determination, PK-PD targets, PD parameter determination and individual treatment adjustments are summarized in Table S1. A narrative summary for the most commonly monitored antibiotics is provided next.

Vancomycin

Vancomycin was monitored in 12 studies (58 individuals) published between 1981 and 2021. Vancomycin concentration was determined by immunoassay (7/12), microbiologic assay (1/12), HPLC (2/12) and 2/12 not stated. Assay limits of detection and/or quantification were reported in 4/12 studies. CSF sampling occurred in 10/12 studies. In CSF, PK-PD targets included T > MIC (3/10), inhibitory quotient (1/10), peak concentration (1/10), trough concentration (1/10), time above 1 mg/L (1/10) and was not specified in 3/10 studies. The timing of CSF sampling in relation to drug dosing varied widely between studies but included peak (5/10), random or midpoint (4/10) and trough (5/10). Individual CSF PK parameter determination was estimated by non-linear regression (2/10), directly observed (5/10) or not stated (3/10). Blood, serum or plasma sampling occurred in 10/12 studies. In blood, PK-PD targets included trough (2/10), peak and trough (1/10), AUC-based (2/10) and was not specified in 5/10 studies. The timing of blood sampling in relation to drug dosing included peak (3/10), midpoint or random (5/10) and trough (6/10). Individual blood PK parameter determination was estimated by non-linear regression (1/10), Bayes (1/10), directly observed (4/10) or not stated 4/10. Targets were set based on the MIC of confirmed infecting organisms in 2/12 studies, estimated (species) MIC in 2/12 studies, population target in 5/12 studies and 3/12 not stated. The most common treatment adjustments resulting from vancomycin TDM were changes to the dose or dose-interval of antimicrobials (occurring in 9/12 studies). This was done according to clinical decision support software (1/12) or calculated from an individual estimate of PK parameters (2/12), but most often the specific framework for making dose adjustments was not reported (9/12). Other changes to individual case management were the administration of vancomycin via the ITV route (4/12) and the administration of an additional/different antimicrobial (2/12). Clinical outcome was reported in 9/12 studies and was positive in 5/9 studies.

Beta-lactam antibiotics

Beta-lactams were monitored in six studies (29 individuals) published between 2012 and 2021. The beta-lactams included were ceftazidime(-avibactam) (1/6), flucloxacillin (1/6), meropenem (3/6) and piperacillin(-tazobactam) (1/6). Ceftazidime and flucloxacillin were administered as single agents, and meropenem and piperacillin were administered alongside other antibacterials. Beta-lactam and beta-lactamase inhibitor (avibactam only) concentrations were determined by HPLC (5/6) or HPLC–MS/MS (1/6). CSF and blood sampling occurred in all studies. Targets in the CSF were T > MIC (1/6), 50%T > MIC (1/6), 100%T > MIC (2/6), maintain >2 mg/L (1/6) and not stated (1/6). Targets in the plasma or serum were identical except in one study investigating continuous infusions that used a higher target. In 5/6 studies, a decision was made to adjust the dose, however, the method of dose adjustment was not stated. For the remaining study, an active decision was made not to change the dose.

Discussion

In recent years, many observational PK-PD studies have shown low and/or variable penetration of many antibiotics into CSF. Several authors therefore recommended the use of TDM to optimize treatment for bacterial CNS infections, and IDSA guidelines include this approach for patients who are being treated via the ITV route.[13] Despite this, the present study found very few reports of patients with bacterial CNS infections in whom TDM lead to any adjustment of individual treatment.

Included studies focussed on TDM of vancomycin and the beta-lactams when given systemically. Methods varied significantly in terms of individual PK-PD targets, sampling strategies, assays for drug concentration analysis, determination of individual PK-PD parameters, protocols for dose adjustment or other treatment changes and clinical outcome reporting. Some studies did not give clinical criteria for TDM initiation, and none included a control group of individuals who did not receive TDM. Therefore, there is a lack of high-quality evidence to inform the optimal use of TDM in patients with bacterial CNS infections and/or design interventional studies.

Challenges to implementing TDM to individualize treatment of CNS infection may include the following:

First, while CNS infections and their treatments are heterogenous, many existing observational studies assessing antimicrobial concentration in CNS have been small with restrictive inclusion criteria. Covariates that may be associated with variable or suboptimal penetration are not robustly assessed, and individual PK-PD parameters are rarely linked to outcome data. Identifying patients who are most likely to benefit from TDM, setting clinically relevant PK-PD targets and choosing appropriate (externally validated) models for assessment of individual PK-PD parameters and adjusting doses is challenging. The present review identified several studies where these details relating to TDM were not reported. Larger studies that describe real-life PK-PD in a broad range of CNS-infected individuals are required. Anecdotally, patients with bacterial CNS infections in many centres across the UK and further afield receive TDM as part of their standard-of-care, during which a wealth of pathological and clinical data (including treatment outcome) is routinely collected but infrequently published in peer-reviewed literature. Therefore, the standardized observation, reporting and cross-site aggregation of this data may be an efficient way to enrich understanding of real-life CSF PK-PD and improve delivery of TDM.

Second, optimal sampling strategies for patients will vary according to the antibiotic being used, its dose schedule and route-of-administration, the selected PK-PD target and the proposed method for determining individual PK-PD parameters. Furthermore, collection of CSF requires expertise in the safe manipulation of ventricular or spinal drainage systems (or lumbar puncture). Therefore, a sparse or opportunistic sampling strategy may be necessary for this sample type. Bayesian dosing software may be used to determine optimal sample timing and/or assess target attainment using drug concentration determinations made at a small number of timepoints. The present review identified only two studies using a Bayesian forecasting approach, in which the blood compartment was monitored (and not CSF).

Third, microbial culture of CSF and/or surgical specimens is slow and insensitive, particularly if samples are taken after antimicrobials have already been initiated. Therefore, patients are often treated empirically, and individual PK-PD targets are based on aggregate species MIC data or serum targets (which are not necessarily appropriate for assessing adequacy of exposure in the CSF compartment). Advances in molecular diagnostics including multiplexed qPCR assays, 16S ribosomal RNA assays and whole-genome sequencing may improve microbiological diagnosis and allow rapid genotypic resistance profiling. Furthermore, novel *in vivo* methods for estimation of antimicrobial PK-PD may be useful.

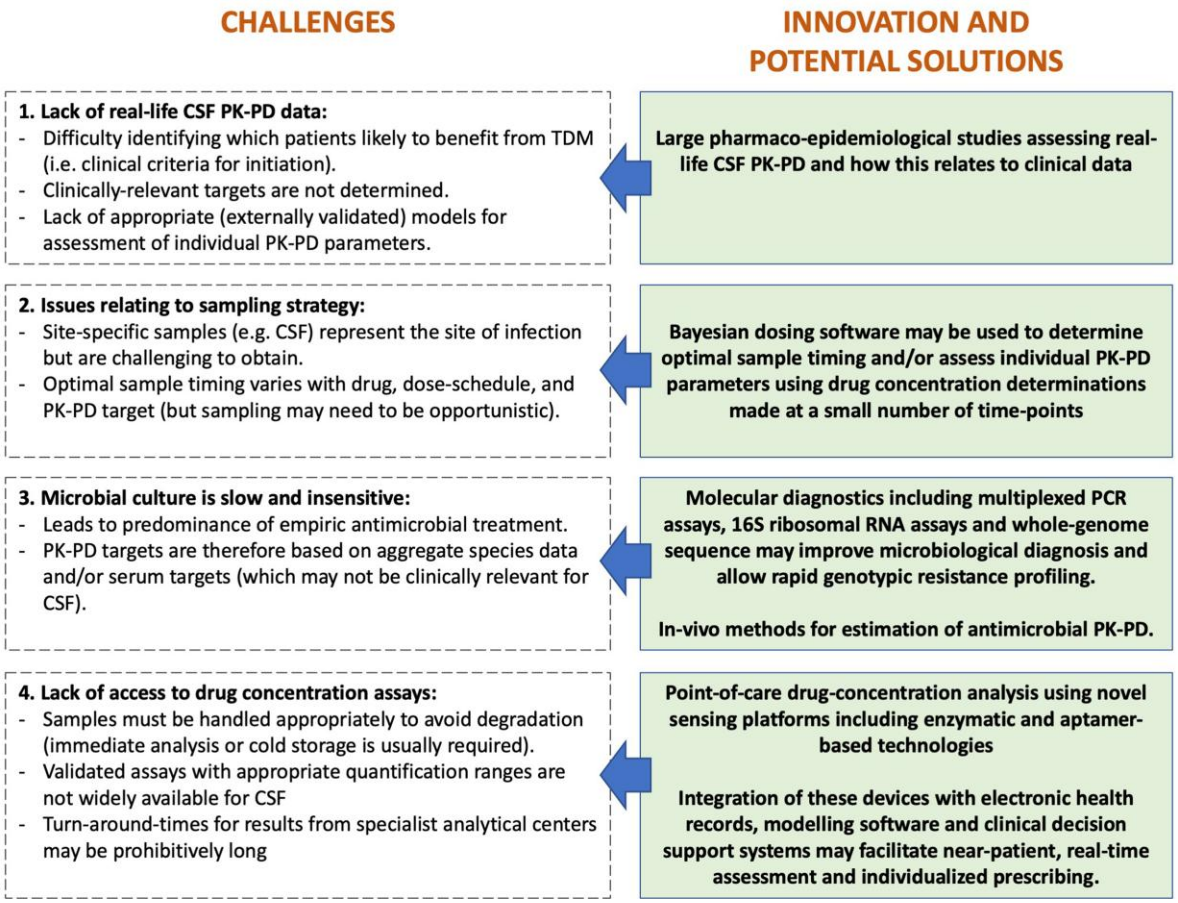

Figure 2. Challenges in delivery of TDM for bacterial CNS infection and potential solutions through innovation and technology. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Fourth, drug concentration assays with appropriate quantification ranges that are validated for CSF may not be widely available and turn-around times of results may be prohibitively long for clinical practice. Studies included in the present review only used laboratory-based assays, and patients were largely recruited at centres offering specialist TDM services. However, novel, point-of-care methods for rapid or real-time detection and monitoring of antibiotic concentrations are in development and could easily be adapted for CSF. These include aptamer, enzymatic and other direct electrochemical methods for antimicrobial sensing.[34–38] These technologies have the potential to be applied in non-specialist settings, where there is limited access to traditional laboratory services. Furthermore, diagnostic devices that are integrated with electronic health records, modelling software and clinical decision support systems would facilitate near-patient, real-time assessment of antibiotic target attainment and individualized prescribing. Challenges in delivery of TDM for bacterial CNS infection and potential solutions through innovation and technology are illustrated in Figure 2.

A limitation to this study is its relatively restrictive search strategy for terms relating to TDM (freetext search terms were 'TDM' or 'drug concentration' OR 'drug level' OR 'drug monitoring' OR 'therapeutic concentration' OR 'therapeutic level' or 'therapeutic monitoring'). Some studies fulfilling inclusion criteria may have been missed, for example if their primary focus was not dose optimization or the authors used another description. Despite this, there is undoubtedly a lack of high-quality evidence to inform the optimal use of TDM for bacterial CNS infection. In this condition, low penetration of antibiotics contributes to suboptimal CSF concentrations. Individualized therapy is likely to be beneficial, particularly with the emergence of cases of NBM caused by multidrug resistant organisms.[12] A standardized approach to the investigation of TDM as a tool to improve treatment is therefore required, especially as innovative technologies are emerging to facilitate TDM in CSF.[11,39]

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Transparency declaration

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Author contributions

P.A., R.W., A.H. and T.M.R. conceived and designed the study. P.A., R.W. and K.W. performed the study. P.A., R.W. and K.W. performed data analysis. P.A. and R.W. drafted the manuscript with all authors having significant contribution to revisions and finalizations for submission.

Patient consent statement

Ethical approval was not required for this study.

Supplementary data

Supplementary data at *JAC* Online.

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