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Assessing Empiric Antimicrobial Therapy With the Modified Dundee Classification for Nonpurulent Skin and Soft Tissue Infections in a Community Hospital System

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Background. The modified Dundee classification has recently been validated in various studies for nonpurulent skin and soft tissue infections. This has yet to be applied in the United States and within community hospital settings to optimize antimicrobial stewardship and ultimately patient care.

Methods. A retrospective, descriptive analysis was performed of 120 adult patients admitted to St. Joseph's/Candler Health System for nonpurulent skin and soft tissue infections between January 2020 and September 2021. Patients were classified into their modified Dundee classes, and frequencies of concordance of their empiric antimicrobial regimens with this classification scheme in the emergency department and inpatient settings were compared, along with possible effect modifiers and possible exploratory measures associated with concordance.

Results. Concordance with the modified Dundee classification for the emergency department and inpatient regimens was 10% and 15%, respectively, with broad-spectrum antibiotic use and concordance positively associated with illness severity. Due to substantial broad-spectrum antibiotic use, possible effect modifiers associated with concordance were unable to be validated, and overall no statistically significant differences among exploratory analyses across classification status were observed.

Conclusions. The modified Dundee classification can help identify gaps in antimicrobial stewardship and excessive broad-spectrum antimicrobial usage toward optimizing patient care.

Keywords. antimicrobial stewardship; modified Dundee classification.

Skin and soft tissue infections (SSTIs) are characterized by a microbial invasion of the skin layers and underlying soft tissues, with severity ranging from mild to life-threatening [1, 2]. Based on a recent 3-year retrospective study, SSTIs are estimated to occur in ~500 episodes per 10 000 person-years [3]. Globally, cases of SSTIs are rising and are among the most common causes of hospitalization for antibiotic treatment [4].

The 2014 Infectious Diseases Society of America (IDSA) guidelines classify SSTIs as nonpurulent (including cellulitis, erysipelas, and necrotizing infection) or purulent (including furuncle, carbuncle, and abscess) [1]. Notably, methicillin-resistant *Staphylococcus aureus* (MRSA) is a highly unusual cause of cellulitis [5]; in a

prospective study of patients with cellulitis in a medical center with a high incidence of other MRSA-related SSTIs, treatment with β-lactams, including cefazolin, was successful in 96% of patients [6]. Therefore, for nonpurulent SSTIs, β-lactams or clindamycin (in the case of true β-lactam allergies) is recommended, except for severe infections. For severe infections, broad-spectrum antimicrobial coverage with vancomycin and piperacillin/tazobactam can be considered, although with a weak strength of recommendation and moderate quality of evidence [5].

Many mild and moderate cases of nonpurulent SSTIs experience overtreatment with broad-spectrum antibiotics, and severe cases are commonly undertreated based on published guidelines, which is concerning for antimicrobial stewardship and broad-spectrum antibiotic side effect profiles. This may be due to the lack of a widely used and accepted severity classification system for SSTIs. Although both the IDSA guidelines and the United Kingdom's Clinical Resource Efficiency Support Team (CREST) guidelines provide recommendations based on severity of infection, they lack clearly defined severity criteria to facilitate these recommendations [4].

The Dundee classification is a relatively new scoring tool developed by Marwick et al. within a retrospective cohort study in Scotland based on the CREST score and incorporates criteria using early warning scores for systemic severity. The

classification is a 4-class severity of illness scale, with class 1 being the least severe and class 4 being the most severe, that has been validated in other prospective and retrospective studies with high clinical applicability and generalizability [4, 7–9]. Notably, in the prospective study in Norway validating a modified Dundee classification, Rath et al. found that based on the IDSA guidelines, overtreatment was most common in the less severe modified Dundee classes and that undertreatment was most common in the more severe classes. Additionally, receipt of broad-spectrum antibiotics or clindamycin was significantly associated with diarrhea (odds ratio [OR], 3.789; 95% CI, 1.611–8.908; P = .002) [4]. Recently, Ritchie et al. implemented a modified Dundee classification within their own institution in New Zealand as an antimicrobial therapy pathway, leading to a decreased length of stay (LOS) by 1.1 days ($P < .001$), decreased 30-day mortality by 1.1% ($P < .001$), and increased concordance with their institutional cellulitis antibiotic guideline by 10% ($P < .01$). This study demonstrated the first real-world safety and efficacy of incorporating the classification into clinical practice [9].

To our knowledge, the modified Dundee classification has yet to be applied in the United States, especially within a community hospital setting. Additionally, many institutions experience significant use of broad-spectrum antibiotics for nonpurulent SSTIs, particularly initiated in the emergency department (ED), which presents an area of opportunity for antimicrobial stewardship and ultimately optimizing patient care. The purpose of this descriptive study was to assess the concordance of empiric antibiotic therapy with the modified Dundee classification for patients with nonpurulent SSTIs, along with examining possible effect modifiers and additional exploratory measures associated with concordance.

METHODS

Study Design
St. Joseph's/Candler Health System is a community health network with 714 beds divided between St. Joseph's Hospital and Candler Hospital. The study design was a retrospective, descriptive analysis of patients age ≥18 years admitted to the health system via the ED from January 1, 2020, to September 30, 2021, with an International Classification of Diseases (ICD), Ninth or Tenth Revision, diagnosis of cellulitis (including erysipelas) or necrotizing soft tissue infection (NSTI). Data were collected through the electronic medical record. Patients were excluded if they were <18 years of age; had signs of purulent lesions, including patients with abscesses or those with history of purulence within 1 week before admission (eg, furuncles/folliculitis); had facial erysipelas; were transferred from outside hospitals; had insufficient documentation to determine the modified Dundee classification; or had a history of intravenous (IV) substance use disorder.

Patient Consent
As a retrospective analysis, no informed consent or human experimentation were performed, and this study was approved by the institutional review board.

Modified Dundee Classification of Nonpurulent SSTI Severity
Using initial documentation in the ED, patients were first classified into their respective modified Dundee classifications using the criteria in Table 1—adapted from Ritchie et al., which utilized the New Zealand Early Warning Score (NZ EWS) [8–10]. The NZ EWS is illustrated in Supplementary Table 1 [9]. Upon classifying patients, both their empiric ED and empiric inpatient antibiotic regimens were categorized as either *concordant* or *nonconcordant* based on Supplementary Table 2, adapted from Rath et al. [4]. Of note, antibiotic *concordance* is signified as aligning with the modified Dundee classification, despite the retrospective nature of this study and without the expectation of providers to align with (or be aware of) the classification. Additionally, empiric antibiotic regimens prescribed by both the ED provider and the inpatient/non-ED provider may differ for the same patient.

Table 1. Modified Dundee Classification Criteria

Modified Dundee Class	Criteria
Class 1	No systemic illness (NZ EWS < 5) AND no risk factors for failure of oral antibiotic treatment,[a] including no treatment failure[b]
Class 2	No systemic illness (NZ EWS < 5) BUT ≥1 risk factor for failure of oral antibiotic treatment,[a] including actual treatment failure[b]
Class 3	Systemically unwell (NZ EWS 5–10) AND/OR ≥1 end-stage comorbidity,[c,d] including actual treatment failure[b]
Class 4	Critically unwell (NZ EWS > 10) AND/OR NSTI

Abbreviations: BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; IV, intravenous; NSTI, necrotizing soft tissue infection; NZ EWS, New Zealand Early Warning Score.

[a]Risk factors for failure of oral antibiotic treatment include BMI >40 kg/m², symptomatic venous insufficiency, symptomatic peripheral vascular disease, and >9% of body surface area affected.

[b]Treatment failure was defined as (1) subsequent hospitalization for a worsening or complication of specifically the SSTI within 30 days or (2) failed outpatient antibiotic therapy that required a change of antibiotics. A change in antibiotics was considered a treatment failure if there was a switch from 1 oral or IV antibiotic to another or "stepping up" therapy from an oral to an IV antibiotic. "Stepdown" therapy from an IV antibiotic to an oral antibiotic was not considered a treatment failure.

[c]End-stage comorbidities include COPD, ESRD, decompensated CHF, decompensated cirrhosis, and severe immune suppression.

[d]Severe immune suppression was defined as active hematological malignancy, solid organ transplant, advanced human immunodeficiency virus (HIV) infection (CD4 count < 200 cells/mm³), or currently receiving immunosuppressive chemotherapy.

Table 2. Characteristics of 120 Patients With Nonpurulent Skin and Soft Tissue Infections

Characteristic	ED Concordant		Inpatient Concordant		
	Yes	No	Yes	No	Total
Demographics					
No. (%)	12 (10)	108 (90)	18 (15)	102 (85)	120 (100)
Mean age (SD), y	64 (12)	61 (16)	64 (17)	61 (15)	62 (15)
Male, No. (%)	8 (7)	64 (53)	12 (10)	60 (50)	72 (60)
Female, No. (%)	4 (3)	44 (37)	6 (5)	42 (35)	48 (40)
Mean BMI (SD)	38 (13)	34 (12)	35 (10)	35 (13)	35 (12)
Risk factors for failure of oral antibiotic treatment					
BMI >40 kg/m^2, No. (%)	6 (5)	27 (23)	5 (4)	28 (23)	66 (55)
Symptomatic venous insufficiency, No. (%)	1 (1)	14 (12)	3 (2)	12 (10)	30 (25)
Symptomatic peripheral vascular disease, No. (%)	2 (2)	5 (4)	2 (2)	5 (4)	14 (12)
>9% BSA affected, No. (%)	2 (2)	16 (13)	3 (2)	15 (13)	36 (30)
End-stage comorbidities					
COPD, No. (%)	2 (2)	10 (8)	2 (2)	10 (8)	24 (20)
ESRD, No. (%)	1 (1)	6 (5)	1 (1)	6 (5)	14 (12)
Decompensated CHF, No. (%)	1 (1)	11 (9)	2 (2)	10 (8)	24 (20)
Decompensated cirrhosis, No. (%)	1 (1)	2 (2)	1 (1)	2 (2)	6 (5)
Active hematological malignancy, No. (%)	0 (0)	6 (5)	0 (0)	6 (5)	12 (10)
Solid organ transplant recipient, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Advanced HIV infection, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Currently receiving immunosuppressive chemotherapy, No. (%)	0 (0)	8 (7)	1 (1)	7 (6)	16 (14)

Abbreviations: BMI, body mass index; BSA, body surface area; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ED, emergency department; ESRD, end-stage renal disease; HIV, human immunodeficiency virus.

Interpretation and Analysis

For both the empiric ED and inpatient antimicrobial regimens, the frequencies of empiric antibiotics concordant with the classification were compared with those nonconcordant with the classification. Accordingly, an exploratory analysis of possible effect modifiers to concordance was performed. These modifiers included NZ EWS, number of risk factors for failure of oral antibiotic treatment, and number of end-stage comorbidities.

Additional exploratory analyses across classification status included:

- hospital LOS;
- acute kidney injury (AKI), defined as an increase in serum creatinine (SCr) of 0.3 mg/dL within 48 hours of antibiotic administration, an increase in SCr to 1.5 times baseline (which is known or presumed to have occurred within the prior 7 days of antibiotic administration), or urine output <0.5 mL/kg/h for 6 hours;
- duration of IV antibiotic treatment;
- total duration of antibiotic treatment;
- duration of broad-spectrum antibiotics during inpatient stay, defined as gram-negative coverage for at least 24 hours;
- occurrences of treatment escalation during inpatient stay, defined as addition of an antimicrobial agent or other change resulting in broader antimicrobial spectrum; and
- occurrences of treatment de-escalation during inpatient stay, defined as discontinuation of an antimicrobial agent, alteration to a regimen with a narrower antimicrobial spectrum, or conversion from IV to oral antimicrobial therapy (regardless of a difference in antimicrobial spectrum).

Descriptive statistics were estimated for continuous measures (means and standard deviations) and dichotomous measures (frequencies/percentages). The Student t test was utilized for the unadjusted analysis of continuous data, and the χ^2 test was utilized for the unadjusted analysis of dichotomous data. A binary logistic regression model was utilized to adjust for potential effect modifiers related to concordance. Statistical analyses were performed using both Microsoft Office Excel, version 1808, and IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA). P values <.05 were considered statistically significant.

RESULTS

Demographics

A total of 120 patients were included. The mean age ranged from 61 to 64 years considering both the ED and inpatient groups. A majority of the patients were male in both the ED (60%) and inpatient (60%) groups, along with being obese, with a mean body mass index (BMI) ranging from 34 to 38 kg/m^2 (Table 2).

Regarding the possible effect modifiers, the frequencies of risk factors for failure of oral antibiotic treatment and end-stage

comorbidities per concordance classification for the ED and inpatient regimens are also described in Table 2. The frequencies of each risk factor and end-stage comorbidity were higher with patients whose regimens were nonconcordant with the classification vs concordant with the classification.

Analyses

Overall concordance with the modified Dundee classification for the empiric ED and inpatient regimens was 10% and 15%, respectively. Concordance demonstrated a positive trend from class 1 to class 4 for both the ED (0% to 36%) and inpatient (0% to 64%) regimens. The differences in concordance were statistically significant across the classes for both the ED ($P = .013$) and inpatient ($P < .001$) regimens (Table 3).

Related to concordance, 86 (72%) empiric ED regimens demonstrated inappropriate MRSA coverage, along with 81 (68%) inpatient regimens. The most common antibiotic associated with inappropriate MRSA coverage was vancomycin, utilized in 60% and 56% of the empiric ED and inpatient regimens for the 120 patients, respectively. Additionally, 71 (59%) empiric ED regimens demonstrated inappropriate gram-negative

coverage, along with 80 (67%) inpatient regimens. The most common antibiotic associated with inappropriate gram-negative coverage was piperacillin/tazobactam, utilized in 40% and 47% of the empiric ED and inpatient regimens for the 120 patients, respectively (Table 4). Within the 14 cases of NSTI, 5 patients (36%) were administered a protein-synthesis inhibitor—namely clindamycin—as part of their empiric ED regimen, while 10 patients (71%) were administered either clindamycin or linezolid as part of their empiric inpatient regimen.

Furthermore, an exploratory analysis of possible effect modifiers associated with concordance was performed. The OR and 95% CI for these effect modifiers for the empiric ED regimens were NZ EWS (OR, 1.14; 95% CI, 0.93–1.40), number of risk factors for treatment failure (OR, 1.36; 95% CI, 0.77–2.41), and number of end-stage comorbidities (OR, 0.96; 95% CI, 0.35–2.61). The values for the empiric inpatient regimens were NZ EWS (OR, 1.18; 95% CI, 0.98–1.42), number of risk factors for treatment failure (OR, 0.92; 95% CI, 0.54–1.56), and number of end-stage comorbidities (OR, 0.89; 95% CI, 0.38–2.13).

Regarding the exploratory analyses across classification status, the only measure that was observed to be statistically significant was the number of treatment de-escalations among the inpatient regimens, with a mean of 1.4 de-escalations in the concordant group and 0.9 de-escalations in the nonconcordant group ($P = .047$) (Table 5).

DISCUSSION

Recently validated in both prospective and retrospective studies, the modified Dundee classification is the first objective severity of illness scoring tool for nonpurulent SSTIs that can be used to optimize both guideline-adherent empiric antimicrobial therapy and patient outcomes.

In this descriptive study, antibiotic utilization greatly departed from concordance with the classification. The statistically significant increasing concordance through the classes is likely explained by the significant use of broad-spectrum antimicrobials with the extensive, inappropriate MRSA and gram-negative coverage, particularly vancomycin and piperacillin/tazobactam, which, however, is appropriate as illness severity increases. This low concordance is also evident with the duplicate gram-negative coverage use by inpatient providers.

Another factor that may have contributed to the minimal concordance was the modest use of protein-synthesis inhibitors in both the empiric ED and inpatient regimens for patients with NSTI, namely 36% and 71%, respectively. The dissimilarity in percentages is likely due to the lack of both recognizing NSTI and prescribing a protein-synthesis inhibitor in the ED setting.

The departure from the classification is further supported by the inability to validate possible effect modifiers associated with

Table 3. Frequencies of Concordance With the Modified Dundee Classification

Modified Dundee Class	ED, per Class, No. (%)[a]	ED, Overall, No. (%)	Inpatient, Per Class, No. (%)[b]	Inpatient, Overall, No. (%)
Class 1	0 (0)		0 (0)	
Class 2	1 (8)	12 (10)	3 (25)	18 (15)
Class 3	6 (8)		6 (8)	
Class 4	5 (36)		9 (64)	

Abbreviation: ED, emergency department.

[a]$P = .013$ across the modified Dundee classes.

[b]$P < .001$ across the modified Dundee classes.

Table 4. Antibiotics Associated With Inappropriate Coverage

Antibiotic	ED, No. (%)	Inpatient, No. (%)
Inappropriate MRSA coverage		
Clindamycin	9 (8)	11 (9)
Clindamycin + vancomycin	2 (2)	2 (2)
Doxycycline	3 (3)	1 (1)
Vancomycin	72 (60)	67 (56)
Inappropriate gram-negative coverage		
Cefepime	14 (12)	14 (12)
Cefepime + meropenem	0 (0)	1 (1)
Cefepime + piperacillin/tazobactam	1 (1)	0 (0)
Ceftriaxone	6 (5)	7 (5)
Ceftriaxone + piperacillin/tazobactam	0 (0)	1 (1)
Meropenem	2 (1)	1 (1)
Piperacillin/tazobactam	48 (40)	56 (47)

Abbreviations: ED, emergency department; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 5. Exploratory Analyses Across Classification Status

	ED Concordant			Inpatient Concordant		
	Yes	No	P	Yes	No	P
Hospital LOS, days	11.0 (10.1)	8.5 (9.2)	.38	11.4 (9.3)	8.3 (9.3)	.18
AKI, No. (%)	12 (10)	108 (90)	.11	18 (15)	102 (85)	.11
Duration of IV antibiotics, days	10.0 (10.3)	8.3 (8.1)	.50	10.9 (9.3)	8.0 (8.1)	.17
Total duration of antibiotics, days	10.4 (10.1)	8.6 (8.1)	.47	11.6 (9.1)	8.3 (8.1)	.12
Duration of broad-spectrum antibiotics, days	7.2 (10.9)	6.8 (8.3)	.88	6.7 (9.4)	6.8 (8.4)	.94
Number of treatment escalations	0.8 (0.9)	0.5 (0.6)	.19	0.7 (0.9)	0.5 (0.6)	.29
Number of treatment de-escalations	1.0 (1.3)	1.0 (0.8)	.97	1.4 (1.2)	0.9 (0.8)	.047

Data expressed as mean (SD) unless otherwise stated.

Abbreviations: AKI, acute kidney injury; ED, emergency department; IV, intravenous; LOS, length of stay.

concordance. These effect modifiers were based on Table 1, with appropriate use of broad-spectrum antibiotics thought to be associated with increasing illness severity and increasing number of baseline comorbidities. Consistent with the higher frequencies of nonconcordant regimens, the frequencies of each risk factor and end-stage comorbidity were higher with patients whose regimens were nonconcordant with the classification. However, statistical significance was not observed with any of these effect modifiers, likely due again to the excessive, inappropriate use of broad-spectrum antibiotics.

Regarding the additional exploratory analyses across classification status, hospital LOS, duration of IV antibiotics, total duration of antibiotics, duration of broad-spectrum antibiotics, and number of treatment de-escalations were expected to decrease with concordance. The incidence of AKI was also expected to decrease with concordance and decreased use of vancomycin, especially in combination with other nephrotoxic agents (particularly piperacillin/tazobactam) [11]. However, this study observed no statistical differences for these measures except for the number of treatment de-escalations with the empiric inpatient regimens. The analysis of hospital LOS contrasts with the Ritchie et al. study, which found that implementation of a modified Dundee classification decreased LOS by 1.1 days ($P < .001$) [9]. Additionally, as a measure of the ineffectiveness of narrow-spectrum empiric regimens, the number of treatment escalations was analyzed, still with no statistically significant differences observed. The results of these exploratory analyses were therefore consistent with the substantial broad-spectrum antibiotic use necessitating a statistically significant number of de-escalations.

Overall, these antibiotic stewardship results are consistent with previous studies evaluating the Dundee classification. For example, Marwick et al. found that only 26% of their patients received appropriate antibiotics, consistent with the 10% and 15% appropriateness with the ED and inpatient regimens in the present study, respectively [7]. Similar to Rath et al., which found a median duration of antibiotics of 12 days, this study found a mean duration of antibiotics of 8 to

11 days, suggesting opportunities for improved risk assessment and empiric antimicrobial stewardship as Rath et al. recommended [4]. Furthermore, Ritchie et al. found that implementation of an institutional pathway reduced the median LOS from 1.8 days to 0.7 days [9]. As the current study's mean hospital LOS of 8 to 11 days may be due to the long duration of IV antibiotics (mean, 8–10 days) requiring de-escalation, an institutional pathway may assist with reducing this LOS. With an estimated institutional cost per inpatient day per patient in the United States of $2873 in 2020, this 1.1-day decrease in LOS could translate to a savings of $3160 per inpatient day per patient, or a substantial $379 236 across 120 patients [9, 12].

The strengths of this study include having a large sample size over a 1-year period and being the first known study in the United States and within a community hospital setting with results consistent with other studies, increasing the external validity of the modified Dundee classification. In addition, this study utilizes a validated classification system to evaluate antibiotic utilization and perform exploratory, patient-level analyses in a disease state without a widely known severity of illness system, with the ultimate goal of optimizing antimicrobial stewardship and patient outcomes.

The limitations of this study include its single health system chart review method and its retrospective application of the classification, limiting its internal and external validity compared with a prospective, multi–health system study. However, this study was conducted with 2 institutions in the same health system with 2 diverse patient populations, which may enhance the external validity.

Still, the retrospective approach lent the interpretation of the results more appropriately as descriptive analyses rather than as formal analyses of treatment outcomes. Therefore, any exploratory analyses are meant to provide an impetus for future studies and applications. For example, future studies could examine concordance and outcomes before and after implementation of treatment pathways and/or order sets related to nonpurulent SSTIs. Future studies could also examine the rates of *Clostridium difficile* infection, readmission, and 30-day

mortality, which are important patient-level outcomes related to appropriate antibiotic use. The widespread application of the first validated classification tool for nonpurulent SSTIs has the potential to immensely optimize antimicrobial stewardship and improve patient outcomes.

In conclusion, application of the modified Dundee classification for nonpurulent SSTIs revealed that broad-spectrum antibiotics were likely more frequently used than necessary in the context of the severity of illness of the patients in this study, particularly with respect to prescribing and de-escalation. The low concordance with the classification may have greatly contributed to the inability to validate possible effect modifiers and observe statistically significant differences regarding exploratory measures across classification status, both of which were thought to be associated with concordance. Given the limited conclusions from these exploratory analyses of the excessive broad-spectrum antibiotic use, future investigations, along with the implementation and evaluation of pathways and order sets incorporating the modified Dundee classification, may substantially assist with improving antimicrobial stewardship and patient outcomes, particularly as inpatient regimens may be continued from ED regimens. This antimicrobial stewardship optimization may also provide a financial incentive in reducing the expenses associated with inpatient stay.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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