Effectiveness and Safety of Beta-Lactam Antibiotics with and without Therapeutic Drug Monitoring in Patients with *Pseudomonas aeruginosa* Pneumonia or Bloodstream Infection

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**ABSTRACT** This objective of this study was to compare clinical outcomes in hospitalized patients with *Pseudomonas aeruginosa* pneumonia (PNA) or bloodstream infection (BSI) receiving beta-lactam antibiotic (BLA) infusions with and without the guidance of therapeutic drug monitoring (TDM). A retrospective, parallel cohort study was conducted at two academic medical centers between December 2015 and January 2020, UF Shands Gainesville, which uses BLA TDM for select patients (BLA TDM), and UF Health Jacksonville, which does not use BLA TDM (No-BLA TDM). All hospitalized adult patients with respiratory or blood culture positive for *P. aeruginosa* who met diagnosis criteria for lower respiratory tract infection with a positive *P. aeruginosa* respiratory culture and who received ≥48 h of intravenous BLA with *in vitro* susceptibility within 72 h of positive culture collection were included. The primary outcome was a composite of presumed treatment failure defined as the presence of any of the following from index-positive *P. aeruginosa* culture collection to the end of BLA therapy: all-cause mortality, escalation of and/or additional antimicrobial therapy for *P. aeruginosa* infection after 48 h of treatment with susceptible BLA due to worsening clinical status, or transfer to a higher level of care (i.e., the intensive care unit [ICU]). Analyses were adjusted for possible confounding with inverse probability of treatment weighting (IPTW). Two-hundred patients were included (BLA TDM, *n* = 95; No-BLA TDM, *n* = 105). In IPTW-adjusted analysis of the primary composite endpoint, BLA TDM demonstrated a significant decrease in presumed treatment failure compared to No-BLA TDM (adjusted odds ratio [aOR] 0.037, 95% confidence interval [CI] [0.013 to 0.107]; *P* < 0.001). BLA TDM had more 30-, 60- and 90-day infection-related readmissions ([aOR], 11.301, 95% CI [3.595 to 35.516]; aOR 10.389, 95% CI [2.496 to 43.239], and aOR 24.970, 95% CI [6.703 to 93.028]) in IPTW analyses. For both unadjusted and IPTW-adjusted cohorts, there was no significant difference in hospital and ICU length of stay, adverse effects while on BLA, or microbiological eradication between BLA TDM and No-BLA TDM. In hospitalized adult patients with *P. aeruginosa* PNA or BSI, the use of TDM-guided BLA infusions decreased the odds of presumed treatment failure compared to patients receiving BLA infusions without TDM guidance. Future studies should evaluate BLA TDM impact on readmission.

**KEYWORDS** therapeutic drug monitoring, beta-lactam antibiotics, *Pseudomonas aeruginosa*, pneumonia, bloodstream infection, beta-lactams

*Pseudomonas aeruginosa* infections can be challenging to treat due in part to its multiple resistance mechanisms, limited antipseudomonal active agents, and patient population pharmacokinetic (PK) variances (1–4). Beta-lactam antibiotics (BLA) are commonly used to treat *P. aeruginosa* infections and demonstrate time-dependent bactericidal activity whereby...
efficacy is optimized when free drug concentrations are 100% time above the MIC (100% fT >MIC) or four times the MIC (100% fT >4×MIC) in critically ill patients (5–7). This is compared to a target of 40 to 70% fT >MIC for noncritically ill patients, depending on the selected BLA, based on preclinical work (8–12). Even though BLAs are considered to have a wide therapeutic index, suboptimal exposures may lead to treatment failure and antimicrobial resistance while high exposure may result in adverse effects (13–16). Additionally, BLA dosing regimens based on manufacturer recommendations may not be optimal for therapeutic efficacy in all patient populations due to altered patient PK and/or reduced BLA susceptibility of P. aeruginosa (2, 17, 18). Administering BLA via prolonged (i.e., extended or continuous) infusions may facilitate optimized BLA exposure and suppress the emergence of resistance (14, 19–21). The additional intervention of using therapeutic drug monitoring (TDM) to help guide BLA regimens may serve to further optimize BLA exposure in certain patient populations, including those with an altered volume of distribution (Vd) or renal clearance and infections with elevated MIC (16, 22–26). While BLA PK/PD target attainment has been studied extensively in vitro and in vivo and has been associated with improved survival, lower rates of clinical failure, and microbiological success, sparse clinical data remain available regarding assessing the impact of TDM-guided BLA dose optimization on clinical outcomes (27–31).

This study aimed to compare clinical outcomes in patients with P. aeruginosa pneumonia (PNA) or bloodstream infection (BSI) receiving BLA infusions with and without the guidance of TDM.

RESULTS

A total of 438 unique patients with blood or respiratory culture positive for P. aeruginosa and treated at UF Shands Gainesville (BLA TDM, n = 220) or UF Health Jacksonville (No-BLA TDM, n = 218) were screened for study inclusion with 200 fulfilling inclusion criteria (BLA TDM, n = 95 (48%); No-BLA TDM, n = 105 [52%]). The most common reasons for study exclusion were cancer (27%), cystic fibrosis (24%), and transfer from an outside hospital with positive P. aeruginosa culture (16%) (Fig. 1). A comparison of baseline demographic and clinical characteristics between BLA TDM and No-BLA TDM is shown in Table 1. Mean age was 58 ± 17 years, 64.5% were male, and 80% were admitted to the ICU at least once during the hospital admission. Baseline characteristics were similar between cohorts although BLA TDM had fewer uninsured patients (1%) and lower median (interquartile range [IQR]) Charlson comorbidity index (4 [2 to 5]) and APACHE II scores (19 [14 to 26]) compared to No-BLA TDM (10%) (5 [3 to 7]), and 22 (17 to 28), respectively; all P < 0.05. Additionally, BLA TDM had more positive blood cultures compared to No-BLA TDM (52% versus 34%; P = 0.015). Other infection types can be seen in Table 1. Regarding infection management, cefepime was the predominant definitive BLA for both BLA TDM (73%) and No-BLA TDM (50%), fewer BLA TDM patients received piperacillin-tazobactam (7% versus 37%; P < 0.001) and prolonged infusions (28% versus 95%; P < 0.001) relative to No-BLA TDM, and BLA TDM had more repeat blood cultures (76% versus 56%; P = 0.005),
TABLE 1 Baseline demographic and clinical characteristics

| Characteristics                        | Total (n = 200) | BLA TDM (n = 95) | No-BLA TDM (n = 105) | P value |
|----------------------------------------|-----------------|------------------|----------------------|---------|
| Age (mean) (yr) ± SD                   | 58 ± 17         | 59 ± 17          | 58 ± 16              | 0.614   |
| Male                                   |                |                  |                      |         |
| BMI (kg/m²)                            | 25 (21–31)      | 26 (22–33)       | 25 (21–31)           | 0.873   |
| Obese (BMI >30 kg/m²)                  | 61 (31)         | 32 (34)          | 29 (28)              | 0.352   |
| Baseline CLcr (ml/min)                 | 69 (39–109)     | 69 (36–111)      | 69 (43–105)          | 0.589   |
| NH/LTC resident                        | 21 (11)         | 7 (7)            | 14 (13)              | 0.169   |
| Insurance                              |                |                  |                      |         |
| Private                                | 43 (21)         | 25 (26)          | 18 (17)              | 0.115   |
| Medicare/Medicaid                      | 146 (73)        | 69 (73)          | 77 (73)              | 0.911   |
| Uninsured                              | 11 (6)          | 1 (1)            | 10 (10)              | 0.005   |
| Immunosuppressed                       | 13 (7)          | 9 (10)           | 4 (4)                | 0.151   |
| IVDU                                    | 33 (17)         | 13 (14)          | 20 (19)              | 0.344   |
| Charlson comorbidity index             | 4 (2–6)         | 4 (2–5)          | 5 (3–7)              | 0.015   |
| Infection severity                     |                |                  |                      |         |
| ICU admission                          | 159 (80)        | 77 (81)          | 82 (78)              | 0.726   |
| SOFA score                             | 5 (2–8)         | 5 (2–8)          | 5 (2–8)              | 0.757   |
| APACHE II score                        | 21 (15–27)      | 19 (14–26)       | 22 (17–28)           | 0.033   |
| Mechanical ventilation during hospitalization |                          |                  |                      |         |
| At hospital admission                  | 54 (27)         | 28 (25)          | 25 (24)              | 0.365   |
| Prior to culture collection            | 106 (53)        | 53 (56)          | 51 (49)              | 0.308   |
| At culture collection                  | 103 (52)        | 53 (56)          | 49 (47)              | 0.197   |
| Start of definitive BLA                | 105 (53)        | 53 (56)          | 51 (49)              | 0.271   |
| During definitive BLA                  | 118 (59)        | 61 (64)          | 56 (53)              | 0.119   |
| RRT during definitive BLA therapy      | 36 (18)         | 14 (15)          | 22 (21)              | 0.253   |
| Intermittent HD                        | 22 (11)         | 7 (7)            | 15 (14)              | 0.118   |
| CRRT                                   | 15 (8)          | 8 (8)            | 7 (7)                | 0.683   |
| ARC during definitive BLA therapy      | 53 (27)         | 28 (30)          | 24 (23)              | 0.287   |
| Hospital-acquired infection            | 91 (46)         | 41 (43)          | 50 (48)              | 0.571   |
| Positive culture source                |                |                  |                      |         |
| Blood                                  | 85 (43)         | 49 (52)          | 36 (34)              | 0.015   |
| Skin and soft tissue                   | 26 (13)         | 11 (12)          | 15 (14)              | 0.057   |
| Urine                                  | 29 (15)         | 17 (18)          | 12 (11)              | 0.688   |
| Catheter associated                    | 10 (5)          | 5 (5)            | 5 (5)                | 0.534   |
| Intra-abdominal                        | 12 (6)          | 7 (7)            | 5 (5)                | 0.959   |
| Other                                  | 9 (5)           | 4 (4)            | 5 (5)                | 0.191   |
| Respiratory                            | 121 (61)        | 54 (57)          | 67 (64)              | 0.189   |
| Blood and respiratory                  | 9 (5)           | 7 (7)            | 2 (2)                | 0.088   |

*Data are presented as number (%), mean ± standard deviations, and median (interquartile range [IQR]), as appropriate. BLA, beta-lactam antibiotic; TDM, therapeutic drug monitoring; SD, standard deviation; BMI, body mass index; CLcr, creatinine clearance; NH/LTC, nursing home/long-term care; IVDU, intravenous drug use; ICU, intensive care unit; SOFA, sequential organ failure assessment; APACHE, acute physiological assessment and chronic health evaluation; RRT, renal replacement therapy; HD, hemodialysis; CRRT, continuous renal replacement therapy; ARC, augmented renal clearance.

Infectious diseases consults (70% versus 27%; P < 0.001), and concomitant Gram-negative antimicrobial therapy (43% versus 17%; P < 0.001) compared to No-BLA TDM (Table 2).

The propensity score distribution between BLA TDM and No-BLA TDM was adequately balanced after IPT weighting, as demonstrated by the Kolmogorov-Smirnov (KS) test with pre- and post-IPT weighting P values of <0.001 and 0.131, respectively. Additionally, before IPT weighting, the standardized mean differences (SMD) between BLA TDM and No-BLA TDM were significantly different for blood infection, definitive BLA, BLA infusion duration (prolonged versus intermittent), ≥24 h of concomitant Gram-negative antibiotic therapy with definitive BLA, and ID consult. After IPT weighting, SMDs for those variables were <0.1.

The prediction ability of the propensity score model with an area under the receiver operating characteristic (AU-ROC) of 95.2% is displayed in Fig. S1 in the supplemental material.
Unadjusted and IPTW-adjusted primary and secondary endpoints are presented in Table 3. In unadjusted cohorts, the composite outcome of presumed treatment failure occurred in 15/95 (16%) of BLA TDM and 26/105 (25%) of No-BLA TDM, respectively (OR 0.662, 95% CI [0.333 to 1.317]; P = 0.240). In the IPTW analysis, BLA TDM had significantly lower odds of presumed treatment failure compared to No-BLA TDM (aOR 0.037, 95% CI [0.013 to 0.107]; P = 0.001).

BLA TDM did have significantly more of the following at 30 and 60 days posthospital discharge in IPTW-weighted analyses, respectively: readmissions (aOR 15.141, 95% CI [4.457 to 45.503] and aOR 11.555, 95% CI [3.770 to 35.418]), infection-related readmissions (aOR 11.301, 95% CI [3.595 to 35.516] and aOR 10.389, 95% CI [2.496 to 43.239]), and readmissions with P. aeruginosa infection recurrence (aOR 5.307, 95% CI [1.247 to 22.577] and aOR 3.760, 95% CI [1.454–31.123]). Additionally, BLA TDM had more 90-day infection-related readmissions compared to No-BLA TDM in both unadjusted (OR 3.307 [1.015 to 10.769]; P = 0.047) and IPTW-adjusted analyses (aOR 24.970; 95% CI [6.703 to 93.028]; P < 0.001). For both unadjusted and IPTW-adjusted cohorts, there was no significant difference in hospital LOS, ICU LOS, adverse effects while on BLA, or microbiological eradication between BLA TDM and No-BLA TDM.

### TABLE 2 Infection management

| Characteristics | Total (n = 200) | BLA TDM (n = 95) | No-BLA TDM (n = 105) | P value |
|-----------------|----------------|-----------------|----------------------|---------|
| Definitive beta-lactam antibiotic used for *P. aeruginosa* infection<sup>b</sup> | | | | |
| Cefepime | 122 (61) | 69 (73) | 53 (50) | <0.001 |
| Meropenem | 29 (15) | 18 (19) | 11 (10) | 0.089 |
| Piperacillin-tazobactam | 46 (23) | 7 (7) | 39 (37) | <0.001 |
| Aztreonam | 1 (0.5) | 1 (1) | 0 (0) | 0.475 |
| Ceftazidime | 1 (0.5) | 0 (0) | 1 (1) | >0.999 |
| Ceftazidime-avibactam | 1 (0.5) | 0 (0) | 1 (1) | >0.999 |
| Prolonged infusion BLA<sup>c</sup> | 127 (64) | 27 (28) | 100 (95) | <0.001 |
| Polymicrobial infections | 79 (40) | 32 (34) | 47 (45) | 0.114 |
| Gram-positive | 19 (10) | 7 (7) | 12 (11) | 0.348 |
| Gram-negative | 56 (28) | 24 (25) | 32 (31) | 0.434 |
| Both | 4 (2) | 1 (1) | 3 (3) | 0.623 |
| Concomitant Gram-negative antibiotic | 59 (30) | 41 (43) | 18 (17) | <0.001 |
| Amikacin IV | 10 (5) | 5 (5) | 5 (5) | >0.999 |
| Ciprofloxacin IV | 5 (3) | 1 (1) | 4 (4) | 0.372 |
| Colistin nebulized | 5 (3) | 3 (3) | 2 (2) | 0.668 |
| Gentamicin IV | 3 (2) | 2 (2) | 1 (1) | 0.605 |
| Tobramycin IV | 11 (6) | 8 (8) | 3 (3) | 0.121 |
| Tobramycin nebulized | 25 (13) | 22 (23) | 3 (3) | <0.001 |
| Duration of concomitant GN antibiotic (days) | 4 (1-9) | 4 (2-9) | 3 (1-7) | 0.272 |
| First dose of active BLA to first level drawn (days) | NA | 3 (2-5) | NA | NA |
| First dose of active BLA to first level result (days) | NA | 5 (3-6) | NA | NA |
| Infectious diseases consult | 94 (47) | 66 (70) | 28 (27) | <0.001 |
| Repeat culture | 131 (66) | 72 (76) | 59 (56) | 0.005 |
| Negative repeat culture | 85 (43) | 45 (47) | 40 (38) | 0.187 |
| Repeat culture with new nonsusceptibility | 20 (15) | 14 (19) | 8 (14) | 0.108 |
| Cefepime | 16 (80) | 10 (71) | 5 (63) | 0.122 |
| Meropenem | 5 (25) | 2 (14) | 2 (25) | >0.999 |
| Piperacillin-tazobactam | 7 (35) | 6 (43) | 1 (13) | 0.055 |
| Ceftazidime | 11 (55) | 9 (64) | 1 (13) | 0.007 |
| Ciprofloxacin | 5 (25) | 2 (14) | 2 (25) | >0.999 |
| Levofloxacin | 7 (35) | 3 (21) | 3 (38) | >0.999 |
| Gentamicin | 6 (30) | 1 (7) | 3 (38) | 0.623 |
| Tobramycin | 4 (20) | 0 (0) | 3 (38) | 0.248 |
| Amikacin | 3 (15) | 0 (0) | 1 (13) | >0.999 |
| Polymyxin | 2 (10) | 0 (0) | 0 (0) | >0.999 |

<sup>a</sup>Data are presented as number (%) and median (interquartile range [IQR]), as appropriate. BLA, beta-lactam antibiotic; TDM, therapeutic drug monitoring; IV, intravenous; GN, Gram-negative.

<sup>b</sup>BLA were renally dose adjusted at least once daily per pharmacy as indicated in the No-BLA TDM group per hospital policy.

<sup>c</sup>Prolonged infusion BLA: extended (infused over 3–4 h) or continuous infusion (infused over 24 h).
concentration and MIC ratios achieved for the three most used BLA (Fig. 2). Target attainment of 100% and 4 days (IQR 2 to 6), respectively. Following the result of the (21%) of BLA TDM patients did not achieve 100% met the primary endpoint of presumed treatment failure (Table S1). In comparison, 20/95 from the October 2022 Volume 66 Issue 10 10.1128/aac.00646-22

DISCUSSION
In response to a growing body of experimental and clinical data assessing the impact of TDM-guided BLA infusions on clinical outcomes, this study aimed to evaluate a contemporary

In the BLA TDM group, 107 serum concentrations were included in the analysis of $C_{inf}$; MIC ratios achieved for the three most used BLA (Fig. 2). Target attainment of 100% $T_{inf}$ and 100% $T_{>4}\times MIC$ was achieved in 86/95 (91%) and 70/95 (74%) of BLA TDM patients, respectively, within 4 days of receiving active BLA therapy in vitro. The median time elapsed from the first administered BLA dose with in vitro susceptibility to the collection of first serum concentration and first serum concentration achieving 100% $T_{>4}\times MIC$ was 3 days (IQR 2 to 5) and 4 days (IQR 2 to 6), respectively. Following the result of the first BLA TDM serum concentration, 75 (79%) BLA TDM patients achieved at least 100% $T_{>4}\times MIC$ and of those, 13/75 (17%) met the primary endpoint of presumed treatment failure (Table S1). In comparison, 20/95 (21%) of BLA TDM patients did not achieve 100% $T_{>4}\times MIC$ and 2/20 (10%) of those patients met the primary endpoint of presumed treatment failure. Following the result of the first serum BLA concentration, 13 BLA TDM patients received dose increases (14%), 19 received dose decreases (20%), 7 were transitioned from 30-minute bolus infusions to continuous intravenous infusions (CIVI) (7%), and 4 were transitioned from 3 to 4 h extended infusions to CIVI (4%). For BLA TDM patients meeting the primary composite outcome of treatment failure, 2/15 (13%) receive dose increases, 5/15 (33%) received dose decreases, and 1 patient was transitioned from bolus 30-minute infusions to CIVI.

TABLE 3 Unadjusted and IPTW-adjusted clinical outcomes

| Outcomes $^a$ | BLA TDM (n = 95) | No-BLA TDM (n = 105) | Unadjusted cohort | Propensity score IPTW cohort $^{ac}$ |
|---------------|-----------------|-----------------|------------------|-----------------------------------|
| Presumed treatment failure | 15 (16) | 26 (25) | 0.662 (0.333–1.317) | 0.240 | 0.037 (0.013–0.107) | <0.001 |
| All-cause mortality during BLA therapy | 12 (13) | 21 (20) | 0.578 (0.267–1.252) | 0.164 | 0.010 (0.002–0.040) | <0.001 |
| Escalation/addition of antibiotic therapy | 1 (1) | 5 (5) | 0.213 (0.024–1.855) | 0.161 | 0.046 (0.005–0.436) | 0.007 |
| Transfer to higher level of care | 2 (2) | 0 (0) | 0.224 | 0.480 |
| All-cause in-hospital mortality | 14 (15) | 23 (22) | 0.652 (0.312–1.363) | 0.256 | 0.022 (0.005–0.094) | <0.001 |
| Hospital length of stay (days) | 21 (15–33) | 21 (11–29) | 1.084 (0.637–1.842) | 0.767 | 1.013 (0.493–2.078) | 0.973 |
| ICU length of stay (days) | 19 (11–28) | 14 (8–23) | 1.192 (0.863–1.648) | 0.286 | 1.157 (0.678–1.973) | 0.593 |
| Adverse effects while on BLA | 39 (41) | 38 (36) | 1.095 (0.592–2.027) | 0.772 | 0.670 (0.196–2.297) | 0.524 |
| AKI | 31 (30) | 29 (28) | 1.205 (0.626–2.320) | 0.440 | 0.554 (0.161–1.904) | 0.348 |
| Clostridiodes difficile $^b$ | 3 (3) | 6 (6) | 0.538 (0.131–2.215) | 0.497 | 0.467 (0.035–6.314) | 0.566 |
| Neurotoxicity | 5 (5) | 3 (3) | 1.702 (0.465–6.228) | 0.626 | 1.149 (0.125–10.602) | 0.905 |
| Documented microbiological eradication | 68 (72) | 86 (82) | 1.462 (0.831–2.573) | 0.187 | 2.053 (0.627–6.724) | 0.235 |
| Readmission rates | | | | | |
| 30 days | 25 (26) | 20 (19) | 1.518 (0.778–2.962) | 0.221 | 15.141 (4.457–45.503) | <0.001 |
| Infection-related readmission | 15 (16) | 13 (12) | 1.327 (0.595–2.957) | 0.443 | 11.301 (3.595–35.516) | <0.001 |
| PSAR infection recurrence | 5 (5) | 8 (8) | 0.674 (0.212–2.136) | 0.502 | 3.307 (1.247–22.577) | 0.024 |
| 60 days | 12 (13) | 14 (13) | 0.940 (0.411–2.149) | 0.883 | 11.555 (3.770–35.418) | 0.005 |
| Infection-related readmission | 7 (7) | 7 (7) | 1.114 (0.376–3.302) | 0.904 | 10.389 (2.496–43.239) | 0.001 |
| PSAR infection recurrence | 2 (2) | 2 (2) | 1.108 (0.153–8.022) | 0.975 | 3.760 (1.456–31.123) | 0.005 |
| 90 days | 17 (18) | 9 (9) | 4.938 (2.885–8.450) | 0.012 | 3.264 (0.509–20.936) | 0.212 |
| Infection-related readmission | 11 (12) | 4 (4) | 3.307 (1.015–10.769) | 0.047 | 24.970 (6.703–93.028) | <0.001 |
| PSAR infection recurrence | 6 (6) | 2 (2) | 3.472 (0.683–17.640) | 0.133 | 2.535 (0.414–15.506) | 0.314 |

$^a$Data are presented as number (%) and median (interquartile range [IQR]), as appropriate. IPTW, inverse probability of treatment weighting; BLA, beta-lactam antibiotic; TDM, therapeutic drug monitoring; OR, odds ratios; CI, confidence interval; aOR, adjusted odds ratios; ICU, intensive care unit; AKI, acute kidney injury; PSAR, P. aeruginosa.

$^b$Positive C. diff nucleic acid amplification test.

$^c$Covariates used to generate propensity score weights: obesity (BMI ≥ 30), positive blood culture, renal replacement therapy (RRT) during BLA therapy, definitive BLA infusion duration, BLA MIC, ≥ 24 h of concomitant Gram-negative antibiotic therapy, ID consult, and continuous covariate APACHE II score. BLA MIC was standardized for each BLA into two categories, high or low. A high BLA MIC was defined as being at or within one dilution of the Clinical and Laboratory Standards Institute (CLSI) breakpoint. A low BLA MIC was defined as being ≤ 2 dilutions of the CLSI breakpoint.

$^d$Outcome bivariate regression was performed with the weighted pseudopopulation and inclusion of BLA TDM and No-BLA TDM groups. Additional covariates not used in the propensity score were considered for entry into the outcome regression model if differences between BLA TDM and No-BLA TDM groups at baseline met a P value significance of ≤0.10, at least 10% of each group had the covariate, and collinearity with propensity score covariates was not present as determined by variance inflation factors.

Data are presented as number (%) and median (interquartile range [IQR]), as appropriate. IPTW, inverse probability of treatment weighting; BLA, beta-lactam antibiotic; TDM, therapeutic drug monitoring; OR, odds ratios; CI, confidence interval; aOR, adjusted odds ratios; ICU, intensive care unit; AKI, acute kidney injury; PSAR, P. aeruginosa.
cohort of patients with culture-positive *P. aeruginosa* PNA or BSI receiving BLA infusions with and without the guidance of BLA TDM at two academic medical centers in Florida. In contrast with previous prospective and retrospective studies where patients with infections caused by *P. aeruginosa* were a very minor subset of an evaluated cohort receiving TDM-guided BLA infusions, this study provides data from 200 unique patients with *P. aeruginosa* PNA or BSI, including 95 who received TDM-guided BLA infusions (27–29). After adjustment for measured confounders, the addition of TDM to BLA infusions resulted in significantly lower odds of presumed treatment failure. With a stagnant antipseudomonal antibiotic pipeline, TDM-guided BLA therapy to ensure PK/PD optimization may be an available solution to preserve the current antipseudomonal armamentarium.

Recently published results from the Target Trial, a randomized, multicenter, controlled trial, evaluating clinical outcomes in patients receiving piperacillin-tazobactam with and without the guidance of TDM, demonstrated improved outcomes, including lower mortality, in the TDM-guided arm compared to those receiving fixed dosing; however, the differences were not statistically significant (30). Approximately 75% of TDM patients in that trial achieved target serum BLA concentrations within 5 days of enrollment, which was defined as 4× (range ±20%) the MIC of the causative pathogen or 16 mg/liter for *P. aeruginosa* with empirical beta-lactam therapy based on the epidemiological cutoff (ECOFF) published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (32). This is in comparison to 62.5% of patients in the trial’s control group, with serum concentrations at or above goal during the same time period without TDM-guided dose adjustments. Notably, 37% of TDM patients achieved target concentrations on individual days, which were significantly higher than those of the No-TDM group at approximately 15%.

In a prospective, partially blinded, randomized controlled trial by De Waele et al. (28) evaluating beta-lactam target attainment with and without TDM within the first 72 h of piperacillin or meropenem therapy, just over one-half of patients met their predefined PK/pharmacodynamic (PK/PD) target of 100% fT>MIC. This is in comparison to this study in which greater than 70% of the BLA TDM group achieved the target attainment of 100% fT>MIC within 4 days of receiving active BLA therapy *in vitro*. It should be noted that the TARGET trial and study by De Waele et al. (28) included BLA TDM patients with both Gram-positive and Gram-negative infections, and of those, only 18 (6.5%) and 6 (22.2%)
were culture-positive \textit{P. aeruginosa} infections, respectively. This is in comparison to the current study, which included 95 BLA TDM patients all with culture-positive \textit{P. aeruginosa} PNA or BSI. Additionally, unlike those studies in which piperacillin-tazobactam or meropenem was the primary BLA administered to TDM patients, the primary BLA for the TDM group in this study was cefepime followed by meropenem, while the majority of the No-BLA TDM group received piperacillin-tazobactam.

Furthermore, this study included \textit{P. aeruginosa} isolates only if they had documented \textit{in vitro} susceptibility and MIC data. Previous retrospective BLA TDM studies substituted the susceptibility breakpoint or applied the ECOFF for \textit{P. aeruginosa} isolates when MIC data were unavailable to ensure a minimum BLA concentration of \( f_{t_{\text{MIC}}} \) for 100% of the dosing interval for all isolates considered to be susceptible \textit{in vitro} (28–30). BLA exposure optimization when treating serious \textit{P. aeruginosa} infections requires an individualized approach that accounts for the MIC to ensure an attainable PK/PD ratio that is predictive of therapeutic efficacy. Although MICs in the susceptible range are not a guarantee of success, they do serve as a surrogate factor into clinical decision-making and are a crucial component when assessing target attainment in clinical and \textit{in vitro} studies. Additionally, both the TDM and No-BLA TDM facilities conducted susceptibility and confirmatory testing using Vitek 2 throughout the study period, decreasing interfacility variability. Thus, this study offers early real-world insight into TDM-guided BLA dose optimization and target attainment for an entire TDM cohort that is reflective of actual documented MICs.

This study highlights the high rate at which standard dosing of cefepime and meropenem, including that administered via intermittent infusion, achieved early target attainment of 100% \( f_{t_{\text{MIC}}} \) and 100% \( f_{t_{\text{>4xMIC}}} \) as seen in the BLA TDM cohort, which almost exclusively received intermittent infusion BLA before collection of the first BLA serum concentration. This contrasts with the No-BLA TDM group who primarily received prolonged infusion BLA. Multiple previous studies demonstrated that prolonged (i.e., extended and continuous) infusions increase antibiotic exposure to bacteria and target attainment compared to intermittent infusions (6, 30). Additionally, receipt of prolonged infusions has resulted in decreased mortality among critically ill patients compared to patients receiving intermittent infusions (28, 30, 33). Data from this study provide insight into clinical outcomes in patients with \textit{P. aeruginosa} PNA or BSI receiving cefepime via intermittent infusion with concomitant TDM compared to extended infusion without TDM. However, without serum concentrations in the No-BLA TDM cohort, it remains to be determined how serum BLA concentrations and target attainment compared between groups and whether it impacted clinical outcomes. Thus, additional prospective studies are warranted to examine this question, especially since it is well-known that critically ill patients undergo drastic pathophysiological changes and oftentimes have highly dynamic BLA plasma concentrations that do not achieve target attainment, even upon receipt of prolonged infusion BLA (13, 14, 28, 30, 34, 35).

Regarding adverse effects, the incidence of BLA-associated neurotoxicity was similar between BLA TDM and No-BLA TDM and aligned with that reported in the literature, which, notably, varies widely (2.6% to 23%), likely due to a lack of standardized diagnostic criteria and a myriad of possible confounders, especially in critically ill patients (1, 3, 26, 36). Limited studies have examined BLA neurotoxicity and its association with supratherapeutic drug serum concentrations using TDM (15, 23, 37–45). In those studies, BLA-associated neurotoxicity was identified in patients with highly variable serum BLA concentrations. Similarly, in this study, patients in the BLA TDM group with documented neurotoxicity had serum BLA concentrations ranging from 100% \( f_{t_{\text{MIC}}} \) to 100% \( f_{t_{>15xMIC}} \) with a mean concentration of 100% \( f_{t_{>6xMIC}} \). However, given that BLA concentrations in the central nervous system (CNS) may have been very different from measured serum concentrations and multiple other factors may have impacted the individual risk of BLA-associated neurotoxicity (i.e., days of therapy, renal function, age, weight), additional studies are warranted in this arena.

This study has important limitations. First, confounding is a potential issue due to inherent baseline differences that exist between groups and differences in treatment management preferences, which were not assigned randomly. We addressed these potential confounders in the study design by (i) excluding potential large enrollment differences in transplant,
oncology, and cystic fibrosis patients between sites, (ii) conducting a dual evaluation of collected data pertaining to the primary outcome completed by an infectious diseases physician and/or pharmacist in a manner blinded to the medical center, and (iii) by developing and incorporating propensity scores, which ensured that the BLA TDM and No-BLA TDM groups were similar regarding certain baseline characteristics (i.e., P. aeruginosa culture source, antibiotic therapy selection and administration, in vitro BLA susceptibility data, and severity of illness at index positive culture collection). We believe the weighted cohort is generalizable to the overall population being considered for BLA TDM; however, as seen with other statistical methods, propensity score weighting is unable to control for potential unmeasured factors that could impact patient selection for BLA TDM. Unmeasured factors in this study may include health disparity differences between campuses with respect to both race and socioeconomic standing, including but not limited to access to follow-up care, which were not directly assessed. Notably, significant differences in hospital readmission rates may be due to inherent baseline differences between sites relative to the number of hospitals in proximity to the BLA TDM site, UF Shands Gainesville, compared to the No-BLA TDM site, UF Health Jacksonville. For example, the city of Jacksonville has roughly three times the competing hospitals in the local vicinity of UF Health Jacksonville that regularly serve the patient population in this study compared to UF Shands Gainesville. Thus, in comparison to UF Health Jacksonville, there may be a much higher likelihood that patients admitted to UF Shands Gainesville would be readmitted to UF Shands. In addition, undocumented health care disparities may have impacted health care access as we observed a larger number of uninsured patients in the No-BLA TDM site.

Second, while BLA TDM process was routine at the TDM facility, it was nonprotocolized throughout the study period, which may have impacted patient selection for BLA TDM and the timing of serum sample collection and concentration results. Because of this, we were unable to determine whether patients in the TDM cohort were selected for BLA TDM because they were thought to be at high risk of treatment failure due to concern of definitive treatment failure or other reason(s) not identified in the electronic health record (EHR). Third, assumptions pertaining to free BLA serum concentrations were made since total BLA serum concentrations were measured. Additionally, although both medical centers used the same methodology for MIC testing, it is important to acknowledge the limitations of MIC values, which can range between 1 and 2 dilutions. Finally, although extensive manual chart review was used to identify BLA-associated neurotoxicity, review of cases by a neurointensivist was not completed, thus, we cannot guarantee with full certainty that the patients identified as having BLA-associated neurotoxicity did experience true neurotoxicity and that it was without question a result of BLA therapy. Prospective studies are warranted to address these limitations.

**Conclusion.** In conclusion, the results of this IPTW-weighted analysis indicate that patients with P. aeruginosa PNA or BSI receiving TDM-guided BLA infusions have significantly lower odds of presumed treatment failure compared to patients receiving BLA infusions without TDM guidance and add considerably to the growing body of clinical data assessing the clinical impact of BLA TDM. Future studies are warranted to evaluate how definitive BLA, infusion duration, and causative pathogen affect clinical outcomes, and the impact of BLA TDM on hospital readmission.

**MATERIALS AND METHODS**

This retrospective, parallel cohort study conducted at UF Shands Gainesville and UF Health Jacksonville evaluated patients with P. aeruginosa PNA or BSI between December 2015 and January 2020. The TDM group was defined for routine BLA TDM (BLA TDM, Gainesville) compared to nonroutine BLA TDM service (No-BLA TDM, Jacksonville). Included patients were hospitalized, ≥18 years of age, had a respiratory and/or blood culture positive for P. aeruginosa, met diagnostic criteria for lower respiratory tract infection with a positive P. aeruginosa respiratory culture, and received ≥48 h of BLA infusion with in vitro susceptibility within 72 h of positive index culture collection. The definition of PNA was a presumed diagnosis for this retrospective study and included patients meeting the following criterion: positive chest radiographic finding, positive respiratory culture, clinical symptoms suggestive of PNA, and the order and receipt of antibiotics targeted for the positive respiratory culture. Patients were excluded if they died before culture result, were transferred from an outside facility with positive P. aeruginosa culture; had cancer or cystic fibrosis; were pregnant, incarcerated, or solid organ/bone marrow transplant recipients; or were admitted for burn injuries. This study was reviewed and approved by the University of Florida Investigational Review Board (IRB no. IRB2020001944, approved 8/6/2020). Informed consent was not required.
The primary outcome was a composite of presumed treatment failure defined as the presence of any of the following from index positive P. aeruginosa culture collection: end of BLA therapy all-cause mortality, eradication of or additional antimicrobial therapy for P. aeruginosa infection after 48 h of treatment with susceptible BLA due to worsening clinical status or transfer to a higher level of care (i.e., the ICU). Each element of the primary composite outcome underwent a dual evaluation of collected data, which was completed by an infectious diseases physician and/or pharmacist in a manner blinded to the medical center.

Microbial eradication was defined as eradication of P. aeruginosa from the index positive culture source up to hospital discharge when confirmed by ≥1 repeat culture. In cases where there were no repeated cultures and the patient had infection resolution, microbial eradication was assumed. Treatment-emergent resistance was defined as the development of resistance of P. aeruginosa to any antipseudomonal BLA in the follow-up culture that originally demonstrated in vitro susceptibility in the index culture. Beta-lactam associated-acute kidney injury (AKI) was measured from the beginning of BLA initiation and included patients meeting either of the following two definitions: RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) or AKIN (Acute Kidney Injury Network) (46, 47). Patients were considered to have BLA-associated neurotoxicity if the following was noted in the patient’s medical record: symptom (i.e., confusion, myoclonus, seizure, encephalopathy, decreased consciousness, or electroencephalogram [EEG] changes) onset occurred after initiation of the BLA resolved after BLA discontinuation, and the medical team documented that other possible contributors (i.e., other neurotoxic drugs) were ruled out. Patients were considered as having a 30-, 60-, or 90-day hospital readmission if they were readmitted to the same hospital within 30, 60, or 90-days of initial hospital discharge. Patients were censored from later readmissions if they were readmitted at an earlier time point (e.g., if a patient was readmitted within both 30- and 90-days from index hospital discharge, then they were considered to have a 30-day readmission and censored from being included in the 90-day readmission group). Infection-related readmission was defined as readmission to the hospital with a positive culture from any source and receipt of antimicrobial therapy for a presumed related readmission with P. aeruginosa recurrence was defined as readmission to the hospital with a positive P. aeruginosa culture from any source and receipt of antimicrobial therapy.

Patient demographics and baseline characteristics were extracted from the electronic health record (EHR) and entered into REDCap (Research Electronic Data Capture, Vanderbilt University) (48). Comorbidity burden was estimated by the Charlson comorbidity index, and measures of organ function and levels of patient sickness severity as described by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission and Sequential Organ Failure Assessment (SOFA) score within 24 h of index P. aeruginosa culture collection (49-52). Respiratory and blood cultures were processed at treatment center-specific microbiology laboratories according to standard procedures. Both treatment centers used Vitek 2 (bioMérieux, Inc., Durham, NC, USA) for bacterial identification and antimicrobial susceptibility testing. Beta-lactam dosing regimen data, including dose, infusion duration, frequency of administration, and duration of therapy, were collected for each BLA. Infusion duration was categorized as intermittent (30 min) or prolonged (i.e., extended [3 to 4 h] or continuous [24 h]). MIC data and beta-lactam dosing regimens, dose adjustments, and serum concentrations for the most three used beta-lactams in total and composite outcome BLA TDM and No-BLA TDM cohorts are displayed in Tables S1 and 2, respectively.

While nonprotocolized throughout the study period, BLA TDM at UF Shands Gainesville was encouraged for critically ill patients with suspected or documented infections and conducted by clinical pharmacists and physicians as part of routine clinical practice. The recommended approach was to order a peak (collected 1 h after the end of the infusion) and trough sample (collected 30 min before the next dose) for each patient. Once collected, samples were sent to the University of Florida Infectious Diseases Pharmacokinetics Laboratory (Gainesville, FL) where total BLA concentrations were determined by validated high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) at a 2 to 100 mg/liter range of detection. The coefficients of variation for the inter-and intraday precision and accuracy were within 10%. The unbound concentration was assumed to be 80% (cefepime), 70% (piperacillin), and 98% (meropenem). The results are delivered to the EHR for clinical interpretation and pharmacokinetic/pharmacodynamic (PK/PD) calculations. From February 2015 through 2019, batched beta-lactam assays were performed once daily on Mondays, Wednesdays, and Fridays and then expanded to Monday through Friday for the remainder of the study period. Additional data collected for TDM patients included the following: BLA administration time immediately preceding sample collection, plasma concentration order, collection and result times, sample concentration, and beta-lactam regimen adjustments, if any. Additionally, follow-up serum sample concentration collection and result data as well as date/time of first serum concentration at goal were collected where available. Trough concentrations associated with the first TDM occasion per patient were used to decide whether 100% f\textsubscript{T1-2MIC} and/or 100% f\textsubscript{T2-4MIC} were achieved. At the No-BLA TDM site, BLA regimens were reviewed and adjusted a minimum of once a day in accordance with the hospital’s pharmacy renal dose adjustment protocol.

Baseline characteristics were evaluated using descriptive statistics. Discrete data are reported as frequencies and percentages. Continuous data are described using medians and interquartile ranges (IQRs) or means and standard deviations (SD) according to the normality of the distribution. Group comparisons were performed using Pearson X\textsuperscript{2} for categorical variables or the Wilcoxon rank-sum for continuous variables. To address nonrandomized allocation of BLA TDM and the primary composite outcome of presumed treatment failure as covariates: obesity (body mass index [BMI] ≥30 kg/m\textsuperscript{2}), type of infection (positive blood versus respiratory versus blood and respiratory culture), renal replacement therapy (RRT) during BLA therapy, definitive BLA, BLA infusion duration (prolonged versus intermittent), BLA MIC, ≥24 h of concomitant Gram-negative antibiotic therapy with definitive BLA, and ID consult (28, 30, 33, 53-57). DEFINITIVE BLA was categorized into three categories: (i) cefepime, (ii) piperacillin-tazobactam and meropenem, and (iii) other. BLA MIC was standardized for each BLA into two categories, high or low. A high BLA MIC was...
defined as being at or within one dilution of the Clinical and Laboratory Standards Institute (CLSI) breakpoint (59–60). A low BLA MIC was defined as being ≤2 dilutions of the CLSI breakpoint. Inverse probability of treatment weighting (IPTW) was applied to create a study pseudopopulation, balanced for potential covariate bias to mimic a randomized treatment situation. The weight for BLA TDM patients = 1/ probability of BLA TDM; while No-BLA TDM patients = 1/(1−probability of BLA TDM) (61, 62). The prediction ability of the propensity score model was assessed with an area under the receiver operating characteristic (AU-ROC) curve, and covariate balance by propensity score was assessed with the Kolmogorov-Smirnov (KS) goodness-of-fit statistic and standardized mean differences (SMD). The mean and maximum of both tests were assessed for covariate balance with an SMD >0.2 and or KS >0.1 indicating an imbalance. Next, to assess whether there was a difference in primary and secondary outcomes between the BLA TDM and No-BLA TDM pseudostudy cohorts, outcome bivariate regressions were performed with the inclusion of the BLA TDM and No-BLA TDM groups. Additional covariates not used in the propensity score were considered for entry into the outcome regression model if differences between BLA TDM and No-BLA TDM groups at baseline met a P value significance of ≤0.10, at least 10% of each group had the covariate, and collinearity with propensity score covariates was not present. Variance inflation factors (VIFs) were used to determine whether collinearity between variables was present. All tests were two-tailed with a P value of ≤0.05 considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA) and JMP Pro v14.0 (SAS Institute, Cary, NC, USA).

SUPPLEMENTAL MATERIAL
Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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