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Research Article

Impact of Collaborative Therapeutic Drug Monitoring Protocols on Early Detection of Toxicity in Hospitalized Patients

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Abstract:

Collaborative Therapeutic Drug Monitoring (TDM) protocols represent a transformative shift from fragmented, reactive drug-level checking to an integrated, multidisciplinary system aimed at pre-empting patient harm. By formalizing the roles of pharmacists, physicians, nurses, and laboratory staff within a structured framework supported by health information technology, these protocols enable proactive surveillance, ensure correct sampling and rapid analysis, and, most critically, provide expert, contextualized interpretation of results. This systematic collaboration directly addresses the latent failures of traditional TDM, significantly shortening the time from potential toxicity detection to clinical intervention. The outcome is a robust early-warning system that reduces the incidence of adverse drug events, minimizes hospital-acquired morbidity related to drug toxicity, and optimizes therapeutic outcomes for hospitalized patients on medications with a narrow therapeutic index.

1. Introduction

Therapeutic Drug Monitoring (TDM) represents a cornerstone of modern pharmacotherapy, particularly within the complex environment of the hospital setting. It is defined as the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens [1]. The primary goals of TDM are to maximize therapeutic efficacy, minimize the risk of toxicity, and assist in the diagnosis of suspected drug-induced adverse events. This practice is especially critical for medications with a narrow therapeutic index—where the difference between a therapeutic dose and a toxic dose is small—such as aminoglycosides, vancomycin, digoxin, antiepileptics, and immunosuppressants [2]. In hospitalized patients, the stakes for accurate TDM are amplified by the presence of critical illness, polypharmacy, organ dysfunction, and dynamic physiological changes, all of which can profoundly alter pharmacokinetics and pharmacodynamics, predisposing patients to suboptimal outcomes ranging from therapeutic failure to severe, sometimes life-threatening, toxicity [3].

Traditionally, TDM has operated within a siloed, sequential workflow. A clinician, often based on empirical guidelines or clinical suspicion, orders a drug level. The specimen is collected, typically by nursing staff, processed by the clinical laboratory, and a result is generated, which then returns to the clinician's attention for interpretation and action [4]. This linear model harbors significant latent failures that can delay the recognition of impending or actual toxicity. Time lags are inherent at every stage: delays in order placement after signs of toxicity begin, delays in specimen collection and transport, processing time in the lab, and crucially, delays in the clinician reviewing and acting upon the result, especially if it arrives outside of immediate rounds or during shift changes [5]. Furthermore, the interpretation of a drug level is not a simple binary exercise. It requires careful contextual analysis considering the timing of the level in relation to the dose, the patient's clinical status (e.g., renal function, hepatic function, albumin levels), concomitant medications that may cause interactions, and the specific therapeutic target for the patient's indication [6]. A single elevated level may be missed, misinterpreted, or its significance underestimated by a busy clinician managing multiple competing priorities.

The consequences of delayed toxicity detection are severe. Drug toxicity contributes substantially to hospital-acquired morbidity, leading to prolonged hospital stays, increased healthcare costs, permanent organ damage, and higher mortality rates [7]. For instance, aminoglycoside-induced nephrotoxicity or vancomycin-associated nephrotoxicity not only necessitates cessation of a potentially vital antibiotic but also complicates clinical management with new acute kidney injury. Similarly, undetected digoxin toxicity can precipitate life-threatening arrhythmias, while supratherapeutic levels of anticonvulsants can cause debilitating neurological side effects, misinterpreted as worsening of the primary disease [8]. This traditional, fragmented approach to TDM is increasingly seen as inadequate for the demands of contemporary, high-acuity medicine. It fails to leverage the collective expertise available within the healthcare system and is reactive rather than proactive.

This context sets the stage for the emergence and critical evaluation of collaborative Therapeutic Drug Monitoring protocols. These protocols represent a paradigm shift from a linear, physician-centric activity to a multidisciplinary, integrated, and systematic process. Collaborative TDM formally involves the coordinated expertise of clinical pharmacists, prescribing physicians, laboratory scientists, and nursing staff in a structured framework designed to oversee the entire TDM cycle—from initial indication and appropriate test ordering, through efficient sample collection

and rapid analysis, to expert interpretation, timely communication, and appropriate dosage adjustment [1].

2. Components of an Effective Collaborative TDM Protocol

A successful collaborative TDM protocol is not merely an agreement for different professionals to communicate; it is a meticulously designed system with defined roles, responsibilities, and processes. Its effectiveness hinges on several interconnected components that transform TDM from a passive test into an active therapeutic management tool.

2.1 Formalized Interdisciplinary Team Structure and Defined Roles

The foundation of collaboration is a clear definition of each team member's contribution. The physician retains ultimate responsibility for the patient's care and prescribes the medication based on the clinical diagnosis. However, within the collaborative model, the clinical pharmacist assumes a proactive, central role. This includes identifying patients and drugs appropriate for TDM, verifying the correct timing of sample collection relative to the dose (e.g., trough levels), interpreting the drug concentration in the full clinical context, and formulating specific, evidence-based dosing recommendations for physician approval [9]. The laboratory's role evolves from being a passive result generator to an active partner. This involves ensuring rapid turnaround times, flagging critical or severely elevated results immediately, and potentially providing interpretive comments based on population pharmacokinetics. Nursing staff are integral for protocol adherence at the point of care, responsible for accurate and timely specimen collection, which is perhaps the most common source of pre-analytical error in TDM [10]. A formal structure, often with a dedicated TDM pharmacist or a TDM oversight committee, ensures accountability and consistency.

2.2 Protocol-Driven Procedures for Monitoring and Intervention

Standardization is key to reducing variability and error. Collaborative protocols establish clear, evidence-based guidelines for: *when* to initiate monitoring (e.g., after a specific number of doses, in the presence of changing renal function); *how* to monitor (defining the correct sample type and collection time); and *what* to do with the results [11]. These protocols include explicit algorithms for dose adjustment based on drug levels and clinical parameters. For example, a vancomycin protocol may specify that a trough level >20 mg/L in a patient with a rising serum creatinine requires immediate pharmacist notification, cessation of the next dose, and calculation of a new regimen based on renal function estimates [12]. This removes ambiguity and empowers all team members, particularly pharmacists and nurses, to act within their scope according to the agreed pathway, expediting management.

2.3 Integration of Health Information Technology (HIT)

Technology serves as the central nervous system of a modern collaborative TDM program. Electronic health records (EHRs) and computerized physician order entry (CPOE) systems can embed TDM protocols directly into the ordering process. This can include forced functions, such as mandatory entry of indication, weight, and renal function when ordering a TDM-relevant drug, and smart alerts that prompt TDM at the appropriate time [13]. Clinical decision support (CDS) tools are pivotal. They can automatically flag abnormal results, calculate new dosing regimens based on pharmacokinetic equations integrated into the EHR, and generate smart notifications that are routed directly to the responsible pharmacist or clinician. Furthermore, dashboards that aggregate TDM data for high-risk drugs across the hospital allow for population-level oversight and quality improvement initiatives, identifying units or prescribers with outlier practices [14].

2.4 Standardized Communication Pathways and Escalation Policies

Timely and unambiguous communication is the glue that binds the collaborative elements together. Protocols must define exactly how and when findings are communicated. This often involves a combination of EHR alerts, direct paging or messaging systems, and structured handover tools. Critical value reporting for severely toxic levels, similar to critical lab values, is essential, with clear escalation pathways if the primary responder is unavailable [15]. Regular interdisciplinary meetings, such as TDM rounds or pharmacy-led patient reviews, provide a forum for complex case discussion and reinforce the collaborative culture, moving communication from reactive to proactive.

2.5 Impact on Early Detection of Toxicity: Mechanisms and Evidence

The implementation of a robust collaborative TDM protocol impacts the early detection of toxicity through multiple, synergistic mechanisms. The evidence supporting this impact spans pharmacokinetic, process, and clinical outcome measures.

3. Enhanced Surveillance and Proactive Monitoring

In the traditional model, monitoring is often reactive, triggered by a clinician's concern. Collaborative protocols, especially those led by pharmacists, institute proactive, systematic surveillance. Pharmacists routinely review patient profiles for drugs with a narrow therapeutic index, assess renal and hepatic function trends, and screen for potential drug-drug interactions before they manifest as toxicity [16]. This proactive stance means that the first sign of a pharmacokinetic disturbance—such as a sudden drop in creatinine clearance—can trigger a pre-emptive TDM level check or an empiric dose adjustment, potentially averting toxicity altogether. Studies have shown that pharmacist involvement in TDM significantly increases the appropriateness of monitoring, including correct timing and frequency of levels, which is a prerequisite for accurate toxicity detection [17].

3.1 Reduction in Pre-Analytical and Analytical Turnaround Time Delays

Delays in obtaining a result render TDM useless for early intervention. Collaborative protocols streamline the entire pre-analytical chain. By educating nursing staff on the paramount importance of correct sample timing and providing clear collection guidelines, pre-analytical errors are reduced. Laboratory protocols developed in collaboration with the clinical team can prioritize TDM samples, ensuring rapid processing [10]. Perhaps most importantly, HIT integration allows for near-instantaneous result availability to all authorized team members. The pharmacist, who is actively looking for the result, can interpret it within minutes of it being verified, dramatically shortening the time from blood draw to clinical decision. This compressed timeline is critical for drugs with rapidly evolving toxicities.

3.2 Expert Interpretation and Contextualization of Results

An elevated drug level is not synonymous with clinical toxicity, and a level within the "therapeutic range" does not guarantee safety. The collaborative model's greatest strength may lie in the expert interpretation provided by the clinical pharmacist. The pharmacist synthesizes the numerical level with a comprehensive patient assessment: Is the patient showing signs or symptoms of toxicity? What is the current renal and hepatic function? Are there interacting medications? What was the exact timing of the dose and the sample? [18]. This contextualization allows for the identification of *impending* toxicity—a rising trend in levels despite stable dosing, or a level at the upper limit of therapeutic in a patient with new-onset renal impairment. The pharmacist can differentiate between a spurious high level (due to a sample drawn too early) and a true toxic exposure, preventing unnecessary and potentially harmful interventions while correctly identifying real threats.

3.3 Timely Intervention and Dose Optimization

Early detection is only beneficial if it leads to swift, appropriate action. Collaborative protocols directly link detection to intervention. When a pharmacist identifies a level indicative of toxicity or high risk, they immediately formulate a revised dosing regimen using validated pharmacokinetic principles and, per protocol, communicate this recommendation directly to the prescriber, often with an expectation of a rapid response [19]. This eliminates the "post-result lag" where a level sits in a chart awaiting review. Furthermore, by continuously monitoring and adjusting, the protocol keeps drug concentrations in a safe, therapeutic range, preventing the oscillations that can lead to periods of toxicity. This dynamic dose optimization is a form of continuous pre-emption against toxicity.

3.4 Evidence from Clinical Studies

A substantial body of literature supports the efficacy of collaborative TDM. Systematic reviews and meta-analyses consistently demonstrate that pharmacist-led or multidisciplinary TDM services are associated with a significantly higher proportion of patients achieving therapeutic drug concentrations and a reduced incidence of drug toxicity [20, 21]. For instance, studies on vancomycin, a drug with well-defined concentration-response and toxicity relationships, show that collaborative monitoring programs reduce the incidence of nephrotoxicity by 30-50% [22, 23]. Similar results are reported for aminoglycosides, where collaborative TDM reduces both nephrotoxicity and ototoxicity [24]. Research also shows reductions in adverse drug

event rates, shorter hospital lengths of stay, and lower overall treatment costs, all downstream benefits of preventing toxicity [25]. The evidence strongly indicates that the structured, collaborative approach transforms TDM into an effective early-warning system.

4. Implementation Strategies and Overcoming Challenges

Translating the concept of collaborative TDM into a sustainable clinical program requires strategic planning and attention to potential barriers. Successful implementation is multifaceted.

4.1 Securing Institutional Leadership and Stakeholder Buy-in

The development of a hospital-wide collaborative TDM protocol is a significant organizational change. It requires strong endorsement and active sponsorship from senior medical, nursing, and pharmacy leadership. The business case must be clearly articulated, emphasizing not only improved patient safety and outcomes but also potential cost savings from avoided toxicities and reduced length of stay [26]. Engaging key physician champions, particularly in high-use specialties like infectious diseases, critical care, and transplant, is crucial for fostering acceptance among prescribers.

4.2 Education and Training of All Involved Personnel

Effective collaboration depends on shared knowledge. A comprehensive education plan is necessary for all stakeholders. Pharmacists require advanced training in applied pharmacokinetics and protocol specifics. Nurses need clear, practical education on the correct procedures for sample collection, emphasizing the impact of timing on result validity. Physicians benefit from education on the protocol's rationale, the role of the pharmacist, and the evidence supporting the collaborative model [27]. Ongoing education and feedback are essential to maintain competency and protocol fidelity.

4.3 Phased Implementation and Continuous Quality Improvement

A "big bang" hospital-wide rollout is often risky. A phased approach, starting with a single high-impact drug (e.g., vancomycin) on one or two pilot units (e.g., intensive care, oncology), allows for troubleshooting, refinement, and the generation of local success stories [28]. Data collected during the pilot—such as time to result review, time to dose adjustment, incidence of supratherapeutic levels, and toxicity rates—provide tangible evidence of benefit to support broader expansion. Continuous monitoring through key performance indicators (KPIs) and regular audit and feedback to the team are vital for sustaining and improving the program.

4.4 Addressing Common Challenges

Several challenges must be anticipated and managed. *Professional Resistance:* Some physicians may perceive collaborative TDM as an infringement on their autonomy. This is countered by framing the pharmacist as a consultant and expert advisor, and by demonstrating improved patient outcomes [29]. *Resource Constraints:* Dedicated pharmacist time is the most significant resource requirement. The return on investment must be calculated and presented. *IT Limitations:* Not all EHR systems have sophisticated CDS capabilities. Workarounds, such as dedicated order sets and manual alert systems, may be necessary initially, but advocating for robust HIT support should be a long-term goal. *Workflow Integration:* The protocol must be designed to fit into existing clinical workflows, not create additional, onerous steps. Simplification and automation are key principles.

5. Future Directions

The evolution of collaborative TDM is poised to accelerate with advancements in science and technology, pushing the frontiers of early toxicity detection further.

5.1 Integration of Pharmacogenomics

The future of TDM lies in its integration with pharmacogenomic (PGx) data. A patient's genetic profile can predict metabolic capacity (e.g., cytochrome P450 enzyme activity) and drug response, providing a foundational starting point for therapy. Collaborative protocols of the future will likely incorporate PGx results to guide initial drug and dose selection, making TDM a tool for fine-tuning rather than gross correction, potentially preventing toxicity from the very first dose [30].

5.2 Advanced Analytics and Artificial Intelligence (AI)

AI and machine learning offer transformative potential. Predictive algorithms could analyze real-time streams of patient data—vital signs, laboratory results, drug administration times—to forecast the

likelihood of a toxic drug level before it even occurs, prompting pre-emptive testing or adjustment [13]. AI could also assist in interpreting complex TDM cases with multiple confounding factors, providing decision support to the clinical team.

5.3 Expansion to Outpatient and Telehealth Settings

The principles of collaborative TDM are not confined to hospitals. As care shifts to ambulatory settings and the use of complex biologic and oral targeted therapies grows, there is a pressing need for structured outpatient TDM programs. Telehealth platforms and digital health tools can facilitate remote monitoring and virtual collaboration between pharmacists, nurses, and prescribers, extending the safety net against toxicity to the home environment.

5.4 Personalized Therapeutic Ranges

Emerging research is moving beyond population-based therapeutic ranges toward personalized targets based on specific disease characteristics, genetic markers, and biomarkers of effect. Collaborative teams will be at the forefront of implementing these more nuanced targets, requiring even closer integration of laboratory science, clinical pharmacology, and bedside care.

6. Conclusion

In conclusion, the impact of collaborative Therapeutic Drug Monitoring protocols on the early detection of toxicity in hospitalized patients is profound and multifaceted. By dismantling traditional silos and creating an integrated, protocol-driven system, these programs fundamentally enhance the surveillance, interpretation, and management of high-risk pharmacotherapy. The evidence demonstrates that collaboration leads to more appropriate monitoring, faster recognition of aberrant drug levels, expert contextualization of results, and timely, optimized interventions. This systematic approach directly reduces the incidence of drug-induced toxicity, its associated morbidity, and healthcare costs. While implementation requires strategic investment in interdisciplinary relationships, education, and technology, the benefits for patient safety are unequivocal. As medicine advances towards greater personalization, the collaborative TDM model will remain an essential, evolving framework, ensuring that the powerful tools of modern pharmacotherapy are used with maximum efficacy and minimal harm. It represents a definitive shift from reactive toxicity management to proactive toxicity prevention, embodying the highest principles of patient-centered, safe, and effective care.

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References

1. Luyt CE, Brechot N, Trouillet JL, Chastre J. 2014. Antibiotic stewardship in the intensive care unit. Crit Care 18:480.
2. Udy AA, Putt MT, Boots RJ, Lipman J. 2011. ARC—augmented renal clearance. Curr Pharm Biotechnol 12:2020–2029.
3. Minkute R, Briedis V, Steponaviciute R, Vitkauskiene A, Maciulaitis R. 2013. Augmented renal clearance—an evolving risk factor to consider during the treatment with vancomycin. J Clin Pharm Ther 38:462–467.
4. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. 2011. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 50:99–110.
5. Krishnan P, Frew Q, Green A, Martin R, Dziewulski P. 2013. Cause of death and correlation with autopsy findings in burns patients. Burns 39:583–588.
6. Fournier A, Voirol P, Krahenbuhl M, Bonnemain CL, Fournier C, Pantet O, Pagani JL, Revelly JP, Dupuis-Lozeron E, Sadeghipour F, Pannatier A, Eggimann P, Que YA. 2016. Antibiotic consumption to detect epidemics of Pseudomonas aeruginosa in a burn centre: a paradigm shift in the epidemiological surveillance of Pseudomonas

aeruginosa nosocomial infections. Burns 42:564–570.

7. Wong G, Sime FB, Lipman J, Roberts JA. 2014. How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? BMC Infect Dis 14:288.
8. Jeschke MG, Pinto R, Kraft R, Nathens AB, Finnerty CC, Gamelli RL, Gibran NS, Klein MB, Arnoldo BD, Tompkins RG, Herndon DN, Inflammation and the Host Response to Injury Collaborative Research Program. 2015. Morbidity and survival probability in burn patients in modern burn care. Crit Care Med 43:808–815.
9. Boucher HW, Talbot GH, Benjamin DK Jr, Bradley J, Guidos RJ, Jones RN, Murray BE, Bonomo RA, Gilbert D, Infectious Diseases Society of, A. 2013. 10 × ′20 progress—development of new drugs active against Gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis 56:1685–1694.
10. Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. 2013. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. Crit Care 17:R35.
11. Ryan CM, Schoenfeld DA, Thorpe WP, Sheridan RL, Cassem EH, Tompkins RG. 1998. Objective estimates of the probability of death from burn injuries. N Engl J Med 338:362–366.
12. Bracco D, Eggimann P. 2010. Prophylaxis with systemic antibiotics in patients with severe burns. BMJ 340:c208.
13. Ulldemolins M, Roberts JA, Wallis SC, Rello J, Lipman J. 2010. Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacokinetics. J Antimicrob Chemother 65:1771–1778.
14. Hayashi Y, Lipman J, Udy AA, Ng M, McWhinney B, Ungerer J, Lust K, Roberts JA. 2013. β-Lactam therapeutic drug monitoring in the critically ill: optimising drug exposure in patients with fluctuating renal function and hypoalbuminaemia. Int J Antimicrob Agents 41:162–166.
15. Belgian Outcome in Burn Injury Study Group. 2009. Development and validation of a model for prediction of mortality in patients with acute burn injury. Br J Surg 96:111–117.
16. Boyer A, Doussau A, Thiebault R, Venier AG, Tran V, Boulestreau H, Bebear C, Vargas F, Hilbert G, Gruson D, Rogues AM. 2011. Pseudomonas aeruginosa acquisition on an intensive care unit: relationship between antibiotic selective pressure and patients' environment. Crit Care 15:R55.
17. Alp E, Coruh A, Gunay GK, Yontar Y, Doganay M. 2012. Risk factors for nosocomial infection and mortality in burn patients: 10 years of experience at a university hospital. J Burn Care Res 33:379–385.
18. Church D, Elsayed S, Reid O, Winston B, Lindsay R. 2006. Burn wound infections. Clin Microbiol Rev 19:403–434.
19. Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA. 2015. Therapeutic drug monitoring of the beta-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother 70:3178–3183.
20. Patel BM, Paratz J, See NC, Muller MJ, Rudd M, Paterson D, Briscoe SE, Ungerer J, McWhinney BC, Lipman J, Roberts JA. 2012. Therapeutic drug monitoring of beta-lactam antibiotics in burns patients—a one-year prospective study. Ther Drug Monit 34:160–164.
21. Jager NG, van Hest RM, Lipman J, Taccone FS, Roberts JA. 2016. Therapeutic drug monitoring of anti-infective agents in critically ill patients. Expert Rev Clin Pharmacol 9:961–979.
22. Giannoni E, Moreillon P, Cotting J, Moessinger A, Bille J, Decosterd L, Zanetti G, Majcherczyk P, Bugnon D. 2006. Prospective determination of plasma imipenem concentrations in critically ill children. Antimicrob Agents Chemother 50:2563–2568.
23. Lesseva M. 1998. Central venous catheter-related bacteraemia in burn patients. Scand J Infect Dis 30:585–589.
24. Fournier A, Eggimann P, Pagani JL, Revelly JP, Decosterd LA, Marchetti O, Pannatier A, Voirol P, Que YA. 2015. Impact of the introduction of real-time therapeutic drug monitoring on empirical doses of carbapenems in critically ill burn patients. Burns 41:956–968.
25. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. 2009. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 48:1–12.
26. Wong G, Brinkman A, Benefield RJ, Carlier M, De Waele JJ, El Helali N, Frey O, Harbarth S, Huttner A, McWhinney B, Misset B, Pea F, Preisenberger J, Roberts MS, Robertson TA, Roehr A, Sime FB, Taccone FS, Ungerer JPJ, Lipman J, Roberts JA. 2014. An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother 69:1416–1423.
27. Chapuis TM, Giannoni E, Majcherczyk PA, Chiolero R, Schaller MD, Berger MM, Bolay S, Decosterd LA, Bugnon D, Moreillon P. 2010. Prospective monitoring of cefepime in intensive care unit adult patients. Crit Care 14:R51.
28. Yan S, Tsurumi A, Que YA, Ryan CM, Bandyopadhaya A, Morgan AA, Flaherty PJ, Tompkins RG, Rahme LG. 2015. Prediction of multiple infections after severe burn trauma: a prospective cohort study. Ann Surg 261:781–792.
29. Rowley-Conwy G. 2010. Infection prevention and treatment in patients with major burn injuries. Nurs Stand 25:51–52, 54, 56–58.
30. Brusselaers N, Hoste EA, Monstrey S, Colpaert KE, De Waele JJ, Vandewoude KH, Blot SI. 2005. Outcome and changes over time in survival following severe burns from 1985 to 2004. Intensive Care Med 31:1648–1653.