Real-world Evidence of Greater Episode Length and Recurrence Rates Associated with Obesity in Patients Hospitalized with Acute Bacterial Skin and Skin-Structure Infections (ABSSSI)

Ruo-Ding Tan, Johnny Huynh, Matthew Barrett, Edward Tuttle

Analysis Group, Inc., Menlo Park, CA

BACKGROUND

- Acute bacterial skin and skin-structure infections (ABSSSI) impose a large and growing economic burden in the United States. The number of hospital stays due to ABSSSI increased by 85% from 1997 to 2009.[1] Approximately 11.6 million outpatient care visits each year can be attributed to ABSSSI.[2]
- Treatment failure, recurrence, and poor outcomes are common in ABSSSI: initial treatment failed in nearly one-quarter of ABSSSI patients between 2000 and 2009[a,3]
- Close to half of patients hospitalized with ABSSSI are obese, and there is both anecdotal and published evidence that this sub-population bears greater disease burden.[4] Changes in hepatic metabolism and renal excretion among obese patients present challenges to antibiotic dosing, and make it more difficult to achieve pharmacokinetic and pharmacodynamics targets for effective antibiotic therapy.[5,6]
- However, to date, real-world challenges in treating ABSSSI among obese patients are not well characterized in the literature. In particular, there is limited evidence on the relationship between obesity status and either episode length or recurrence rate – both of which are important measures of the burden of disease in terms of patient outcomes and resource utilization

PURPOSE

This longitudinal cohort analysis aims to:

- Characterize real-world ABSSSI patients and their associated treatment episodes
- Assess the relationship between obesity, duration of ABSSSI episodes, and recurrence of ABSSSI episodes

METHODS

Data Source

IMS PharMetrics Plus™ and Ambulatory EMR database, one of the largest and most comprehensive integrated claims and electronic medical records (EMR) databases, was utilized for the study

- The database links enrollment records, medical and prescription drug claims, and clinical information from patients enrolled in commercial health plans covering all 50 states between October 2009 and September 2014
- Patient-level data provides insight into obesity status and outpatient treatment
- Patient demographics (e.g., age, gender), vital records (body mass index [BMI], weight, and height), diagnostic codes (ICD-9-CM), and medical resource utilization (prescription fills, hospital admissions, and outpatient visits) are included

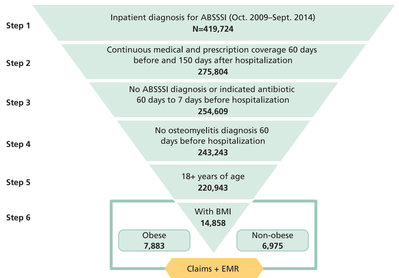
Sample Selection

Figure 1 illustrates the sample selection flow:

- Inclusion criteria:
  - Adult patients with an inpatient diagnosis for ABSSSI. The earliest inpatient ABSSSI diagnosis is the *index date*
  - Continuously enrolled in medical and prescription drug plans 60 days prior to the index date and 150 days after the discharge to allow for longitudinal analysis of patients' treatment history
- Exclusion criteria:
  - To ensure the inpatient ABSSSI diagnosis was associated with a new infection, patients who had an ABSSSI diagnosis or a prescription drug claim for ABSSSI-related antibiotics within 2 months prior to the index date were excluded
  - Patients with an osteomyelitis diagnosis (OM) within 2 months prior to the index date were also excluded, given the potential for ongoing ABSSSI treatment associated with OM.[21]

A sub-sample of selected patients was identified based on the presence of valid BMI measures or weight/height records that can be used to calculate BMI. Patients within this sub-sample were stratified into non-obese (BMI < 30 kg/m²) and obese (BMI ≥ 30 kg/m²) groups. In the subgroup analysis, class II/III obese (BMI ≥ 35.0 kg/m²) and morbidly obese (BMI ≥ 40.0 kg/m²) patients were further identified.

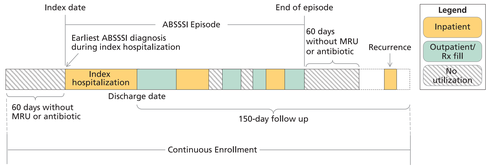
Figure 1. Sample Selection of ABSSSI Patients



Measures and Definitions

- *ABSSSI-related medical resource utilization (MRU):* Occurrence of any inpatient and/or outpatient claims associated with an ABSSSI diagnosis (e.g., physician visit, drug administration, hospital stay)
- *ABSSSI-related antibiotics:* Antibiotics with an ABSSSI indication dispensed up to 30 days after an ABSSSI diagnosis in the patient's claims history
- *Index date:* date of the earliest inpatient ABSSSI diagnosis within an episode[b]
- *ABSSSI treatment episode:* An episode that begins with the index date and concludes with the last receipt of ABSSSI-related MRU or antibiotics on hand (whichever was later), followed by 60 consecutive days without ABSSSI-related MRU or antibiotic use **[Figure 2]**
- *Recurrence:* Inpatient stay with an ABSSSI diagnosis after the 60-day gap used to define the end of the initial episode **[Figure 2]**

Figure 2. Schematic of ABSSSI Treatment Episode



Statistical Analysis

Among all selected patients:

- Demographic and clinical characteristics were descriptively summarized for all patients and subsamples of obese and non-obese patients
- Statistical comparison tests were run to test the hypothesis that obese and non-obese patients are equivalent in terms of demographic and clinical metrics. Wilcoxon rank-sum tests compared the distributions of continuous variables, and chi-squared tests compared categorical variables

Among all ABSSSI treatment episodes for the selected patients:

- Duration was measured from the index date to the end of the episode, and stratified into 30-day intervals (0 to 30 days, 31 to 60, 61 to 90, greater than 90)
- Unadjusted odds ratios (OR) and their 95-percent confidence intervals (CI) compared the proportion of treatment episodes within each 30-day stratum by obesity status
- Recurrence rates were also compared by obesity status

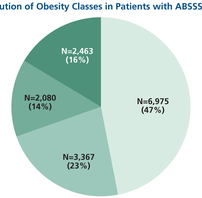
RESULTS

Characteristics of ABSSSI Patients

Table 1 shows the characteristics of all selected ABSSSI patients and compares between obese and non-obese patients:

- Overall 220,943 patients met sample selection criteria, with a mean age of 52 years and 54% male
- 86% of patients had an ABSSSI diagnosis on admission to the hospital[c]
- The majority of ABSSSI patients (83%) had abscess and cellulitis infections and nearly one-quarter (23%) had a surgical wound infection
- A subgroup of patients (N=14,858, 7%) had BMI data with a mean BMI of 31.6 kg/m². Among them 53.1% of patients were obese (BMI ≥ 30 kg/m²) and 30.4% of patients had BMI greater than 35 kg/m². Close to one-third of obese patients (one-sixth of the total) were morbidly obese (BMI ≥ 40 kg/m²) **[Figure 3]**

Figure 3. Distribution of Obesity Classes in Patients with ABSSSI



- Compared to non-obese ABSSSI patients in the selected sample, obese ABSSSI patients were:
  - Less likely to be older than 65 years (12% vs. 16%, $p<0.0001$)
  - More likely to have combined abscess and cellulitis infections (83.8% vs. 78.6%, $p<0.0001$)
  - Less likely to have a surgical wound infection (23.7% vs. 27.4%, $p<0.0001$)

Table 1. Patient Characteristics[i]

	All patients	Non-obese (BMI < 30)	Obese (BMI ≥ 30)	*p*-value
Demographics				
Patient count	220,943	6,975	7,883	<0.0001
Male, N (%)	119,584 (54.1%)	3,656 (52.4%)	4,143 (52.6%)	0.8642
Age at admission, Mean (SD)	52.0 (15.17)	51.5 (15.54)	52.6 (12.21)	0.0010
Age categories, N (%)				
18–30	22,595 (10.2%)	877 (12.6%)	446 (5.7%)	<0.0001
31–44	41,457 (18.8%)	1,181 (16.9%)	1,402 (17.8%)	0.1708
45–54	53,509 (24.2%)	1,623 (23.3%)	2,197 (27.9%)	<0.0001
55–64	65,268 (29.5%)	2,149 (30.8%)	2,900 (36.8%)	<0.0001
65 and older	38,114 (17.3%)	1,145 (16.4%)	938 (11.9%)	<0.0001
BMI,[ii] Mean (SD)	31.6 (7.59)	25.2 (3.17)	37.3 (5.52)	<0.0001
Type of ABSSSI, N (%)				
Non-admitting infection[iii]	30,306 (13.7%)	1,091 (15.6%)	944 (12.0%)	<0.0001
Infection type				
Abscess only	5,566 (2.5%)	189 (2.7%)	185 (2.3%)	0.1588
Cellulitis only	14,458 (6.5%)	513 (7.4%)	517 (6.6%)	0.0565
Abscess and cellulitis	182,715 (82.7%)	5,485 (78.6%)	6,608 (83.8%)	<0.0001
Ulcer	1,040 (0.5%)	43 (0.6%)	39 (0.5%)	0.3174
Surgical wound infection	50,009 (22.6%)	1,910 (27.4%)	1,871 (23.7%)	<0.0001
Non-surgical wound infection	5,036 (2.3%)	192 (2.8%)	164 (2.1%)	0.0075

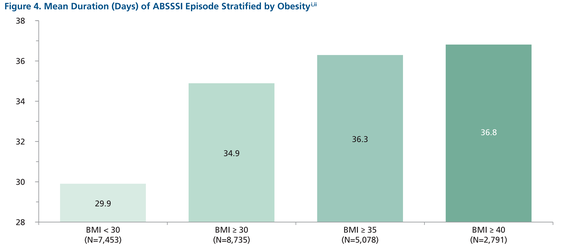
Notes:
i. Time-variant patient characteristics were measured as of the index date. For those with multiple ABSSSI episodes, characteristics were measured as of the earliest treatment episode.
ii. Mean BMI was measured among 14,858 (7%) patients with an available BMI reading.
iii. Non-admitting infection is defined as an ABSSSI infection whose date of diagnosis is received after the date of admission into the index hospitalization.

Duration of ABSSSI Treatment Episodes

Among 238,094 treatment episodes identified among selected patients [**Table 2**]:

- The average ABSSSI episode lasted for 31 days, with 68% of episodes ending within 30 days, 17% between 30 to 60 days, 7% between 60 to 90 days, and 8% extending past 90 days
- The obese population experienced longer time to recovery. Treatment episodes for obese patients lasted 5 days longer ($p<0.001$) than episodes for non-obese patients (35 vs. 30 days). The incremental duration increases to 7 days for morbidly obese patients ($p<0.0001$) [**Figure 4**]

Figure 4. Mean Duration (Days) of ABSSSI Episode Stratified by Obesity[i,ii]



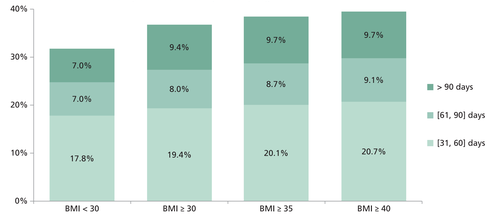
Notes:
i. Differences in mean duration of ABSSSI episode are measured against non-obese patients (BMI<30)
ii. Differences are all statistically significant at 99% ($p<0.001$)

Table 2. Mean Duration (Days) of ABSSSI Episode Stratified by Obesity

	All episodes	Non-obese	Obese								
		BMI < 30	BMI ≥ 30	Difference[i]	*p*-value	BMI ≥ 35	Difference[i]	*p*-value	BMI ≥ 40	Difference[i]	*p*-value
Number of episodes, N	238,094	7,453	8,735			5,078			2,791		
Episode duration (days)											
Mean (SD)	31.2 (41.2)	29.9 (39.2)	34.9 (43.3)	5.0	<0.0001	36.3 (43.9)	6.4	<0.0001	36.8 (43.7)	6.9	<0.0001
Median (IQR)	15 (4-40)	14 (4-39)	18 (5-45)	4	<0.0001	20 (6-47)	6	<0.0001	20 (6-48)	6	<0.0001

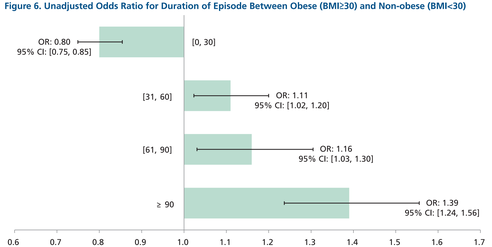
- Over 30% of treatment episodes took more than 30 days to resolve, with this proportion growing with increasing obesity. Failure to resolve within 30 days frequently results in long-term treatment: only half of such episodes resolve within 60 days, and close to one-quarter of episodes unresolved at 30 days had ongoing ABSSSI-related MRU or antibiotic use at 90 days after the initial hospitalization [**Figure 5**]

Figure 5. Duration of ABSSSI Episode Stratified by Obesity Segment[d]



- Compared to treatment episodes for non-obese patients:
  - Episodes for obese patients were 20% less likely to resolve within 30 days (OR=0.80, $p<0.0001$) [**Figure 6**]
  - Episodes for obese patients were 39% more likely to experience ongoing ABSSSI-related MRU or antibiotic utilization for longer than 90 days (OR=1.39, $p<0.0001$) [**Figure 6**]. Slightly stronger results were found among episodes for morbidly obese patients, who were 44% more likely than non-obese patients to have a treatment episode lasting longer than 90 days (OR=1.44, $p<0.0001$)

Figure 6. Unadjusted Odds Ratio for Duration of Episode Between Obese (BMI≥30) and Non-obese (BMI<30)

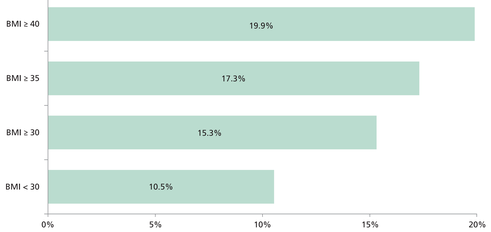


Recurrence

Recurrence was defined as a new episode requiring an inpatient stay, i.e. an inpatient stay with an ABSSSI diagnosis beginning after the 60-day gap used to define the end of the initial episode.

- The rate of recurrence among all episodes was 11.6%[e] and the likelihood of recurrence increased with BMI [**Figure 7**]
- Compared with the non-obese group, episodes for obese patients were 4.8 percentage point (pp) more likely to experience recurrence ($p<0.001$)
- Morbidly obese patients were particularly at risk for recurrence: they were 9.4 pp more likely than non-obese patients to have a recurrent ABSSSI episode ($p<0.001$)

Figure 7. ABSSSI Recurrence Rate Between Non-obese (BMI<30) and Obese, Stratified by Obesity Status



LIMITATIONS

- The study data comprised a subset of U.S. commercial patients, who were younger and may be healthier than the general population
- Given that at most 5 years of administrative claims data were available for a single patient, results were censored at the end of health plan eligibility or the end of the data cut. Our findings may underestimate the true rate of recurrence and average duration of real-world treatment episodes
- This study characterizes treatment episodes of ABSSSI among patients with different types of infection and comorbidity profiles. Potential confounding factors such as age, gender, and health status may affect the association between obesity and clinical outcomes
- Medical charts are not available in the source administrative claims database to confirm the timing and nature of disease and treatment (e.g., timing of disease onset and resolution; ABSSSI-related use of antibiotics; recurrent vs. new infection). In particular, though the algorithm used to define an ABSSSI episode was based on a review of relevant literature and consultation with clinicians, results may be sensitive to alternative approaches to inferring clinical status from claims data

CONCLUSIONS

This study demonstrated the real-world challenges of treating ABSSSI, particularly among obese patients.

- Over half of ABSSSI patients in a large commercial patient population were obese, with close to one third of them being morbidly obese
- There is a strong association between obesity, longer ABSSSI treatment episodes, and recurrence of ABSSSI
  - Obese patients overall experience longer time to recovery with higher recurrence rates; this result is stronger in more obese sub-populations
  - Compared with non-obese patients, the likelihood of an ABSSSI episode resolving within 30 days is significantly lower, while the likelihood of having an ABSSSI episode lasting longer than 90 days is significantly higher

These treatment outcomes underscore the challenges of treating obese patients with ABSSSI. Further data are needed to understand factors contributing to longer ABSSSI episodes and higher recurrence rates among the obese. Additional research is needed to understand how specific antibiotic therapies impact outcomes in obese patients.

Notes:

[a] Initial treatment failure was defined as 1) receipt of an antibiotic not included in the initial therapy after 24 hours from admission, or 2) drainage, debridement or amputation after 72 hours.
[b] Given how episodes are defined (see Figure 2), this is the earliest inpatient ABSSSI diagnosis at least 60 days after any previous ABSSSI-related MRU or antibiotic use.
[c] As noted above, the episode was defined as the earliest ABSSSI diagnosis during the index hospitalization; for these patients this was observed one or more days following admission.
[d] Totals are less than 100% because only episodes longer than 30 days are shown.
[e] Note that this underestimates true recurrence rates, since we had at most 5 years of data for any single patient.

REFERENCES

1. Wier, L. M., Pfuntner, A., Maeda, J., Stranges, E., Ryan, K., Jagadish, P., ... & Elixhauser, A. (2011). HCUP facts and figures: statistics on hospital-based care in the United States, 2009. Rockville, MD: Agency for Healthcare Research and Quality.
2. Marton, J. P., Jackel, J. L., Carson, R. T., Rothermel, C. D., Friedman, M., & Menzin, J. (2008). Costs of skin and skin structure infections due to Staphylococcus aureus: an analysis of managed-care claims. Current Medical Research and Opinion®, 24(10), 2821–2828.
3. Berger A., et. al (2011). Consequences of Failure of Initial Antibiotic Therapy in Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in US Hospitals, 2000–2009, IDSA, 2011
4. Ayyagari, R., Revol, C., Tang, W., Faust, E., & Tuttle, E. G. (2015). Association of Obesity with 30-day readmission rates among patients Hospitalized with Acute Bacterial Skin and Skin-Structure Infections (ABSSSI). Value in Health, 18(3), A186.
5. Janson, B., & Thursky, K. (2012). Dosing of antibiotics in obesity. Current opinion in infectious diseases, 25(6), 634–649.
6. Falagas, M. E., & Kompoti, M. (2006). Obesity and infection. The Lancet infectious diseases, 6(7), 438–446.

DISCLOSURE

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Ruo-Ding Tan: Consultant – Melinta Therapeutics
Johnny Huynh: Consultant – Melinta Therapeutics
Matthew Barrett: Consultant – Melinta Therapeutics
Edward Tuttle: Consultant – Melinta Therapeutics

Presented at the 50th ASHP® Midyear Clinical Meeting, New Orleans, LA, USA, December 6–10, 2015

This study was funded by Melinta Therapeutics, Melinta Therapeutics, CT, USA