Therapeutic drug monitoring in the past 40 years of the Journal of Antimicrobial Chemotherapy

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Since the Journal of Antimicrobial Chemotherapy was first published in 1975, papers addressing therapeutic drug monitoring (TDM) have been a regular feature. Initially they focused on laboratory aspects of drug concentration measurement then they changed more to the application of TDM in a clinical setting. Over its history, the Journal has provided its readership with the latest technological and scientific advances in TDM and has helped to drive changes in TDM that have directly impacted on patient care. These have varied from improvement in the quality of antimicrobial measurements through better identification of dosage regimens and TDM targets that help predict outcome and adverse events. Despite these advances in our understanding of the science and practice of TDM, there remain many areas of uncertainty. As we move into the next 40 years, it is clear that the Journal will continue to provide the readership with the latest science and opinion in this important area.

In the 40 years since the Journal of Antimicrobial Chemotherapy was first published, the papers within it have reflected the cutting edge of therapeutic drug monitoring (TDM) in the field of antimicrobial chemotherapy and provide a fascinating ‘roadmap’ illustrating how the science underpinning it has developed.

While TDM has traditionally been thought of as a process to help reduce the risk of adverse events in patients receiving toxic drugs, increasingly it is being recognized as important for optimizing therapeutic outcomes, either in terms of cure or resistance suppression. However, irrespective of objectives, TDM relies on the rapid, and accurate, determination of drug levels in a patient with adjustment of dose if these are not consistent with the expected, or target, concentration ranges.

In the early years of the Journal, there was a clear focus around practical aspects of TDM and laboratory support for the clinical use of antimicrobials.1 This was largely driven by the increasing use of the aminoglycosides and during the first decade of the Journal’s publication, there were frequent reports of methodological advancement. While early reports addressed developments in bioassays to shorten turnaround times and prevent interference from other agents, new approaches started to be reported within a few years. Initially, these were based around either bacterial enzymes (transferase assay) or growth (bioluminescence), but by the early 1980s immunoassay reports dominated the publications.2 These started with simple descriptions of the methods but very quickly shifted to publications reporting comparisons between the different assay systems as it became clear that these assays were highly specific, accurate and rapid.3 While some of the assays reported in the early 1980s are no longer relevant, those based around homogeneous reactions largely remain in use to the current date. In the main, this change was driven by technological advances and commercial factors, but publications in the Journal highlighting the relative performance of such methods in external quality assessments certainly advanced the withdrawal of those methods that performed poorly.4

During these early years, although there were significant advancements in the technology supporting delivery of TDM services, understanding of the targets and objectives for TDM largely lagged behind. Aminoglycosides had long been known to have the potential for ototoxicity and nephrotoxicity, and during the early years of the Journal there were many studies reporting the incidence of toxicity of aminoglycosides.5 These concerns over toxicity dominated TDM approaches for both aminoglycosides and other less toxic classes of antimicrobials6 and persist to the present day. However, although the first report of once-daily administration of gentamicin appeared in the Journal in 1978,7 it was not really until the late 1990s that TDM objectives became clearer thanks to the increasing volume of information coming from pharmacokinetic (PK)/pharmacodynamic analysis.8

Immunoassay methods and liquid chromatography were introduced almost contemporaneously into the microbiology laboratory.9 This was initially reflected in the Journal publications by methodological papers reporting assay conditions to measure different agents but rapidly developed during the early 1980s to reflect the application of these methods in a TDM setting. This started with reports describing their use in plasma PKs of existing and the rapidly increasing number of new agents, but by the mid-1980s the focus had expanded to include studies of antimicrobial penetration into extravascular sites.10 While some of these studies addressed surrogates of penetration, such as the blister fluid or implanted thread methods, as frequently reported by Wise and colleagues,11 increasingly the focus changed to penetration into tissues recovered during routine operations, particularly bone.12 Most of the published studies reported data for

tein binding is again topical and important in dose optimization

general potential for underdosing in those with severe sepsis, pro-
have highlighted the impact of sepsis on protein binding and the
some of the findings reported during this period has been

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During the mid-1990s, traditional approaches to antimicrobial TDM began to change. For aminoglycosides, discussions focused on the need to achieve high \( C_{\text{max}}/\text{MIC} \) ratios to optimize efficacy and low troughs to reduce the risk of toxicity. Traditional 8 hourly dosage regimens were replaced by ‘high-dose, extended-interval’ regimens and peak and trough monitoring by single, mid-dose concentration measurements interpreted using a nomogram.\textsuperscript{8}
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During the 1990s, PK studies and reviews rarely reported data from healthy volunteers but instead examined the influence of clinical characteristics, such as renal replacement therapy,\textsuperscript{20} on drug handling and dose requirements. Over time, studies using population PK (PopPK) methodology, which could handle ‘sparse’ concentration data from many patients, began to replace traditional PK studies that involved taking multiple blood samples from a small number of patients. This enabled research to be con-
ducted using TDM data\textsuperscript{19} and in patients who were often excluded from traditional PK studies, such as paediatric patients and patients with renal impairment, liver disease, critical illness, burn injury, cystic fibrosis and malignant disease.

From the mid-2000s to the present day, new laboratory techni-

None to declare.

References
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