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META-ANALYSIS

Economic evaluations of therapeutic drug monitoring interventions in acute hospital-based settings: A systematic review

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Abstract

Aims: Therapeutic drug monitoring (TDM) aims to optimize drug therapy. As demand on health resources increases, and the technology underpinning TDM becomes more sophisticated, the economic benefits of TDM in hospitals is unclear. The aim of this systematic review was to summarize the economic evidence that could be used to support investment in TDM in hospital settings. In so doing, we sought to provide guidance for future economic evaluations.

Methods: Medline, Embase, CENTRAL, Econlit and NHS Economic Evaluation databases were searched (inception to December 2022) for economic evaluations of hospital-based TDM. Two authors reviewed the studies and extracted data. Overall quality of economic analysis reporting was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Results: Ten prospective studies (including six randomized studies) and nine retrospective studies were eligible. Overall study reporting was poor, publications meeting a median (range) of 61% (46–82%) of CHEERS checklist criteria. An antimicrobial TDM intervention for adult patients was the focus of most studies ($n = 18$). Variable clinical outcomes were reported, and length of stay was the primary economic outcome for most studies ($n = 13$). The majority of studies determined that TDM was economically and clinically favourable ($n = 14$), four studies reporting a cost-reduction in patient sub-populations.

Conclusions: Significant improvements in both economic and clinical outcomes may be realized with TDM interventions, particularly when targeted to complex patient populations. Attainment of therapeutic target could serve as a feasible surrogate measure of benefit for hospital-based TDM interventions. However, systematic reporting of economic outcomes is needed to inform investment decisions.

KEYWORDS
antimicrobials, CHEERS, economic evaluations, systematic review, therapeutic drug monitoring

1 | INTRODUCTION

Increasing costs in healthcare prompt questions on the necessity of all clinical practices. Spending on hospitals accounted for 41% of all Australian health expenditure in the 2020–2021 financial year.[1] Records show that this figure has increased steadily since 2016 and is likely to be further inflated by higher supply and staffing costs post-COVID. Given that evidence suggests that up to 25% of healthcare is unnecessary,[2] this necessitates the identification of practices that deliver no benefit. Making investment or disinvestment decisions is best made when both economic and clinical evidence are available to decision makers.

Therapeutic drug monitoring (TDM) is recommended for drugs with a narrow therapeutic index, significant interindividual pharmacokinetic variability and/or established relationships between drug concentration and efficacy/toxicity.[3] It requires the measurement of drug concentrations in biological fluids, often blood, during drug therapy. The drug concentration is used to modify the dosage in order to maximize therapeutic outcomes while minimizing toxicity. Although conceptually simple, TDM is complicated by the requirement for a multidisciplinary team and the reliance on the collection and interpretation of timed samples in the busy clinical environment. This complexity is reflected in audits that repeatedly describe suboptimal TDM processes.[4–8] Incorrectly timed sample collection and mis- (or no) interpretation of concentrations represent missed opportunities to optimize therapeutic outcomes and potentially undermine investment into (the benefits of) targeted TDM interventions.

Individualized dosing using TDM may improve clinical outcomes and reduce costs, but it can also add to the cost of patient care. Recent evidence suggests that compared to usual care, TDM is cost effective for some drugs. In oncology, clinical and economic evidence support the move from traditional dosing adjusted to body surface area to TDM-guided dosing for a number of drugs, including 5-flurouracil and the tyrosine kinase inhibitor, imatinib.[9–11] This work in ambulatory patients provides a framework to inform future economic evaluations of TDM for oncology drugs. However, for other medicines that are commonly administered for acute conditions in hospitals and dose-adjusted using TDM, the evidence is less clear. For instance, although Telles et al.[12] and Touw et al.[13] report cost benefits of TDM for commonly used antimicrobials such as aminoglycosides, vancomycin, voriconazole and beta-lactams, few studies report economic evaluations of TDM interventions for the broader range of medicines used in hospitals to treat acute conditions.[9,12,13]

As the sophistication and costs of the technology and supports (including expertise) underpinning TDM increases, there are also changes in drug assays and other components of TDM, prompting a need to better define the potential economic value of TDM interventions in hospital settings. This paper sought to fill this gap in evidence by summarizing the economic evidence that could be used to support investment in TDM for acute conditions in hospital settings. In so doing, we provide guidance for future economic evaluations.

2 | METHODS

The literature search aimed to identify economic evaluations of hospital-based TDM interventions. Electronic databases Medline, Embase, CENTRAL, Econlit and NHS Economic Evaluation were searched from inception to 20 December 2022. The World Health Organization clinical trials registry was also searched and reference lists of identified studies were screened. The search strategy (see Supporting information) was restricted to studies published in English. The review protocol was registered on PROSPERO: CRD42020161066.

Two authors (J.E.C. and T.L.) independently reviewed titles and abstracts and read potentially eligible full texts. Discrepancies were resolved by consensus. Studies were included if they reported on the economic/financial outcomes of hospital-based TDM used to guide pharmacotherapy for patients treated with drug(s) for an acute indication during their admission, for which TDM was used. There were no restrictions with respect to type of drug or TDM intervention, measure of economic benefit or study design. Studies were excluded if they did not include a comparator (no TDM or usual care). Usual care was defined as dosing without the TDM intervention and includes physician-led and/or pharmacist-led care.

Two reviewers (J.E.C. and T.L.) independently extracted data from eligible studies using a custom data collection form in Excel. Data collected included study design, setting and participants, TDM intervention characteristics (including drug class and drug(s), resources allocated, tools used), comparator and outcomes and aspects of the economic evaluation (including type of evaluation, perspective, time horizon(s) and healthcare costs and economic outcomes reported). The quality of economic reporting was assessed by one reviewer (T.L.) using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist by the International Society for Pharmacoeconomics and Outcomes Research.[14] Costs were converted to 2023 US dollars using the Evidence for Policy and Practice Information and Coordinating Centre calculator.[15] If year of pricing was not provided, year of publication was used. The earliest year of pricing available was 1980. Where available, quality of life years (QALY) and incremental cost-effectiveness ratio (ICER) were reported.

Outcomes were reported as a narrative synthesis, organized by the Participant, Intervention, Comparison, Outcome (PICO) framework.

3 | RESULTS

A total of 4043 studies were identified, of which 19 were eligible for full-text review (Figure 1, Tables 1, 2 and 3). The majority of studies were undertaken in North America ($n = 12$) and most ($n = 15$) were single site studies (Table 1). Ten studies used prospective study designs: six used randomized designs[17,22,25,26,29,34] and three used non-randomized designs.[19,28,33] One study did not report if randomization was used.[24] Nine studies were retrospective; one used case–control design,[32] one used a decision analysis framework[20] and seven were retrospective cohort studies.[16,18,21,23,27,30,31]

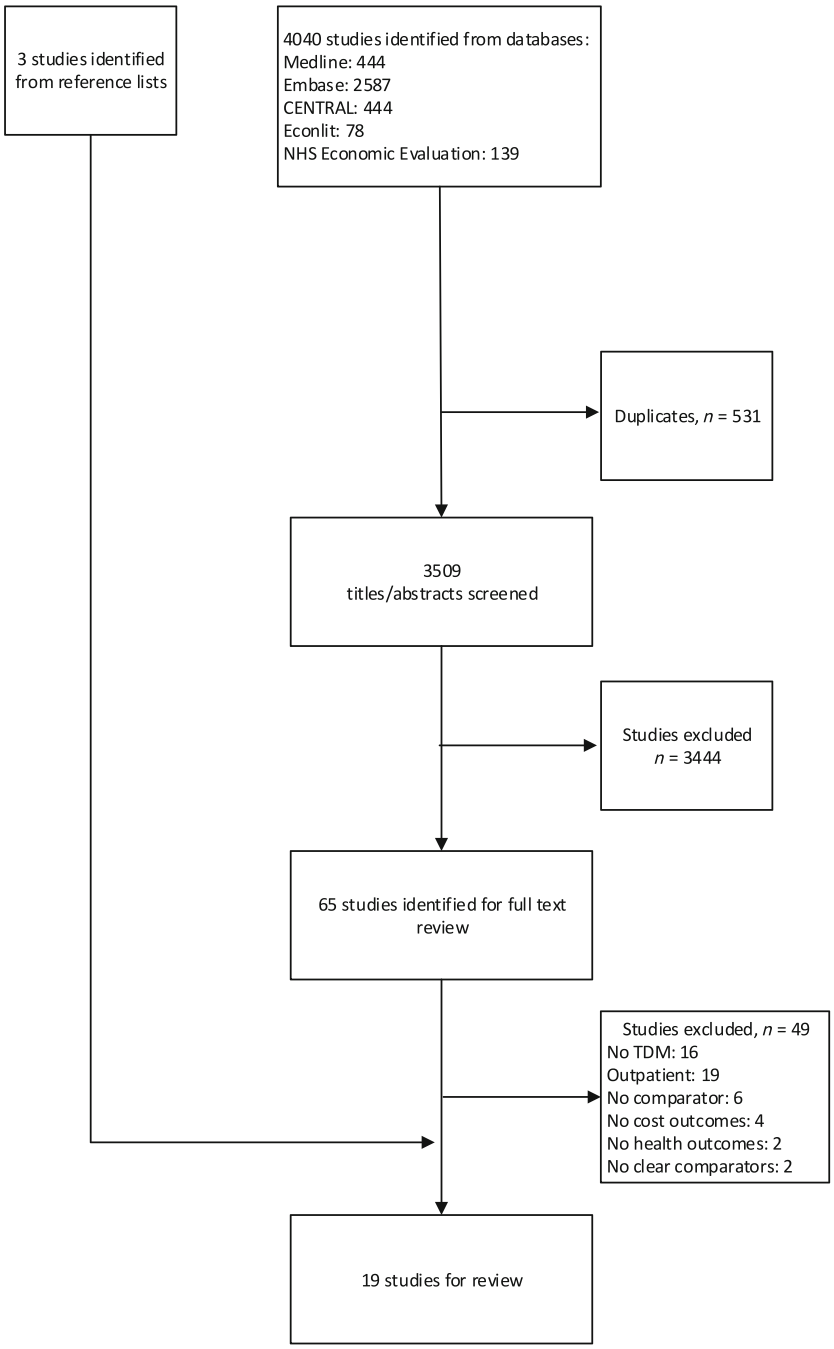

FIGURE 1 A preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the systematic literature review.

3.1 | Economic study design and quality

Seven studies were cost–benefit analyses,[16,17,22,23,28,31,32] seven were cost-effectiveness analyses[20,25–27,30,33,34] and four were cost consequences analyses.[18,19,21,24] One study did not clearly describe the method of economic evaluation used.[29] Overall quality of reporting was poor (Table S1), with a median of 61% of CHEERS checklist items met (range: 46%–82%). One of the included studies provided a health economics plan[25] and only six studies reported study perspective (primarily from the hospital perspective). The time horizon for all studies was implicit, with costs captured across a hospital admission. Two studies[24,25] captured data across the course of drug therapy. Just under half of studies reported year of currency[18,20,23,25–27,32–34] and three studies[16,17,23] applied a discount rate to outcomes and costs that extended beyond the study period. One study[25] used QALY as an outcome but did not discuss how it was valued. Heterogeneity and uncertainty were rarely characterized, with only four studies[20,21,27,33] reporting on variations by subgroup, most only reporting point estimates. Most studies ($n = 12$)[16–21,23,24,26,28,29,32] did not report funding source.

3.2 | Participants

Most studies captured data for adult (>18 years) patients ($n = 18$), with one reporting on TDM in paediatric patients with cystic fibrosis[18]

TABLE 1 Characteristics of studies evaluating in-hospital TDM interventions.

Study (country)	Drug class (drug)	Population (sample size, TDM/ctrl)	Study design	Economic analysis	Patient outcome(s)	Economic outcome
Bootman, 1979[16] (US)	Aminoglycoside antibiotics (Gentamicin)	Adult burn patients *Inclusion*: Gentamicin therapy ≥3 d; ≥1 Gram-negative septic episode; 3rd degree or combination of 2nd and 3rd degree burns; <24 h between time of burn and admission; no prior renal disease; internally consistent and complete data (N = 105, 66/39)	Retrospective cohort (unmatched) Single site	CBA	Survival Length of infection[a] No. of adverse drug reactions (nephrotoxicity, ototoxicity)[a] Number of septic episodes[a] LOS[a] *No primary outcome reported*	Benefit-to-cost ratio
Burton, 1991[17] (US)	Aminoglycoside antibiotics (Amikacin, gentamicin, tobramycin)	Adult patients *Inclusion*: Aminoglycoside therapy ≥48 h; no aminoglycoside therapy ≥14 d prior; suspected infection; SCr ≤ 2 mg/dL; serum aminoglycoside concentrations available; renal function tests available; relevant demographic and clinical data available (*n* = 147, 72/75)	Prospective, randomized, controlled Single site	CBA	Response to therapy[b] Incidence of toxicity (nephrotoxicity) LOS[a] *No primary outcome reported*	Benefit-to-cost ratio
Cies, 2013[18] (US)	Aminoglycoside antibiotics (Tobramycin)	Paediatric CF patients *Inclusion*: Aminoglycoside therapy ≥48 h; admitted for acute CF pulmonary exacerbation; ≥ 2 serum aminoglycoside concentrations (*n* = 51, 29/22)	Retrospective cohort Single site	CCA	LOS[a] *Number of patients who achieve PK/PD target* Number of orders and dose changes Time (days) to achieve PK/PD targets	Resource cost
Crist, 1987[19] (US)	Aminoglycoside antibiotics (Gentamicin, tobramycin)	Adult patients *Inclusion*: Aminoglycoside therapy >24 h; proven or suspected gram-negative infection (*n* = 221, 118/103)	Prospective, non-randomized Single site	CCA	LOS[a] Length of therapy Total dose per course of therapy[a] *No primary outcome reported*	Cost per course of therapy
Darko, 2003[20] (US)	Glycopeptide antibiotic (Vancomycin)	Adult (≥18 years) patients *Inclusion*: Received IV vancomycin ≥48 h for infection treatment; ≥ 2 vancomycin serum samples, *n* = 200	Decision analysis Single site	CEA Decision analysis framework	*Incidence of nephrotoxicity*[a]	Cost of treating nephrotoxicity Cost of vancomycin TDM

(Continues)

TABLE 1 (Continued)

Study (country)	Drug class (drug)	Population (sample size, TDM/ctrl)	Study design	Economic analysis	Patient outcome(s)	Economic outcome
Destache, 1989[21] (US)	Aminoglycoside antibiotics (Gentamicin, Tobramycin)	Adult (>18 years) patients *Inclusion*: Aminoglycoside therapy ≥72 h; no aminoglycoside therapy in 4 weeks prior; culture-proven gram-negative infections treated with gentamicin or tobramycin; no change in aminoglycoside at any time during treatment; CrCL >10 mL/min; not under the care of ID; CPS recommendations followed ($n = 46$, 23/23)	Retrospective cohort Single site	CCA	Resolution of infection[c] Incidence of decreased renal function LOS[a] Length of therapy[a] Number of dose adjustments *No primary outcome reported*	Cost of aminoglycoside therapy Cost of CPS Cost to hospital (use of CPS results in reduced LOS, translates to reduced cost to hospital)
Destache, 1990[22] (US)	Aminoglycoside antibiotics (Amikacin, gentamicin, tobramycin)	Adult (>18 years) patients *Inclusion*: Receiving IM or IV aminoglycoside for proven or suspected gram-negative infection or systemic enterococcal infection ($n = 145$, 75/70)	Prospective, randomized Single site	CBA	Incidence of death Resolution of infection[d] Incidence of nephrotoxicity LOS[a] Length of therapy *No primary outcome reported*	Benefit-to-cost ratio
Destache, 1994[23] (US)	Aminoglycoside antibiotics (Amikacin, gentamicin, tobramycin)	Adult (>18 years) patients *Inclusion*: Received an aminoglycoside for ≥48 h for proven or suspected gram-negative infection ($n = 95$, 50/45)	Retrospective cohort Single site	CBA	Mortality Incidence of nephrotoxicity LOS[a] Length of therapy *No primary outcome reported*	Benefit-to-cost ratio
Dvorackova, 2019[24] (Czech Republic)	Aminoglycoside antibiotics (Amikacin, Gentamicin)	Adult (>18 years) patients *Inclusion*: Receiving an aminoglycoside for infection treatment for ≥5 days ($n = 63$, 52/11)	Pilot, prospective Single site	CCA	Incidence of chronic renal failure[a] Length of therapy Total dose Total dose to day 5 *No primary outcome reported*	Cost of HD sessions Cost of clinical pharmacist service 0.2 FTE
Ewoldt, 2022[25] (The Netherlands)	Fluroquinolone antibiotic (Ciprofloxacin) Beta-lactam antibiotics (Amoxicillin with or without clavulanic acid, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, flucloxacillin, meropenem, and piperacillin with tazobactam)	Adult (≥18 years) ICU patients *Inclusion*: Expected to receive at least one dose of antibiotic for ≥2 days ($n = 388$, 189/199)	Open-label, randomized clinical trial Multi-site	CEA	28 d mortality ICU mortality Hospital mortality 6-month mortality Delta-SOFA score[e] Delta-CRP[f] Delta-WBC[g] Incidence of adverse events within 7 days *ICU LOS*[a] PD target attainment	ICER per QALY

TABLE 1 (Continued)

Study (country)	Drug class (drug)	Population (sample size, TDM/ctrl)	Study design	Economic analysis	Patient outcome(s)	Economic outcome
					QoL[a,h]	
Fernández de Gatta, 1996[26] (Spain)	Glycopeptide antibiotic (Vancomycin)	Adult (>18 years) immunocompromised, febrile patients *Inclusion*: Received an aminoglycoside for ≥48 h for proven or suspected gram-negative infection (n = 95, 50/45)	Prospective, randomized (Site not reported)	CEA	Response to therapy[a,i] Number of days of fever[a] Time to apyrexia[a] Incidence of nephrotoxicity[a] LOS[a] Length of therapy[a] *No primary outcome reported*	Incremental cost per case of nephrotoxicity prevented
Kim, 2022[27] (Republic of Korea)	Glycopeptide antibiotic (Vancomycin)	Adult (≥65 years) patients *Inclusion*: Received IV vancomycin ≥72 h; hospitalization <30 days (n = 1944, 850/1094)	Retrospective cohort Single site	CEA	Mortality[a] Microbiological cure[a] Duration of fever[a] Nephrotoxicity[a] LOS[a] Length of therapy[a] Daily dose[a] *No primary outcome reported*	Cost
Kimelblatt, 1986[28] (US)	Aminoglycoside antibiotics (Gentamicin, tobramycin)	Patients treated with gentamicin or tobramycin (n = 118, 65/53)	Prospective, non-randomized, pre-post Single site	CBA	Mortality rate[a] Fever reduction within 3 days[a] Incidence of nephrotoxicity[a] Incidence of ototoxicity[a] *No primary outcome reported*	Cost:benefit ratio
Lehmann, 1982[29] (US)	Methylxanthine (Theophylline)	Adult patients with asthma or COPD *Inclusion*: Theophylline therapy ≥48 h (n = 60, 30/27)	Prospective, randomized Single site	NR	*Quality of care*[j] LOS[a] Days on IV fluids[a] Number of patients requiring home oxygen on discharge[a]	Cost
Liu, 2024[30] (China)	Glycopeptide antibiotic (Vancomycin)	Adult (>18 years) patients with postoperative intracerebral haemorrhage *Inclusion*: Vancomycin therapy >3 days; admitted to Department of Neurosurgery and underwent neurosurgery (n = 184, 92/92)	Retrospective cohort study Single site	CEA	*14-day mortality* Proportion of patients with inflammatory markers in normal range Incidence of nephrotoxicity LOS	ICER of WBC, neutrophil, procalcitonin and CRP
Pinilla, 1992[31] (Canada)	Aminoglycoside antibiotics (Amikacin, gentamicin, tobramycin)	Adult and paediatric patients *Inclusion*: Serial aminoglycoside serum concentrations (n = 48, 24/24)	Retrospective, observational analytic cohort Single site	CBA	Renal failure[a,k] LOS[a] Length of therapy[a] No. of doses administered per day[a] No. tests of renal function	Cost of service provision

(Continues)

TABLE 1 (Continued)

Study (country)	Drug class (drug)	Population (sample size, TDM/ctrl)	Study design	Economic analysis	Patient outcome(s)	Economic outcome
					No primary outcome reported	
Streetman, 2001[32] (US)	Aminoglycoside antibiotics (Gentamicin, tobramycin)	Adult (≥18 years) patients *Inclusion*: Receiving gentamicin or tobramycin for ≥48 h for suspected or proven infection ($n = 2405$, 2253/152)	Retrospective, case control Multi-site	CBA	Outcome[a,l] *Incidence of nephrotoxicity*[b] LOS[a]	Cost savings associated with individualized PK monitoring
van Lent Evers, 1999[33] (The Netherlands)	Aminoglycoside antibiotics (Gentamicin)	Adult (>18 years) patients *Inclusion*: Gentamicin administered for ≥48 h; suspected or proven gram-negative infection ($n = 232$, 105/127)	Prospective, observational Multi-site	CEA	Mortality[a] Length of febrile period Incidence of nephrotoxicity Incidence of ototoxicity Morbidity ICU LOS[a] *LOS*[a] Length of therapy	Cost effectiveness ratios
Zhang, 2020[34] (China)	Glycopeptide antibiotic (Vancomycin)	Adult (≥18 years) patients with mild/moderate renal insufficiency *Inclusion*: Vancomycin therapy ≥3 days; diagnosis of Gram-positive bacterial infection; mild–moderate renal insufficiency (eGFR 30–89 mL/min/1.73 m^2) ($n = 138$, 69/69)	Prospective, randomized, open-label trial Single site	CEA (Decision tree model)	Eradication of bacteria Rate of treatment failure *Incidence of VAN*[a], *Probability of trough target attainment* LOS	ICER per nephrotoxic episode

Abbreviations: CBA, cost–benefit analysis; CCA, cost consequences analysis; CEA, cost-effectiveness analysis; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CPS, clinical pharmacokinetic service; CrCL, creatinine clearance; CRP, C-reactive protein; Ctrl, control; d, day; eGFR, estimated glomerular filtration rate; FTE, full-time equivalent; h, hour; HAMD, Hamilton Depression Rating Scale; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; ID, infectious diseases; IV, intravenous; LOS, length of stay; No., number; NR, not reported; PK/PD, pharmacokinetic/pharmacodynamic; QALY, quality adjusted life year; QoL, quality of life; SCr, serum creatinine; SOFA, sequential organ failure assessment; TDM, therapeutic drug monitoring, VAN, vancomycin associated nephrotoxicity.

[a]Outcome used in economic evaluation.

[b]Response to therapy, defined as cure, response, failure, death or indeterminate.

[c]Resolution of infection, defined as time for elevated temp to decrease to baseline or ≤37.6 °C, time for elevated HR to return to baseline or <80 beats/min, time for respiratory rate to return to baseline or <24 breaths/min.

[d]Resolution of infection, defined as time for temperature decrease <99.8 °F, time for elevated HR to decrease <90 beats/min, time for respiratory rate to decrease <24 breaths/min.

[e]Delta-SOFA score, difference between SOFA score at T0 and T5 where T0 is the first day of antibiotic dose.

[f]Delta-CRP, difference between CRP at T0 and T5 where T0 is the first day of antibiotic dose.

[g]Delta-WBC, difference between WBC count at T0 and T5 where T0 is the first day of antibiotic dose.

[h]QoL, expressed as VAS-score and QALY (as assessed by EuroQoL 5D-5L questionnaire) at 6 months.

[i]Response to therapy defined as improvement, failure or indeterminate.

[j]Quality of care defined by pulmonary function tests, complications of primary disease, concurrent medical therapy, a complete profile of theophylline therapy, complications of theophylline therapy.

[k]Renal failure necessitating special diet or dialysis.

[l]Outcome defined as recovered, died or lost to follow-up.

TABLE 2 Summary of TDM interventions and patient outcomes assessed in economic evaluations.

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
Bootman, 1979[16] (Gentamicin)	PK individualized dosing (Usual care)	Clinical pharmacist (Not reported)	NR	NR	**Survival** **63.6% *vs.* 33.3%** **(*P* < 0.005)** ***Length of infection[c] (days)*** ***Survived*** ***10.3 ± 4.8 vs. 8.1 ± 2.3*** ***(P = 0.05)*** ***Died*** ***11.2 ± 4.9 vs. 5.7 ± 3.2*** ***(P = 0.001)*** ***LOS [c] (days)*** ***Survived*** ***93.2 ± 32.4 vs. 72.3 ± 24.3*** ***(P = 0.05)*** *Died* *36.1 ± 30.4 vs. 26.3 ± 31.2* *(P > 0.05)* *Number of adverse drug reactions* *0 vs. 3* ***Number of septic episodes*** ***66 vs. 39 (P < 0.05)***	PK gentamicin service was positively correlated with survival.
Burton, 1991[17] (Amikacin, gentamicin, tobramycin)	PK individualized dosing (Physician-led dosing)	NR (NR)	Bayesian dosing program	Amikacin C_{max} 20–30 mg/L C_0 < 5 mg/L Gentamin & Tobramycin C_{max} 5–10 mg/L C_0 < 2 mg/L *Outcomes*: **Maximum C_{max} (mg/L)[d]: 5.3 ± 1.8 *vs.* 4.4 ± 1.7 (*P* = 0.001)** Maximum C_0 (mg/L)[d]: 1.1 ± 0.9 *vs.* 1.2 ± 0.8	***LOS (days): 16 vs. 20.3 (P = 0.028)*** Response to therapy Cure: 25.7% *vs.* 25.3% Response: 60% *vs.* 48% Failure: 2.9% *vs.* 5.3% Death: 1.4% *vs.* 4% Indeterminate7.1% *vs.* 8% Incidence of toxicity (nephrotoxicity) 5.1% *vs.* 9.7%	PK individualized aminoglycoside dosing improved response to therapy and significantly reduced LOS
Cies, 2013[18] (Tobramycin)	Clinical pharmacist managed TDM and PK individualized dosing (Usual care)	Clinical pharmacist (Monitor drug concentrations, direct dose	1-cpt PK model	C_{max} 20–30 μg/mL C_0 < 1 μg/mL *Outcomes*:	**Courses that achieved PK/PD target: 98% *vs.* 69% (*P* < 0.001)**	Clinical pharmacist managed tobramycin TDM significantly reduced LOS

(Continues)

TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
		adjustments using patient PK parameters)		**Courses that achieved PK/PD targets (peaks and troughs): 98% *vs.* 69% (*P* < 0.001)**	**Time to PK/PD target (days): 1.9 ± 1 *vs.* 4.8 ± 3.4 (*P* < 0.001)** ***LOS (days): 9 ± 5 vs. 12 ± 7 (P = 0.03)***	and increased courses that achieved PK/PD.
Crist, 1987[19] (Gentamicin, tobramycin)	Pharmacist managed TDM and PK individualized dosing (Usual care)	Pharmacists (Schedule and interpret serum drug concentrations, monitor patient daily)	PK calculations performed using the methods of Sawchuck et al[35]	NR *Outcomes*: Target plasma concentration achieved per study group: 93% *vs.* 58%	***LOS (days): 8.4 ± 1.9 vs. 11.8 ± 2.4 (P < 0.005)*** **Length of therapy (days): 5.98 ± 1.56 *vs.* 10.31 ± 2.74 (*P* < 0.0001)** *Total dose per course of therapy (mg): 1253 ± 338* vs. *1982 ± 593*	Individualized aminoglycoside dosing significantly reduced total dose and LOS.
Darko, 2003[20] (Vancomycin)	PK individualized dosing (No intervention)	Pharmacists (Chart review, interpret results, perform PK calculations, follow-up evaluation) Nurses (Blood extraction, drug administration)	NR	C_0 = 10 mg/L *Outcomes*: C_0 > 10 mg/L All: 6.5% *vs.* 14.9% ICU: 8.7% *vs.* 23.6% Oncology: 3% *vs.* 11% Concomitant nephrotoxins: 5.5% *vs.* 18.4% C_0 ≤ 10 mg/L All: 93.5% *vs.* 85.1% ICU: 91.3% *vs.* 76.3% Oncology: 97% *vs.* 89% Concomitant Nephrotoxins: 94.5% *vs.* 81.6%	*Probability of nephrotoxicity prevention* *All: 0.900* vs. *0.894* *Oncology: 0.839* vs. *0.853* *ICU: 0.887* vs. *0.898* *Concomitant nephrotoxins: 0.904* vs. *0.943*	PK vancomycin monitoring and dose adjustment reduced nephrotoxicity for patients receiving concomitant nephrotoxins.
Destache, 1989[21] (Gentamicin, tobramycin)	PK individualized dosing (No clinical PK service)	Clinical pharmacists (Initial dose recommendation, interpret drug concentrations, provide dose recommendations by phone)	1-cpt IV infusion model	NR *Outcomes*: Mean (SD) C_{max} (μg/mL): 6.31 ± 1.90 *vs.* 5.82 ± 1.93 Mean (SD) C_0 (μg/mL): 1.61 ± 1.01 *vs.* 1.75 ± 0.78	***LOS (h): 314.1 ± 146. 4 vs. 458.7 ± 312.8 (P < 0.05)*** Length of therapy (h): 150.4 ± 57.7 *vs.* 183.5 ± 99.3 No. with decreased renal function: 2 *vs.* 5 No. of dosage changes: 1.5 ± 1.2 *vs.* 1.1 ± 0.87 Resolution of infection	Aminoglycoside clinical PK service reduced LOS and improved resolution of infection.

TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
					Time for elevated temp to decrease to baseline or ≤37.6 °C (h) **42.2 ± 47.1 *vs.* 76.3 ± 51.0 (*P* < 0.05)** **Time for elevated HR to return to baseline or <80 beats/min (h)** 24.0 **± 11.6 *vs.* 90.1 ± 65.1 (*P* < 0.0005)** **Time for respiratory rate to return to baseline or <24 breaths/min (h)** **39.2 ± 23.0 *vs.* 94.9 ± 58.8 (*P* = 0.05)**	
Destache, 1990[22] (Amikacin, gentamicin, tobramycin)	PK individualized dosing (Usual care)	Clinical pharmacists (Initial dose and dosing interval recommendation [verbal], interpret drug concentrations, provide dose recommendations in patient chart)	Computerized Bayesian forecasting (1-cpt model)	Amikacin C_{max} 20–25 μg/mL C_0 5–10 μg/mL C_{max} dependent on indication[k] [Pneumonia] Gentamicin and tobramycin C_{max} 6.0–8.0 μg/mL C_0 < 2.0 μg/mL *Outcomes*: No. (%) second C_{max} **Low: 4 (9%) *vs.* 14 (40%) (*P* < 0.05)** Adequate: 22 (40%) *vs.* 11 (31%) (*P* > 0.05) Not drawn: 18 (42%) *vs.* 10 (29%) (*P* > 0.05) No. (%) high C_0 pre- and post-dose modification: 8 (11%) to 3 (4.3%) *vs.* 14 (25%) to 8 (14%) (*P* > 0.05)	*LOS (h): 322.67 ± 270.28* vs. *442.89 ± 536.81* Resolution of infection Length of therapy: 109.81 ± 90.31 *vs.* 108.95 ± 79.09 Resolution of infection **Time for elevated temp to decrease to 99.8 °F (h)** **50.05 ± 79.38 *vs.* 92.23 ± 122.50 (*P* < 0.05)** **Time for elevated HR to return to <90 beats/min (h): 81.33 ± 121.45 *vs.* 86.43 ± 179.77 (*P* < 0.005)** **Time for respiratory rate to return to <24 breaths/min (h): 17.84 ± 36.42 *vs.* 29.14 ± 75.33 (*P* = 0.02)** Incidence of nephrotoxicity: 8% *vs.* 14.4% Incidence of death: 18.7% *vs.* 10%	Aminoglycoside clinical PK service was associated with achievement of target concentrations, reduced LOS and faster resolution of infection.

(Continues)

TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
Destache, 1994[23] (Amikacin, gentamicin, tobramycin)	Clinical pharmacist managed TDM and PK individualized dosing (<10% patients receiving Clinical PK Service monitoring)	Clinical pharmacist (Initial dose recommendation based on suspected/proven organism, site of infection and alteration in PK parameters; daily monitoring and progress note in patient medical record; interpret serum concentration, provide dose recommendations)	Computerized Bayesian PK predictive program (1-cpt model)	NR *Outcomes*: **Mean (SD) C_{max} (μg/mL): 6.90 ± 1.50 *vs.* 4.80 ± 1.70 (*P* < 0.0001)Mean (SD) C_0 (μg/mL): 1.20 ± 0.60 vs 1.50 ± 1.00 (*P* < 0.05)**	***LOS (days): 13.48 ± 13.32 vs. 18.04 ± 5.46 (P < 0.05)*** Length of therapy (days): 7.13 ± 3.57 *vs.* 6.27 ± 2.82 **Incidence of nephrotoxicity: 4% *vs.* 24% (*P* < 0.01)** Mortality: 12% *vs.* 6.6%	Aminoglycoside clinical PK service significantly reduced LOS, improved achievement of therapeutic targets and reduced the incidence of nephrotoxicity
Dvorackova, 2019[24] (Amikacin, gentamicin)	Clinical pharmacist managed TDM and PK individualized dosing(Physician-led therapy, no PK analysis)	Clinical pharmacist (Initial dosage regimen recommendation; interpret aminoglycoside concentrations using PK software; provide dose, dosing interval and timing of next TDM sample collection recommendation; discuss recommendation with treating physician; enter recommendation in electronic request system)	Computerized Bayesian PK predictive program (2-cpt model; MwPharm version 4.0)	Amikacin C_0 < 1 mg/L C_{max} > 20 mg/L Gentamicin C_0 < 2 mg/L C_{max} > 10 mg/L *Outcomes*: C_0 achieved 76% *vs.* 63% C_{max} achieved 70% *vs.* 54%	*Incidence of chronic renal failure: unchanged* Length of therapy (days): 10.5 ± 6 *vs.* 10.2 ± 5 Total dose (mg): 5659.12 ± 5340 *vs.* 5581.1 ± 3290 Total dose to day 5 (mg): 2641.9 ± 1671 *vs.* 2595.5 ± 3563	No change in outcomes with clinical pharmacist managed aminoglycoside TDM.
Ewoldt, 2022[25] (Ciprofloxacin, Beta-lactam antibiotics)	PK individualized dosing(Usual care or physician-led dosing)	NR(Interpret serum concentration [days 1, 3, 5], provide dose recommendations)	Computerized Bayesian PK predictive program (InsightRX™, version 1.15.16, San Francisco, CA; Parametric population PK models of critically ill patients)	Ciprofloxacin AUC_{0-24}/MIC_{ECOFF} > 125 Beta-lactams fT > MIC_{ECOFF} for 100% of the dosing interval *Outcomes*: T1 target attainment 55.6% *vs.* 60.9%T3 target attainment 59.5% *vs.* 60.4%T5 target attainment 60% *vs.* 50%	*Median (IQR) ICU LOS*[d, c] *(days): 10 (5–20)* vs. *8 (3–19)* 28 d mortality: 26.5% *vs.* 24.6% ICU mortality 21.7% *vs.* 18.1%Hospital mortality 28% *vs.* 25.6%6-month mortality 36.5% *vs.* 32.2% Median (IQR) Delta-SOFA score[e]	No beneficial effect of MIPD of ciprofloxacin and beta-lactam antibiotics on ICU LOS in critically ill patients.

TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
					4 (1–7) *vs.* 4 (1–7)Median (IQR) Delta-CRP[f] 61 (9–160) *vs.* 75 (17–190) Median (IQR) Delta-WBC[g] 0.02 (−6.7–4.7) *vs.* 0.7 (−4.9–4.9) Incidence of adverse events within 7 days 138 *vs.* 119 QoL[a,h] QALY at 6 months 0.78(0.57–0.89) *vs.* 0.72 (0.51–0.85)	
Fernández de Gatta, 1996[26] (Vancomycin)	Clinical pharmacist managed TDM and PK individualized dosing (No TDM)	Clinical pharmacist (PK interpretation of serum vancomycin concentrations, provide dose recommendations, provide follow-up plan for future monitoring)	Nomogram to determine loading dose Computerized Bayesian PK predictive program (Abbottbase Pharmacokinetic Systems, version 1, Abbott Laboratories; 1-cpt PK model)	C_{max} 18–26 mg/L C_0 5–10 mg/L *Outcomes*: NR	*Response to therapy* *Improvement: 24* vs. *19* *Failure: 6* vs. *9* *Indeterminate:7* vs. *5* ***Incidence of nephrotoxicity: 13.5* vs. *42% (P < 0.05)*** *LOS (days): 24.5 ± 15.5* vs. *24.1 ± 15.0* *Days of fever: 5.6 ± 4.7* vs. *7.1 ± 5.3* *Time to apyrexia (days): 4.1 ± 3.9* vs. *5.4 ± 4.9* *Length of therapy (days): 18.5 ± 8.1* vs. *19.8 ± 9.6*	Clinical pharmacist managed vancomycin TDM significantly reduced incidence of nephrotoxicity in patients with haematologic malignancies
Kim, 2022[27] (Vancomycin)	Clinical pharmacologist-led TDM and PK individualized dosing (No TDM or TDM > 3 d therapy)	Clinical pharmacologists[i] (Review patient medical records; provide dosing and monitoring regimen using software)	Computerized Bayesian PK predictive program (Abbottbase Pharmacokinetic Systems, version 1.10, Abbott Laboratories)	C_0 > 10 mg/L or 15–20 mg/L for complicated infections[j] *Outcomes*: NR	***Length of therapy[a] (days)*:** • ***All: 10.8 ± 7.9 vs. 9.5 ± 9.1 (P < 0.0001)*** • ***ICU: 11.4 ± 8.2 vs. 8.5 ± 7.8 (P < 0.0001)*** • ***Non-ICU: 10.4 ± 7.7 vs. 10.0 ± 9.7 (P < 0.0001)*** ***Daily dose[a] (mg/day/kg)*:** • ***All: 29.8 ± 23.3 vs. 31.0 ± 20.6 (P = 0.003)*** • *ICU: 28.6 ± 29.7 vs. 26.8 ± 14.1 (P = 0.61)*	Vancomycin TDM in elderly patients was not associated with better clinical outcomes

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TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
					• ***Non-ICU: 30.5 ± 19.0 vs. 33.3 ± 23.1 (P = 0.0003)*** ***LOS[a] (days)***: • ***All: 17.4 ± 10.6 vs. 16.3 ± 11.2 (P = 0.002)*** • *ICU: 17.9 ± 11.4 vs. 16.5 ± 10.4 (P = 0.18)* • ***Non-ICU: 17.2 ± 10.2 vs. 16.3 ± 11.6 (P = 0.004)*** ***Duration of fever[a] (days)***: • ***All:1.7 ± 3.1 vs. 1.4 ± 2.9 (P = 0.005)*** • ***ICU: 0.7 ± 0.2 vs. 0.5 ± 1.7 (P = 0.009)*** • *Non-ICU:2.2 ± 3.4 vs. 1.9 ± 3.2 (P = 0.06)* ***Microbiological cure[a]***: • ***All: 61.2% vs. 71.7% (P < 0.0001)*** • ***ICU: 40.6% vs. 61.9% (P < 0.0001)*** • *Non-ICU:72.3% vs. 77.1% (P = 0.053)* *Nephrotoxicity[a]*: • *All:31.8% vs. 28.1% (P = 0.08)* • *ICU: 45% vs. 42.3% (P = 0.48)* • *Non-ICU:24.6% vs. 20.3% (P = 0.06)* ***Mortality[a]***: • ***All: 27.5% vs. 18.2% (P < 0.0001)*** • ***ICU: 51.3% vs. 32.0% (P < 0.0001)*** • ***Non-ICU: 14.7% vs. 10.6% (P = 0.03)***	

TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
Kimelblatt, 1986[28] (Gentamicin, tobramycin)	Clinical pharmacist managed TDM and PK individualized dosing (Usual care)	Pharmacists(Recommend drug choice, initial dose recommendation using 1-cpt linear model, co-ordinate TDM sampling, review recommendations with other pharmacist/ patient's physician, write consultation notes in medical record, provide education for physicians and nurses)	Hewlett Packard 41C hand-held calculator (Equations for a 1-cpt linear PK model) Population values for V_d and elimination rate used for initial dosing; individual values used for subsequent recommendations Pre-printed instruction cards to co-ordinate TDM sampling	NR	*LOS*[d] *(days) 36.0 ± 41.2* vs. *30.5 ± 40.5 Length of therapy*[d] *(days): 7.0* ± 6.6 vs. 9.6 ± 10.1 *Incidence of nephrotoxicity: 14%* vs. *11% Incidence of ototoxicity: 0%* vs. *3% Fever reduction within 3 days: 74%* vs. *64% Mortality rate*: 25% vs. 19%	Clinical pharmacist managed aminoglycoside TDM did not have a significant effect on clinical outcomes
Lehmann, 1982[29] (Theophylline)	Clinical pharmacist managed TDM and PK individualized dosing (No pharmacist intervention)	Clinical pharmacist (Provide dose recommendations based on PK estimations and clinical judgement; chart recommendations; provide clinical follow-up throughout hospitalization)	PK equations used to determine individual clearance	8–10 μg/mL *Outcomes*: NR	Quality of care: No. pulmonary toilet: 0 *vs.* 1 No. complications of primary disease: 4 *vs.* 4 Discharge medications: 29% *vs.* 26% No. complications of theophylline therapy: 3 *vs.* 4 ***LOS (days): 8.6 ± 4.5 vs. 6.2 ± 2.6 (P = 0.017)*** ***Days on IV fluids 5.1 ± 2.6 vs. 3.7 ± 2.2 (P = 0.026)*** *No. of patients requiring home oxygen on discharge: 2* vs. *2*	Theophylline PK service appeared to extend hospitalization without offering benefits.
Liu, 2024[30] (Vancomycin)	TDM (No TDM)	NR (NR)	NR	C_0 15–20 mg/L *Outcomes*: Mean conc TDM group 9.16 ± 1.43 mg/L	*14-day mortality* 4.34% *vs.* 7.6% **WBC attainment: 83.7% *vs.* 56.5% (P = 0.00)** **Neutrophil attainment: 57.6% *vs.* 25.0% (P = 0.00)** **CRP 80% reduction: 78.3% *vs.* 41.3% (P = 0.00)** **Procalcitonin 80% reduction: 65.2% *vs.* 10.9% (P = 0.00)** **Incidence of nephrotoxicity:**	Vancomycin TDM in patients with postoperative intracerebral haemorrhage improved inflammatory factors and prevented the development of nephrotoxicity

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TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
					6.5% *vs.* 17.4% ($P = 0.023$) Median (IQR) LOS (days): 30 (28,40) *vs.* 27 (20,36)	
Pinilla, 1992[31] (Amikacin, gentamicin, tobramycin)	PK individualized dosing (Physician based recommendations)	Pharmacist (Interpret TDM samples, provide dosing [dose and dose interval] recommendation report to physician)	Microcomputer kinetic program (methods of Sawchuk and Zaske[35]) Info provided by kinetic program incl V_d, elimination kinetics, $t_{1/2}$	Dependent on indication[k] [Pneumonia, severe gram-negative infections] Amikacin (mg/L) C_{max} 25–28 C_0 < 8 Toxic C_{max} > 30 Toxic C_0 > 8 Gentamicin, tobramycin C_{max} 7–10 C_0: <2 Toxic C_{max} > 2 Toxic C_0 > 2 *Outcomes*: No. subtherapeutic concentrations: 33 *vs.* 12 No. toxic C_{max}: 1 *vs.* 0 No. toxic C_0: 0 *vs.* 1	*Mean LOS (days): 26.83 vs. 17.25* ***Mean length of therapy (days): 9.63 vs. 6.29 days ($P < 0.05$)*** Mean no. of doses/day: 2.82 *vs.* 2.86 *Renal failure: 0* vs. *0*	Pharmacy-based aminoglycoside TDM service recommendations were favourably received by treating doctors, with a reduction in length of therapy observed.
Streetman, 2001[32] (Gentamicin, tobramycin)	PK individualized dosing (Dosing via physicians' directions)	Clinical pharmacist (Serum concentration data analysed using a 1-cpt model, PK dose recommendation provided, serum C_0 assessed every 72 h)	Serum concentration data analysed by a Bayesian model OR by the method of Sawchuck and Zaske[36] Data fit to a 1-cpt IV infusion model	C_{max} target dependent on indication[k] [Pneumonia] C_{max} 6–10 μg/mLC_0 < 2 μg/ml *Outcomes*: Not reported	**Incidence of nephrotoxicity[b]** **7.9% *vs.* 13.2% ($P = 0.024$)**	Individualized PK monitoring decreased the frequency of aminoglycoside associated nephrotoxicity and related costs
van Lent Evers[33] (Gentamicin)	Pharmacist managed TDM and PK individualized dosing (No proactive pharmacist intervention)	Hospital pharmacist(On call 24 h/day; Initial dosage regimen (including loading and initial maintenance dose) using MWPharm; co-ordinate serum sample (peak and trough) collection; interpret TDM samples; calculate dose regimen using the MAP Bayesian method of	Population model within MW/PHARM program (Mediware, Groningen, The Netherlands) Bayesian forecasting (using a 1-cpt PK model and linear regression)	Dependent on indication[k] [non-culture proven] C_{max} (mg/L) 8–10C_0 (mg/L) 1.0–1.5 *Outcomes*: **Mean (SD) C_{max} (mg/L): 10.6 ± 2.8 *vs.* 7.6 ± 2.2 ($P < 0.001$)** **Mean (SD) C_0 (mg/L): 0.7 ± 0.6 *vs.* 1.4 ± 1.3 ($P < 0.01$)**	**Length of febrile period (days): 2.8 ± 2.4 *vs.* 2.3 ± 2.9 ($P = 0.024$)** Length of therapy (days): 5.9 ± 2.9 *vs.* 8.0 ± 4.9 **ICU LOS (days): 0.2 *vs.* 0.72 ($P = 0.044$)LOS (days): 20.0 ± 13.7 vs 26.3 ± 31.5 ($P = 0.045$)**	Model-based aminoglycoside dosing resulted in higher antibiotic efficacy, shorter LOS and reduced incidence of nephrotoxicity

TABLE 2 (Continued)

Study (drug)	Intervention (comparator)	Staff (role)	Dose decision support	Therapeutic target(s) and outcomes (TDM *vs.* ctrl)	Patient outcomes[a, b] (TDM *vs.* ctrl)	Findings
		adaptive control; interpret concentrations; dosage recommendation and advice for follow-up TDM samples provided to attending physician by phone; review charts every 1–3 days until discharge)			**Incidence of nephrotoxicity 2.8% *vs.* 13.4% ($P = 0.003$)** Incidence of ototoxicity: NRMorbidity: NRMortality: 8.6% *vs.* 14.2%	
Zhang 2020[34] (Vancomycin)	Pharmacist managed TDM and PK individualized dosing (Physician-led dosing based on renal function and clinical response)	TDM Pharmacist(Daily monitoring, adjusting vancomycin dosages using SmartDose, communicating recommendations to the physician, documenting conditions patient charts, patients followed until discharge)	SmartDose PK software (1-cpt model)	C_0 10–20 mg/L *Outcomes*: **Proportion of courses therapeutic C_0: 67.8% *vs.* 47.6% ($P < 0.05$)**	**Incidence of VAN: 7% *vs.* 19% ($P = 0.022$)** Bacteria eradication: 28% *vs.* 23% Rate of treatment failure: 23% *vs.* 30% **LOS (days): 23 (19–26) *vs.* 27 (23–32) ($P = 0.035$)**	Intervention (vancomycin TDM coupled with Bayesian forecasting) increased C_0 target attainment and reduced the incidence of nephrotoxicity

Note: Significant values are in bold.

Abbreviations: 1-cpt, one compartment; AUC_{0-24}, area under the drug concentration–time curve over 24 h; C_0, trough concentration; C_{max}, peak concentration; CRP, C-reactive protein; Ctrl, control; f, free; MIC_{ECOFF}, minimum inhibitory concentration epidemiological cut off value; PK, pharmacokinetic; ID, infectious diseases; IQR, interquartile range; IV, intravenous; MAP, maximum a posteriori probability; MIC, minimum inhibitory concentration; MIPD, model-informed precision dosing; NR, not reported; SD, standard deviation; SOFA, sequential organ failure assessment; T, time; WBC, white blood cell count.

[a]Outcomes used in economic evaluation are italicized.

[b]Data are mean standard deviation or percentage, unless otherwise stated.

[c]Length of infection and stay for patients who survived and died in the study groups.

[d]Amikacin serum concentrations were normalized to be equivalent to gentamicin or tobramycin with division by a factor of 3.

[e]Delta-SOFA score, difference between SOFA score at T0 and T5 where T0 is the first day of antibiotic dose.

[f]Delta-CRP, difference between CRP at T0 and T5 where T0 is the first day of antibiotic dose.

[g]Delta-WBC, difference between WBC count at T0 and T5 where T0 is the first day of antibiotic dose.

[h]QoL, expressed as VAS-score and QALY (as assessed by EuroQoL 5D-5L questionnaire) at 6 months.

[i]Medical doctors, clinical pharmacists, clinical pharmacokineticists.

[j]Target concentrations for complicated infections, including meningitis, endocarditis, hospital-acquired pneumonia, and osteomyelitis, and improved penetration.

[k]Dependent on indication, target for most common indication provided.

TABLE 3 Characteristics and outcomes of economic evaluations (costs in 2023 US dollars).

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
Bootman, 1979[16] (Gentamicin)	CBA	NR	Hospital admission	NR, Discount rates 1%, 5%, 10%	Intervention costs *Operational costs*: Drug analysis (drug assay kits, medical supplies), Staff time (administrative, professional, supportive personnel) *Fixed costs*: Infrastructure (facility costs, equipment costs, journal subscriptions, equipment leasing)	• Intervention cost Total annual costs (operational costs + fixed costs): $215518.27 ($213273.44 + $2244.83)Total cost per patient: $352.02Total cost to individualize dosing of 66 patients: $23233.14 • Resource differences Cost per gentamicin sample: $50.06 vs $22.28 • Benefit/cost Benefit to cost ratios 1% - 24.0 6% - 8.7:1 10%: 4.5:1 • Economic outcome Benefits associated with the PK dose intervention for burn patients with Gram-negative septicaemia outweigh the costs associated with operating the service	64%
Burton, 1991[17] (Amikacin, gentamicin, tobramycin)	CBA	NR	Hospital admission	NR, Discount rate 6%	Direct Medical Costs Drug costs (length of therapy), hospital stay	• Intervention cost Cost per patient: $550.77 • Resource differences Cost of hospital stay difference: $2430.12 • Benefit/cost 4.09:1.00Cost avoidance per patient: $2430.12Total potential cost avoidance: $206754.80 • Economic outcome On the basis of reduced LOS, intervention (computer-assisted drug administration) could achieve potential cost savings.	61%
Cies, 2013[18] (Tobramycin)	CCA	NR	Hospital admission	2010, NR	Intervention costs *Operational costs*: Drug Analysis Direct Medical Costs Drug costs, Hospital stay	• Intervention cost NR • Resource differences Resource utilization (TDM vs Ctrl):Drug levels: $33693.21 vs $51630.60 (p < 0.001)Dosing adjustments: $17854.90 vs $35296.07 (p < 0.001)LOS: $,132079.78 vs $,462044.51 (p < 0.001) **Total cost: $,183685.00 vs $,548971.18 (p < 0.001)** • Benefit/cost	64%

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
						Total difference: -$365343.29 (−14.5%) **p < 0.001** • Economic outcome Cost analysis of clinical pharmacist managed TDM was favourable.	
Crist, 1987[19] (Gentamicin, tobramycin)	CCA	Patient	Hospital admission	NR	Intervention costs *Operational costs*: Drug analysis Direct medical costs Drug costs (IV bags and sets), Hospital stay (room charge, pharmacy fees)	• Intervention cost Not determined • Resource differences Hospital costs per course of therapy (TDM vs Ctrl): $3874.29 vs $5424.44 • Benefit/cost Cost savings per patient course of therapy: $1550.15 Total annual savings: $1368404.30 • Economic outcome TDM program can result in hospital cost savings	54%
Darko, 2003[20] (Vancomycin)	CEA	Health System	Hospital admission	2003, NR	Intervention costs *Operational costs*: Drug analysis (drug assay kit, calibration, medical supplies), Staff time (pharmacist, nursing, technician) Direct medical costs Cost of nephrotoxicity (drug-induced renal failure)	• Intervention cost Drug analysis: $248.21Pharmacist time (40 min): $64.09 ($60.72–69.14)Nursing time (5 min): $8.84 (8.21–9.49) • Resource differences Cost of treating nephrotoxicity: $16596.22 (unchanged) • Benefit/cost Mean (range) cost of PK dose adjustment and monitoring per nephrotoxic episode preventedAll patients: $37181.56 ($22161.78-40629.93)ICU patients: $12356.88 ($6454.13-15513.25)Oncology patients: $7387.26 ($2493.20 – 19576.24) Patients receiving concomitant nephrotoxins: -$8220.69 ($-18362.61 – 4024.79) • Economic outcome PK monitoring and dose adjustment not cost-effective for all patients. Significant cost savings are possible through implementation of targeted monitoring of selected subgroups	75%

(Continues)

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
Destache, 1989[21] (Gentamicin, tobramycin)	CCA	NR	Hospital admission	NR, NR	Intervention costs *Operational costs*: Drug analysis (assay, plasma concentration), Staff time *Fixed costs*: Infrastructure costs (computer equipment, paper, quality assurance office space) Direct medical costs Drug costs, Hospital stay	• Intervention cost Cost per patient: $111.29 • Resource differences Staff time per patient (30 min initial work-up, 10 min daily follow-up): $96.39 Total fixed costs per patient: $11.92Mean (SD) cost of drug therapy (TDM vs ctrl): $905.51 ± 649.98 vs $1226.04 ± 820.10 Mean (SD) patient charge for assay: $415.15 vs $363.00 • Benefit/cost CPS net savings per patient: Private $ 3833.67 ICU $5884.66 One-on-one ICU $7601.76 • CPS cost savings due to reduced therapy per patient: $268.30 • CPS cost savings due to reduced LOS per patient: Private $3565.38 ICU $5616.36 One-on-one ICU $7333.46 • Economic outcome Annual savings of $226432.65 (assuming 365 patients per year, assuming one day reduction in LOS) Use of CPS decreasing LOS by 6-days (assuming private room and 365 patients per year) – annual savings in hospital charges of $1300497.54	43%
Destache, 1990[22] (Amikacin, gentamicin, tobramycin)	CBA	NR	Hospital admission	NR, NR	Intervention costs *Operational costs*: Drug analysis (assay, plasma concentration), Staff time *Fixed costs*: Infrastructure costs (computer equipment, consumable office supplies, desk, chair, filing cabinets, journal subscriptions, quality assurance office space) Direct medical costs Drug costs, Hospital stay	• Intervention cost Mean (SD) operational costs per patient: $72.87 ± 41.92Fixed costs per patient: $90.04Direct costs per patient: $162.83 • Resource differences Direct cost/patient (TDM vs ctrl): $13606.31 ± 17046.19 vs $26357.31 ± 43820.12 ($p < 0.02$) • Benefit/cost Annual cost savings ($n = 500$ patients/y; 68% acceptance rate): $,335286.72Benefit-to-cost ratio: 52.25 • Economic outcome	61%

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
						CPS patients incurred lower direct hospitalization costs	
Destache, 1994[23] (Amikacin, gentamicin, tobramycin)	CBA	NR	Hospital admission	1992, Discount rates 5% and 10%	Intervention costs *Operational costs*: Staff time *Fixed costs*: Infrastructure costs (computer equipment, paper, consumable office supplies, desk, chair, filing cabinets, journal subscriptions quality assurance, office space) Direct medical costs Hospital stay	• Intervention cost Operational costs per year: $212188.56Fixed costs per year: $5031.14Total cost of Service per year: $217219.71 • Resource differences Median direct hospitalization costs per patient: $15557.23 vs $24784.32 per patient • Benefit/cost Total savings per patient: $9227.09Total cost savings of using CPS: $6426202.68Average benefit-to-cost ratio 29.6:15% 10.7:110% 5.57:1 • Economic outcome The use of CPS is economically and clinically beneficial for patients	61%
Dvorackova, 2019[24] (Amikacin, gentamicin)	Cost avoidance	NR	Length of therapy	NR, NR	Intervention costs *Operational costs*: Staff salary (0.2FTE pharmacist) Direct medical costs HD sessions related to drug-related adverse effect	• Intervention cost Operational cost: $6503.35per year • Resource differences Intervention prevented average 8 HD sessions per year: $2270.32/year • Benefit/cost The difference is negative (−$4233.03/year)The costs of the pharmacist are higher than the net cost of HD. • Economic outcome Trend towards safety and cost avoidance with computer assisted TDM of AGs (not significant)	50%
Ewoldt, 2022[25] (Ciprofloxacin, Beta-lactam antibiotics)	CEA	Hospital	Length of therapy	2020, NR	Intervention costs *Operational costs*: Drug analysis (laboratory costs) "costs of the intervention" Direct Medical costs Drug costs, Hospital stay (ICU and non-ICU), Diagnostic interventions	• Intervention cost NR • Resource differences Mean total costs (MIPD vs Std Dosing): $69888.90 (95% CI − $69992.28 – 209771.42) vs $64725.37 (95% CI – $86027.95 – 215480.03) • Benefit/cost	57%

(Continues)

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
						Average decrease in 6 months QALY of 0.03 (range − 0.5 to 0.5) (MIPD vs Std Dosing)ICER of -$237723.75 • Economic outcome The intervention is not cost-effective	
Fernández de Gatta, 1996[26] (Vancomycin)	CEA	NR	Length of admission	1996, NA	Intervention costs *Operational costs*: Drug analysis (drug assay kits, calibration, quality control, medical supplies), Staff time (pharmacy, nursing) Direct Medical costs Drug costs, Hospital stay	• Intervention cost Total cost per monitoring; $76.67 [Assay, $50; Nursing time $6.67; Clinical pharmacist time, $20]Total cost per patient: $176.67 (∼2.3 monitorings per patient) • Resource differences Mean (SD) cost of treatment (TDM vs Ctrl): $1078.85 ± 776.85 vs $1071.85 ± 674.85Mean (SD) cost of additional antibiotics (TDM vs Ctrl): $2095.04 ± 1583.36 vs $3676.74 ± 2003.37 • Benefit/cost Incremental cost of $725.01 per case of mild or moderate nephrotoxicity prevented with TDM • Economic outcome TDM is cost-effective in this high-risk population	57%
Kim, 2022[27] (Vancomycin)	CEA	NR	Until discharge	2017 (USD), NA	Intervention costs *Operational costs*: Drug analysis (laboratory tests), "TDM Services" Direct Medical costs Drug costs, Hospital stay	• Intervention cost Mean (SD) TDM Service cost per patient: All: $105.76 ± 80.23 ICU: $115.25 ± 85.0 Non-ICU: $100.68 ± 76.95 • • Resource differences **Mean (SD) total medical expenses:** **All $7484.22 ± 8511.11vs $9477.99 ± 10290.53 (p = 0.0070)** **ICU: $11491.36 ± 10222.60 vs $14763.82 ± 10827.89 (p = 0.0070)** Non-ICU: $4207.14 ± 4015.44vs $5153.25 ± 6067.31 (p = 0.5394) • Benefit/cost Difference in total medical expenses per patient (TDM – non-TDM): All -$950.73 (p = 0.0062)Difference in total medication	64%

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
						expenses per patient (TDM – non-TDM): All -$18.87 (p = 0.0178)Difference non-significant when analysed for ICU admission • Economic outcome TDM in elderly patients was associated with economic benefits, but not with better clinical outcomes	
Kimelblatt, 1986[28] (Gentamicin, tobramycin)	CBA	NR	Hospital admission	Not reported, NA	Intervention costs *Operational costs*: Drug analysis, Staff time (pharmacy) Direct Medical costs Drug costs, Hospital stay	• Intervention cost Staff time (study period): $5758.00Drug analysis: $289.21 • Resource differences AG acquisition cost: $11.37 vs $21.52**Mean (range) cost per course of therapy (Both drugs): $80.06 (6.57–679.22) vs $204.1 (6.57–1533.71) (t = 2.45, d.f. = 116)** • Benefit/cost Cost:benefit ratio: 1.13Drug expenditure: -$6819.22 • Economic outcome Service was an appropriate use of resources – had a favourable impact on use and cost antibiotics.	54%
Lehmann, 1982[29] (Theophylline)	Not reported	NR	Hospital admission	NR, NR	Intervention costs *Operational costs*: Drug analysis, Staff time (pharmacy)Direct Medical costs Hospital stay, Days on IV fluids, Home oxygen on discharge	• Intervention cost NR • Resource differences Approximate increase in total charge $1737.80 per patient for intervention group • Benefit/cost NR • Economic outcome Service appears to extend hospital stay without offering benefits	54%
Liu, 2024[30] (Vancomycin)	CEA	NR	NR	NR, NR	NR	• Intervention cost Cost of each additional assay: $16.15 • Resource differences Mean (SD) total direct medical costs: $20213.69 ± 8894.56 vs $20743.24 ± 13925.91 • Benefit/cost	46%

(Continues)

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
						ICER of WBC 3.46ICER of NEUT 3.46ICER of PCT 1.95ICER of CRP 3.13 • Economic outcome It was more economical to perform TDM in patients with postoperative intracerebral haemorrhage.	
Pinilla, 1992[31] (Amikacin, gentamicin, tobramycin)	CBA	NR	Hospital admission	NR, NR	Intervention costs *Operational costs*: Drug analysis (equipment), Medical consumables, Staff time (phlebotomy, pathology, pharmacy) *Fixed costs*: Infrastructure costs (computer, software) Direct Medical costs Drug costs, Hospital stay, Renal function tests, Special diet or therapy for renal failure	• Intervention cost Phelbotomy: $5.27 per sampleDrug assay: $5.74 per assayKinetic profile: $47.06 per profileDrug cost: Gentamicin (80 mg): $5.94 Tobramycin (80 mg): $13.30Hospital stay: Gross cost $752.47 Drugs per day $18.80 per patient Food cost $8.34 per dayRenal function tests: Creatinine: $5.71 per test Urea: $5.89 per test Diet or therapy for renal failure: $7.42 per day • Resource differences Pharmacy based recommendation cost $39.30 more than physician-based recommendation • Benefit/cost NR • Economic outcome Although the service yields appropriate recommendations and is well received, no statistically significant benefits are associated with pharmacy-based recommendations	64%
Streetman, 2001[32] (Gentamicin, tobramycin)	CBA	Hospital	Hospital admission	1999, NR	Intervention costs *Operational costs*: Drug analysis, Staff time (pharmacy) *Fixed costs*: Infrastructure costs (paper, photocopying) Direct Medical costs Drug costs, Hospital stay, Cost of AAN	• Intervention cost Cost per patient: $297.07Total salary cost (90 min initial work-up, 10 min daily follow-up, 20 min daily follow-up when PK profile generated): $199.64 per patientMean cost serum concentrations per patient: $95.83Cost of additional supplies per patient: $1.60 • Resource differences NR • Benefit/cost	64%

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
						Individualized PK monitoring decreased drug-associated nephrotoxicity costs by $145332.25/100 patientsOverall cost savings per patient: $1437.43 • Economic outcome Individualized PK monitoring is associated with a significant decrease in total cost.	
van Lent Evers[33] (Gentamicin)	CEA	Hospital	Hospital admission	NR, NR	Direct Medical costs Hospital stay, Major diagnostic and therapeutic interventions	• Intervention cost Cost of TDM service per patient: $329.18 • Resource differences Cost per patient: $329.18 vs $120.57**Mean (SD) total hospital costs for patients with suspected or proven Gram-negative infection during stay: $25119.13 ± 17735.54 vs $32271.15 ± 33915.13; p = 0.027** **Mean (SD) total hospital costs for patients admitted with suspected or proven Gram-negative infection: $17000.63 ± 7230.48 vs $22474.21 ± 14233.22; p = 0.007** • Benefit/cost Difference in survival: 5.6 ± 0.17% Difference in days after being discharged from hospital alive: 8.3 ± 13.6% • Economic outcome With active TDM, total costs were reducedAll patients treated with antibiotic benefited from active TDM, greatest benefit observed for patients who were admitted to hospital with suspected of proven Gram-negative infection	79%
Zhang 2020[34] (Vancomycin)	CEA	Health system	Hospital admission	2017, NA	Intervention costs *Operational costs*: Drug analysis (drug assay kit, calibration, medical supplies), Staff time (nursing, pharmacy) Direct Medical costs Treatment of VAN	• Intervention cost Drug assay: $53.99Pharmacist time (40 min): $13.94Nursing time (5 min): $1.92Laboratory test: $32.14 • Resource differences Total cost: $3680.11 vs $1751.06 • Benefit/cost ICER: $7275.46 per nephrotoxic episodeWillingness-to-pay threshold:	82%

(Continues)

TABLE 3 (Continued)

Study (drug)	Type	Perspective	Time horizon	Year of pricing, discount rates	Cost categories	Economic outcomes	Quality[a]
						$20775.46 per nephrotoxic episode • Economic outcome TDM was cost-effective and could prevent the occurrence of drug-associated nephrotoxicity	

Note: Significant values are in bold.
Abbreviations: CBA, cost benefit analysis; CCA, cost consequences analysis; CEA, cost-effectiveness analysis; CNY, Chinese yen; CRP, C-reactive protein; Ctrl, control; DFL, Dutch gilders; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; ID, infectious diseases; IV, intravenous; LOS, length of stay; NA, not applicable; NR, not reported; PD, pharmacodynamic; PK, pharmacokinetic; QALY, quality adjusted life years; SD, standard deviation; SOFA, sequential organ failure assessment; TDM, therapeutic drug monitoring; USD, US dollars; VAN, vancomycin associated nephrotoxicity; WBC, white blood cell count.
[a]Proportion of applicable items met on the CHEERS checklist.

(Table 1). One study reported on a TDM intervention at a hospital that provided care for adult and paediatric patients, but outcomes were not differentiated according to age.[31] One study reported on older adult (≥65 years) patients,[27] one study on burns patients,[16] one on patients admitted to the ICU,[25] one on immunocompromised, febrile patients[26] and one on patients with intracerebral haemorrhage.[30] For studies evaluating TDM for antibiotics ($n = 18$), most ($n = 11$) had inclusion criteria of suspected[17] and/or proven infection.[19–24,26,32–34]

3.3 | Intervention

Antibiotics were the target drug of the majority ($n = 18$) of TDM interventions (Table 1). Twelve studies reported on the use of aminoglycoside antibiotics,[16–19,21–24,28,31–33] five studies reported on the glycopeptide antibiotic, vancomycin[20,26,27,30,34] and one reported on ciprofloxacin and a range of beta-lactam antibiotics.[25] One study reported on TDM of the bronchodilator, theophylline.[29]

Most interventions incorporated pharmacist-led TDM[18–20,23,24,26,28,29,33,34] (Table 2). The majority were staffed by clinical pharmacists ($n = 15$)[16,18–24,26,28,29,31–34] or clinical pharmacologists ($n = 1$).[27] Three studies did not report staffing.[17,25,30]

One study described the use of education to introduce the TDM intervention to doctors and nurses, along with pre-printed instruction cards to co-ordinate plasma sampling.[28] Some ($n = 6$) interventions provided initial dose recommendations,[21–24,28,33] but most ($n = 9$) provided dose recommendations after the first drug concentration became available[18,20,25–27,29,31,32,34] (Table 2). Interventions commonly relied on population pharmacokinetic models alone or embedded in Bayesian dosing programs to interpret drug concentrations and provide individualized recommendations (Table 2). Programs used included Abbottbase,[26,27] InsightRX,[25] MWPharm[24,33] and SmartDose PK.[34] Six studies did not identify the Bayesian forecasting program.[17,18,21–23,31] Three studies undertook pharmacokinetic calculations using the Sawchuk and Zaske method,[19,31,32] while two studies reported using pharmacokinetic equations to determine individual clearance.[28,29] Two studies did not report on tools used to provide dose recommendations.[16,20] One study provided minimal description of the intervention.[30]

3.4 | Comparator

The majority of studies evaluated the efficacy of TDM individualized dosing compared to usual care (Table 2). Usual care was described as physician-led[17,24,31,32,34] or non-guided[20,21,23,28,29,33] dosing. For three studies, the comparator was no TDM.[26,27,30]

Most studies ($n = 15$) provided therapeutic targets for the intervention drug with 12 studies reporting achievement of therapeutic targets either as a proportion of target achievement ($n = 8$)[18–20,22,24,25,31,34] or mean/average concentration ($n = 4$)[17,21,23,33] (Table 2). Four studies did not provide therapeutic targets,[16,19,23,28] six did not comment on target achievement[16,26–29,32] and one study

provided a mean concentration for the intervention group.[30] Five studies reported significant improvement in achievement of aminoglycoside therapeutic targets[17,18,22,23,33] and one study reported improved achievement of target trough concentration for vancomycin.[34]

3.5 | Outcomes

3.5.1 | Clinical outcomes

Length of stay was the most common patient outcome used in economic evaluations of TDM ($n = 13$)[16–19,21–23,26,27,29,31–33] with two studies reporting ICU length of stay[25,33] (Table 2). Four studies considered length of therapy,[21,26,27,31] while three considered a measure of dose size.[19,27,31] Six studies considered response to therapy, such as duration of fever, microbiological cure and length of infection.[16,26–29,32]

Nephrotoxicity was considered in eight studies,[16,20,24,26–28,31,34] with two studies also considering ototoxicity.[16,28] Mortality was the patient outcome used in the economic evaluation of three studies.[27,28,33] One study considered quality of life measures.[25] One study did not report the patient outcome considered in the economic evaluation.[30] Most studies ($n = 12$) reported some improvement in a patient outcome[16–19,21,23,26,27,29,32–34] Four studies reported no change in clinical outcomes with TDM intervention.[20,24,25,28]

3.6 | Economic evaluation outcomes

3.6.1 | Costs reported

Most ($n = 15$) studies incorporated the intervention and direct medical costs in their economic evaluation (Table 3). Two studies used direct medical costs alone[17,33] and one study used intervention costs alone.[16] One study reported total direct medical costs but did not disaggregate the source of costs.[30] Fifteen studies attributed intervention costs to operational costs associated with drug analysis ($n = 14/15$)[16,18–22,25–29,31,32,34] and/or staff time ($n = 12/15$)[16,20–24,26,28,29,31,32,34] Staff time captured included pharmacy ($n = 8/15$),[20,24,26,28,29,31,32,34] nursing ($n = 4/15$),[20,26,31,34] technical/pathology staff ($n = 2/15$)[20,26] and phlebotomy ($n = 1/15$).[31] Four studies did not report specific staff.[16,21–24] Six studies reported fixed costs of the intervention associated with infrastructure.[16,21–24,31,32] One study captured software costs.[31] Direct medical costs included hospital stay ($n = 14/17$),[17–19,21–23,25–29,31–33] drug costs ($n = 12/17$)[17–19,21,22,25–28,31,32] and medical treatment or interventions ($n = 8/17$).[20,24,25,29,31–34] Most medical treatment costs were attributed to treatment for nephrotoxicity ($n = 5/8$).[20,24,31,32,34]

3.6.2 | Economic outcomes

Eight studies[16,17,21,22,26,27,32,33] reported per patient intervention costs ranging from $105.76[27] to $550.77[17] (Table 3). Three studies[16,23,24] provided total intervention costs per year, ranging from $6503.35[24] to $217219.71.[23] Four studies did not report intervention costs.[18,19,25,29]

Most economic evaluations determined that the TDM intervention was favourable compared to the comparator. For studies that reported cost differences, five[17,19,21,23,32] reported patient-level cost savings ranging from $1437.43[32] to $9227.09.[23] One study[29] reported an increase in per patient costs of ~$1737.80. Seven studies[18,21–23,27,30,33] reported a reduction in total costs, while one study reported that the TDM intervention cost $39.30 more than physician-led dosing.[31] Three studies attributed costs to nephrotoxic episodes, one reporting a reduction in aminoglycoside-associated nephrotoxicity costs[32] and two reporting a net increase in costs[20,24] when all patients were monitored. Of the seven studies that reported on complex patient populations, six reported an economic benefit.[16,18,26,27,30,34] An additional four studies reported a cost reduction with application of TDM in sub-populations.[20,21,27,33] Three studies reported an economic benefit, without a significant improvement in clinical outcome.[17,27,28]

Three studies reported ICERs.[25,30,34] One study found a model informed precision dosing (MIPD) intervention not to be cost-effective, reporting an ICER per QALY of −$237723.75 (2020),[25] reflecting the higher cost accompanying a worse outcome. Two studies reported positive ICERs; one with ICERs >1 relative to the proportion of patients achieving normal values of inflammatory factors[30] and one with an ICER below the willingness to pay ratio.[34] Cost–benefit ratios reported for five studies[16,17,22,23,28] ranged from 1:1.13[28] to 1:52.25.[22] For cost–benefit evaluations that did not generate a cost–benefit ratio, one reported that costs associated with treatment of nephrotoxicity were reduced,[32] but two found no significant benefits.[29,31]

4 | DISCUSSION

TDM is employed in hospitals to optimize therapeutic outcomes of some drugs, but whether it is a good investment for hospitals is less well defined. The majority of studies identified in this review reported improved patient outcomes and reduced costs attributed to an antimicrobial TDM intervention. Of note, there is the suggestion that optimal outcomes are more likely to be achieved when interventions are tailored for complex patient populations, such as those in ICU.

As with previous work,[13] most studies reported on TDM interventions designed to individualize dosing of antimicrobials, predominantly for aminoglycosides. Despite the 40-year period across which studies were identified, and the increasing push to consider costs of clinical practices, the quality of the economic evaluations described was consistently poor. Many missed key features outlined in the CHEERS framework, though it must be acknowledged that most ($n = 13/19$) of the included studies were published prior to the initial publication of the framework in 2013.[14] Note, the median number of checklist items met before (61%) and after (57%) publication of the framework is unchanged. The absence of some features was not

necessarily deleterious. Time horizon, for example, is implicit given that costs were largely contained to patient admission. The absence of other features may reflect the age of the studies. For instance, patient engagement is a more recent concept, and may not reasonably be expected to be included in earlier studies. However, some of the economic descriptors that were missing are useful and can facilitate comparison between interventions. Study perspective is needed to help understand whose costs are being considered and who pays but was only defined in six studies. Currency price was only stated in nine studies. Structured reporting of economic evaluations provides baseline guidance to enable translation of an intervention between sites, regardless of regional variations that contribute to differences in costs and resources. Consistent use of a reporting framework can provide valuable insights necessary to determine the appropriateness of an intervention for a patient population and available infrastructure at a proposed site. While describing outcomes at one site may be of academic interest, extending benefits to wider patient populations serves to achieve the overall aim of medical science: to improve patient outcomes.

One key feature missing from most economic evaluations was consideration of heterogeneity. It is necessary to consider if the benefits of an intervention are distributed differently across individuals or if adjustments need to be made to reflect priority populations. Most studies identified in this review were undertaken in adult patients, with only a few considering differences in clinical presentation or presenting some measure of heterogeneity. However, outcomes suggest that there is value in tailoring an intervention to target specific patient populations. For example, Darko et al.[20] found increased costs associated with a vancomycin TDM intervention when all patients were considered, reduced costs were reported for patient subgroups; patients receiving concomitant nephrotoxins, as well as ICU patients. Differential TDM outcomes in priority population groups have been reported previously. For example, young age, male gender and augmented renal clearance are characteristics shared by clinically ill patients who achieve therapeutic benefits from beta-lactam TDM.[37] Characterizing TDM outcomes in different patient populations is necessary to target TDM interventions appropriately. That exploration of patient subgroups was largely lacking in the studies identified likely reflects the small sample size of most. More importantly, it demonstrates a missed opportunity to provide the necessary information to tailor interventions to bring in more efficiencies, thus likely improve cost–benefits.

Important methodological considerations when conducting economic evaluations of TDM interventions have been outlined by recent work exploring TDM-guided dosing in oncology.[9] Broadly, the key costs to be considered for a TDM intervention include drug costs, TDM assay costs, staff time and adverse-event-related costs.[9] Most studies identified in this review captured some aspect of these costs, although few considered implementation or maintenance costs. This is important given increased literature on the use of software to guide TDM and the subsequent need to fund software over time. However, consideration needs to be given to the economic and clinical outcome measures selected for hospital-based TDM interventions. As opposed to chronic and high-cost cancer treatments, the outcomes captured in this review are aligned with the short-term (across hospital stay) application of TDM. Only one study reported QALY,[25] length of stay was instead the most cited measure of economic outcome. Although relatively easy to capture and cost, it is influenced by factors beyond TDM and drug therapy. Significant changes in length of stay may not be plausible for a general patient population receiving antimicrobials and any changes observed must be considered alongside the clinical context. For example, Bootman et al.[16] reported that length of stay of adult burn patients was significantly increased for patients in the TDM intervention group. Although contrary to the hypothesis that improved drug therapy would reduce length of stay, increased stay likely reflected the increased probability of survival for patients in the TDM group—optimized drug dosing achieving improved therapeutic outcomes. What is apparent in the studies identified is a lack of a common measure of benefit to value the investment case for TDM interventions in hospitals. As put forward by Erku et al.,[9] the more relevant measures of economic outcomes for hospital-based TDM are the costs associated with avoiding over- or under-dosing—attaining therapeutic target and avoiding toxic concentrations.

The overall goal of TDM is to improve therapeutic outcomes by using information from drug concentrations to adjust drug dosing. Given that monitoring drug concentrations forms the basis of a TDM intervention, capturing target attainment could serve as a surrogate for both clinical and economic benefits. As it stands, the heterogeneity of therapeutic outcomes reported limits the generalizability of findings. Unlike for studies describing outcomes for chronic conditions, such as cancer, no study used a validated framework to describe clinical outcomes. For antimicrobial TDM, variable clinical outcomes were reported—from length of febrile period to changes in inflammatory markers. Some studies reported adverse effects. This measure is relevant for some drugs, such as vancomycin and the aminoglycoside antibiotics, where the drug-related adverse effect (e.g., nephrotoxicity) can be captured and the required treatment (e.g., haemodialysis) can be costed. However, this is not applicable for all drugs. More uniform evaluations could be achieved by reporting target attainment. Of the 12 studies that reported target attainment, eight[17–19,21–23,33,34] reported trends towards improved target attainment and clinical outcomes; this was significant for both measures for six studies.[17,18,22,23,33,34] Determining achievement of therapeutic target would provide a feasible approach to describe outcomes of hospital-based TDM interventions. Costs captured could reflect avoidance of adverse effects where relevant, but also changes in drug therapy (e.g., drug dosing and length of therapy).

There are some limitations to this review. Of the studies identified, most were retrospective. The reporting of clinical and economic outcomes was variable, with most missing key features from the CHEERS reporting framework. Regardless, the review highlights the need to consider subpopulations when designing and evaluating hospital-based TDM interventions. Future work is needed to investigate the role of TDM interventions in ambulatory care, for example TDM for immunosuppressants in transplant patients.

5 | CONCLUSION

TDM is a clinical tool that provides clinicians with the ability to guide drug dosing to achieve therapeutic targets in complex patients. Significant improvements in both economic and clinical outcomes may be realized when interventions are targeted to populations for whom achievement of therapeutic targets is compromised by pharmacokinetic variability. Monitoring attainment of therapeutic target could serve as a feasible surrogate measure of benefit.

AUTHOR CONTRIBUTIONS

J.E.C. and T.L. conceived the original concept. J.E.C., T.L., D.J.C., D.M.R., J.B., S.L.S. and R.O.D. designed the methodology. J.E.C. and T. L. collected the data and conducted the analyses. All authors critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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