

Children, Adolescents, and Young Adults Hospitalized with COVID-19 and Diabetes in Summer 2021

Short Title: Pediatric COVID-19 & DM Hospitalizations

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

This activity was reviewed by CDC and other participating institutions and was conducted consistent with applicable federal law and CDC policy (§ See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

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Abbreviations: Body mass index (BMI), CDC (US Centers for Disease Control and Prevention), Coronavirus disease 2019 (COVID-19), Diabetic ketoacidosis (DKA), Hemoglobin A1c (HbA1C), Intensive Care Unit (ICU), Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM)

Contributors' Statement Page

N.A. collected data, drafted the initial manuscript, and reviewed and revised the manuscript.

A.K. and D.S. conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, collected data, and reviewed and revised the manuscript.

V.W. and L.W. carried out the analyses and reviewed and revised the manuscript.

B.W., R.W., and H.D. collected data and reviewed and revised the manuscript.

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Key Words: Pediatrics, COVID-19, Diabetes

Abstract

Introduction

More information is needed to understand the clinical epidemiology of youth hospitalized with diabetes and COVID-19. We describe the demographic and clinical characteristics of patients <21 years old hospitalized with COVID-19 and either Type 1 or Type 2 Diabetes Mellitus (T1DM or T2DM) during peak incidence of SARS-CoV-2 infection with the B.1.617.2 (Delta) variant.

Methods

This is a descriptive sub-analysis of a retrospective chart review of patients aged <21 years hospitalized with COVID-19 in six US children's hospitals during July-August 2021. Patients with COVID-19 and either newly diagnosed or known T1DM or T2DM were described using originally collected data and diabetes-related data specifically collected on these patients.

Results

Of the 58 patients hospitalized with COVID-19 and diabetes, 34 had T1DM and 24 had T2DM. Of those with T1DM and T2DM, 26% (9/34) and 33% (8/24), respectively, were newly diagnosed. Among those >12 years old and eligible for COVID-19 vaccination, 93% were unvaccinated (42/45). Among patients with T1DM, 88% had diabetic ketoacidosis (DKA) and 6% had COVID-19 pneumonia; of those with T2DM, 46% had DKA and 58% had COVID-19 pneumonia. Of those with T1DM or T2DM, 59% and 46%, respectively, required ICU admission.

Conclusion

Our findings highlight the importance of considering diabetes in the evaluation of youth presenting with COVID-19; the challenges of managing young patients who present with both COVID-19 and diabetes, particularly T2DM; and the importance of preventive actions like COVID-19 vaccination to prevent severe illness among those eligible with both COVID-19 and diabetes.

INTRODUCTION

During the COVID-19 pandemic, increases in newly diagnosed type 1 (T1DM) and type 2 (T2DM) diabetes mellitus,[1-5] and diabetic ketoacidosis (DKA) at presentation,[4, 6] among youth have been reported. Associations between SARS-CoV-2 infection and newly diagnosed

diabetes, and between underlying diabetes and severe COVID-19, have also been noted.[7, 8] To inform clinical and public health recommendations, we describe the demographic and clinical characteristics and illness course of youth <21 years of age hospitalized with COVID-19 and either T1DM or T2DM during peak incidence of SARS-CoV-2 infection with the B.1.617.2 (Delta) variant.

METHODS

This is a descriptive sub-analysis of an investigation in which CDC partnered with 6 U.S. children's hospitals (located in Arkansas, District of Columbia, Florida, Illinois, Louisiana, and Texas) to retrospectively review electronic medical records of all hospitalized patients <21 years old with laboratory-confirmed COVID-19 (based on recorded medical history or test results) during July 1 – August 31, 2021. We abstracted demographics, medical history (including reported COVID-19 vaccination status), and clinical features, diagnoses, treatments, and outcomes [9].

In this sub-analysis, we identified patients in the cohort who had diabetes and abstracted additional diabetes-related data: type of diabetes; timing of diabetes diagnosis (diagnosed before or during current hospitalization); presence of diabetes-related complications, including DKA; related treatments, including insulin and metformin; HbA1c levels; serum pH, glucose and bicarbonate levels among those with DKA; and serum c-peptide and autoantibody levels among those with newly diagnosed T1DM. We described patients with COVID-19 who had either newly diagnosed or known T1DM or T2DM. Those with newly diagnosed T1DM or T2DM didn't have a known history prior to hospitalization and had documentation of being newly

diagnosed during the hospitalization; while those with known T1DM or T2DM had a past medical history documented at the time of hospitalization.

Lastly, we compared patients hospitalized with COVID-19 from the initial cohort with and without diabetes using chi-square tests.

This activity was reviewed by CDC and other participating institutions and was conducted consistent with applicable federal law and CDC policy (§ See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

RESULTS

Of 947 patients hospitalized with COVID-19, 58 (6%) had a diagnosis of T1DM or T2DM. Seventeen (29%) patients were newly diagnosed during the hospitalization (9 with T1DM; 8 with T2DM) and 41 (71%) had known diabetes (25 with T1DM; 16 with T2DM). Among those with T1DM and T2DM, 55% (32/58) were male, and the mean ages of those with T1DM or T2DM were 13 and 16 years, respectively. Approximately 56% (19/34) of patients with T1DM and 75% (18/24) with T2DM were either non-Hispanic Black or Hispanic/Latino (Table 1).

All patients with T2DM (24/24) and 24% with T1DM (8/34) had obesity. Approximately 63% of patients with T2DM (15/24) and 38% with T1DM (13/34) had an additional underlying condition excluding obesity. Among 45 patients ≥ 12 years old (and eligible for COVID-19 vaccination during the study period), one (2%) was fully vaccinated and two (4%) were partially vaccinated against COVID-19. Among those with known T1DM or T2DM, mean HbA1C was 10.9% and 11.1%, respectively, and 84% (21/25) of patients with known T1DM and 69% (11/16) with known T2DM had HbA1C $\geq 8\%$. Approximately 33% with T1DM presented with

shortness of breath or difficulty breathing compared with 71% of patients with T2DM (Table 2). Compared to those without diabetes in the original cohort, patients with diabetes were more likely to be older and have headache, fatigue, abdominal pain, or nausea/vomiting ($P < 0.05$, supplement table).

All patients with T1DM (34/34) had admission or discharge diagnoses of DKA or other diabetes-related complications; 88% had DKA (30/34; including 89% of patients with newly diagnosed T1DM). Two patients (6%) with T1DM were diagnosed with COVID-19 pneumonia. Those with T1DM and DKA presented with mean pH of 7.1, glucose of 431.4 mg/dL, and bicarbonate of 10.8 mEq/L; these values were similar between those with newly diagnosed and known T1DM. Among those with T1DM, 12% (4/34) required respiratory support, 18% (6/34) presented with or developed shock, and 59% (20/34) were admitted to the ICU.

Among patients with T2DM, 46% (11/24) had DKA and 13% (3/24) had other diabetes-related complications, including hypoglycemia and nonacidotic hyperglycemia with or without ketosis. Approximately 58% (14/24) with T2DM had COVID-19 pneumonia; 58% (14/24) received remdesivir and 67% (16/24) received glucocorticoids; 46% (11/24) required high-flow nasal cannula or greater respiratory support, 46% (11/24) were admitted to the ICU, and one patient died (Table 2).

DISCUSSION

These findings describe youth <21 years of age hospitalized with COVID-19 with newly diagnosed or known T1DM and T2DM during the Delta variant surge and provide helpful information for healthcare providers who care for youth with COVID-19 or diabetes.

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Approximately 6% of our cohort hospitalized with COVID-19 had diabetes, of which 70% had known diabetes prior to hospitalization; in comparison, data from the COVID-19 Associated Hospitalization Surveillance Network (COVID-NET) noted 4% of children hospitalized with COVID-19 in the US during March 2020-May 2021 had underlying diabetes.[8] Conversely, nearly one-third of the 58 patients with diabetes in this report had a new diagnosis during hospitalization. This finding is consistent with observations that incidence of T1DM and T2DM have increased during the pandemic. Possible mechanisms explaining these increases include direct pathologic effects of COVID-19, such as SARS-CoV-2 interactions with pancreatic beta cells, and pandemic-associated increases in BMI and other comorbidities and delayed receipt of care.[10]

Many patients in our sample hospitalized with diabetes and COVID-19 developed severe illness, but most had other independent risk factors for severe COVID-19 including obesity and lack of COVID-19 vaccination.[8, 11] Limited geography and timing of our study may partially explain the high prevalence of obesity and low vaccination rates; adolescents aged 12-15 years were eligible for COVID-19 vaccination starting in May 2021, only 2-3 months before our sample was hospitalized.[12] Minority racial and ethnic groups were also overrepresented in our sample: Hispanic/Latino and non-Hispanic Black persons comprise 47% of all children and youth <20 years old in the Southern US (2020 census data), where 5 of the 6 hospitals resided, but constituted 64% of our sample with diabetes and 75% with T2DM specifically.[13] This overrepresentation highlights the health inequities affecting this population. T2DM and obesity disproportionately affect youth of minority racial and ethnic groups,[14] and the COVID-19 pandemic has exacerbated inequities.[15]

We identified distinct illness courses among youth hospitalized with COVID-19 and T1DM or T2DM. Among those with COVID-19 and T1DM, nearly all had DKA with moderate-to-severe illness indicators; only two had COVID-19 pneumonia and few needed respiratory support. Almost 50% with T2DM and COVID-19 had DKA. Studies have demonstrated increased incidence and severity at presentation among youth with diabetes during the pandemic with significantly increased cases of DKA among those with T2DM (23% in one study). These studies consisted primarily of those without COVID-19, which may explain the lower proportion of patients with T2DM and DKA.[16, 17] In our analysis, a greater proportion with T2DM compared to T1DM were diagnosed with COVID-19 pneumonia, needed respiratory support, and received treatment for severe COVID-19.

There were limitations to our sub-analysis. We used a convenience sample of six children's hospitals primarily in the southern US during two months of the pandemic, which could hinder our findings' generalizability. These hospitals were Children's Hospital Association members, located in communities with high levels of COVID-19 transmission during July–August 2021, and not represented by the COVID-NET surveillance system. We did not attempt to describe associations or make causal inferences between severe illness and demographic or clinical factors. Because our cohort only included children hospitalized with COVID-19, we could not make inferences about the association between COVID-19 and diabetes. Lastly, patients with new diagnoses of diabetes in our sample may have had undiagnosed DM for some time before SARS-CoV-2 infection and presentation to care (as inferred from elevated Hb-A1c levels).

Despite these limitations, our findings have important clinical and public health implications. Given the high proportion of new diabetes diagnoses and disproportionate frequency of diabetes symptoms among our sample, our findings suggest the importance of screening for diabetes

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symptoms, like fatigue, dehydration, and gastrointestinal symptoms, in patients presenting with COVID-19 (or history of COVID-19) and considering diabetes evaluation. These symptoms could be manifestations of either COVID-19 illness or DM complications; for example, shortness of breath could represent COVID-19-related respiratory illness or Kussmaul breathing with DKA. Youth presenting with both T2DM and COVID-19 may develop multiple manifestations of severe illness complicating evaluation and management; for example, two thirds of the patients in our sample with T2DM received glucocorticoids, which may simultaneously ameliorate COVID-19 severity but exacerbate hyperglycemia and diabetes-related complications. Lastly, our findings hint at important ways to prevent COVID-19-related hospitalizations and severe illness among youth: being up to date on COVID-19 vaccinations; enacting behavioral changes to prevent and mitigate COVID-19 and diabetes; and among youth living with diabetes contacting their diabetes specialist and seeking care promptly when signs or symptoms of acute illness occur and regularly ensuring adequate glycemic control.

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Table 1: Demographics and Past Medical History of Children, Adolescents, and Young Adults Hospitalized with COVID-19 and Either Newly Diagnosed or Known Type 1 or Type 2 Diabetes from July-August 2021 in 6 US Children's Hospitals

Characteristics	Type 1 Diabetes			Type 2 Diabetes			Type 1 and Type 2 Diabetes
	Newly Diagnosed (n=9)	Known (n=25)	All (n=34)	Newly diagnosed (n=8)	Known (n=16)	All (n=24)	Total (n=58)
Age (mean, range, years)	12.6 (0.6, 18.0)	13.0 (0.9, 19.0)	12.9 (0.6, 19.0)	14.3 (10.0, 19.0)	16.5 (12.0, 20.0)	15.8 (10.0, 20.0)	14.1 (0.6, 20.0)
<1	1 (11%)	1 (4%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
1–4	0 (0%)	1 (4%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
5–11	1 (11%)	7 (28%)	8 (24%)	2 (25%)	0 (0%)	2 (8%)	10 (17%)
12–17	6 (67%)	10 (40%)	16 (47%)	5 (63%)	12 (75%)	17 (71%)	33 (57%)
18–20	1 (11%)	6 (24%)	7 (21%)	1 (13%)	4 (25%)	5 (21%)	12 (21%)
Sex	9 100.0%	25 100.0%	34 100.0%	8 100.0%	16 100.0%	24 100.0%	58 100.0%
Male	5 (56%)	14 (56%)	19 (56%)	4 (50%)	9 (56%)	13 (54%)	32 (55%)
Female	4 (44%)	11 (44%)	15 (44%)	4 (50%)	7 (44%)	11 (46%)	26 (45%)
Race/Ethnicity	9 100.0%	25 100.0%	34 100.0%	8 100.0%	16 100.0%	24 100.0%	58 100.0%
Another race or ethnicity ^a	1 (11%)	1 (4%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Hispanic	2 (22%)	5 (20%)	7 (21%)	2 (25%)	1 (6%)	3 (13%)	10 (17%)
Multiracial	0 (0%)	2 (8%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Non-Hispanic Black	3 (33%)	9 (36%)	12 (35%)	4 (50%)	11 (69%)	15 (63%)	27 (47%)
Non-Hispanic White	2 (22%)	7 (28%)	9 (27%)	1 (13%)	3 (19%)	4 (17%)	13 (22%)
Unknown race or ethnicity	1 (11%)	1 (4%)	2 (6%)	1 (13%)	1 (6%)	2 (8%)	4 (7%)
Insurance Type							
Medicaid	3 (33%)	16 (64%)	19 (56%)	5 (63%)	14 (88%)	19 (79%)	38 (66%)

Private	5 (56%)	7 (28%)	12 (35%)	2 (25%)	0 (0%)	2 (8%)	14 (24%)
Uninsured	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Other/Unknown	1 (11%)	2 (8%)	3 (9%)	1 (13%)	2 (13%)	3 (13%)	6 (10%)
Underlying conditions							
Obesity ^b	1 (11%)	7 (28%)	8 (24%)	8 (100%)	16 (100%)	24 (100%)	32 (55%)
Severe obesity ^b	0 (0%)	3 (12%)	3 (9%)	6 (75%)	10 (63%)	16 (67%)	19 (33%)
Other conditions (except obesity and DM)	3 (33%)	10 (40%)	13 (38%)	4 (50%)	11 (69%)	15 (63%)	28 (48%)
COVID-19 Vaccination Status	9 100.0%	25 100.0%	34 100.0%	8 100.0%	16 100.0%	24 100.0%	58 100.0%
Fully vaccinated ^c	0 (0%)	1 (4%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Partially vaccinated ^c	0 (0%)	1 (4%)	1 (3%)	0 (0%)	1 (6%)	1 (4%)	2 (3%)
Not vaccinated, eligible	7 (78%)	14 (56%)	21 (62%)	6 (75%)	15 (94%)	21 (88%)	42 (72%)
Ineligible (age <12 years)	2 (22%)	9 (36%)	11 (32%)	2 (25%)	0 (0%)	2 (8%)	13 (22%)
Hemoglobin A1c, %							
Mean (range)	(7.6, 12.6 14.0)	(6.0, 10.9 14.0)	(6.0, 11.4 14.0)	(6.9, 10.4 14.0)	(5.8, 11.1 14.1)	(5.8, 10.8 14.1)	(5.8, 11.2 14.1)
≥8%	8 (89%)	21 (84%)	29 (85%)	5 (63%)	11 (69%)	16 (67%)	45 (78%)

^aThe race or ethnicity of the 2 patients in the ‘Another Race or Ethnicity Category’ was captured as ‘Other’ in the data collection form. In addition to the race or ethnicity categories listed in the table, ‘Asian’, ‘American Indian/Alaskan Native’, and ‘Native Hawaiian or Pacific Islander’ were also options in the data collection form, but none of the patients included in this sub-analysis were in those categories.

^bBody mass index (BMI) (kg/m²) was calculated for children aged ≥2 years using weight and height; and percentiles were calculated using BMI, age, and sex. Children with BMI percentiles ≥95% and BMI ≥120% of the 95th percentile were considered to have obesity and severe obesity, respectively (<https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm>). If height or weight was

missing, BMI data extracted from medical records were used. If BMI was missing or unable to be calculated, a diagnosis of obesity recorded in the medical record was used; in these instances, severity of obesity could not be assessed. Obesity was not assessed for children aged <2 years.

^cFully vaccinated was defined as having received 2 doses of an mRNA-based COVID-19 vaccine ≥ 14 days before hospital admission date. Partially vaccinated was defined as having received only 1 dose of an mRNA-based COVID-19 vaccine ≥ 14 days before hospitalization. All 3 vaccinated patients described in this report received the Pfizer-BioNTech (BNT162b2) vaccine.

Table 2: Clinical Presentation and Hospital Course of Children, Adolescents, and Young Adults Hospitalized with COVID-19 and Either Newly Diagnosed or Known Type 1 or Type 2 Diabetes from July-August 2021 in 6 US Children's Hospitals

Characteristics ^a	Type 1 Diabetes			Type 2 Diabetes		
	Newly Diagnosed (n=9)	Known (n=25)	All (n=34)	Newly diagnosed (n=8)	Known (n=16)	All (n=24)
Presenting Signs and Symptoms						
Shortness of breath/difficulty breathing	3 (33%)	8 (32%)	11 (32%)	6 (75%)	11 (69%)	17 (71%)
Fever	3 (33%)	5 (20%)	8 (24%)	4 (50%)	11 (69%)	15 (63%)
Cough	1 (11%)	12 (48%)	13 (38%)	6 (75%)	11 (69%)	17 (71%)
Rhinorrhea/congestion	2 (22%)	7 (28%)	9 (27%)	4 (50%)	6 (38%)	10 (42%)
Fatigue/lethargy	6 (67%)	12 (48%)	18 (53%)	2 (25%)	13 (81%)	15 (63%)
Nausea/vomiting	3 (33%)	20 (80%)	23 (68%)	6 (75%)	8 (50%)	14 (58%)
Abdominal pain	3 (33%)	13 (52%)	16 (47%)	2 (25%)	5 (31%)	7 (29%)
Headache	1 (11%)	8 (32%)	9 (27%)	0 (0%)	8 (50%)	8 (33%)
Altered mental status	0 (0.0%)	3 (12%)	3 (9%)	1 (13%)	0 (0%)	1 (4%)
Clinical Diagnoses and Complications						
<i>Diagnoses</i> ^b						
Diabetic Ketoacidosis	8 (89%)	22 (88%)	30 (88%)	4 (50%)	7 (44%)	11 (46%)
Non-DKA Diabetes-related Complications ^c	1 (11%)	3 (12%)	4 (12%)	0 (0%)	3 (19%)	3 (13%)
COVID-19 Pneumonia	0 (0%)	2 (8%)	2 (6%)	5 (62%)	9 (56%)	14 (58%)
<i>Complications</i>						
Acute Respiratory Failure/ARDS	0 (0%)	1 (4%)	1 (23%)	3 (38%)	4 (25%)	7 (29%)
Shock	0 (0%)	6 (24%)	6 (18%)	1 (13%)	1 (6%)	2 (8%)

Encephalopathy	2 (22%)	3 (12%)	5 (15%)	0 (0%)	1 (6%)	1 (4%)
Labs on Presentation among those with DKA						
pH (mean, range)	7.1 (6.8, 7.3)	7.1 (6.8, 7.3)	7.1 (6.8, 7.3)	7.2 (7.0, 7.3)	7.2 (7.0, 7.5)	7.2 (7.0, 7.5)
Serum glucose, mg/dL, mean (range)	403.4 (218.0, 750.0)	441.5 (152.0, 738.0)	431.4 (152.0, 750.0)	826.5 (362.0, 1,487.0)	396.7 (192.0, 600.0)	568.6 (192.0, 1,487.0)
Serum bicarbonate, mEq/L, mean (range)	15.1 (5.0, 29.0)	9.1 (3.9, 19.7)	10.8 (3.9, 29.0)	14.4 (8.6, 20.7)	11.8 (4.0, 24.0)	12.8 (4.0, 24.0)
Duration of Hospitalization, days (mean, range)	2.9 (2.0, 6.0)	3.4 (0.0, 28.0)	3.3 (0.0, 28.0)	20.5 (5.0, 101.0)	5.2 (1.0, 12.0)	10.3 (1.0, 101.0)
ICU Admission	5 (56%)	15 (60%)	20 (59%)	5 (63%)	6 (38%)	11 (46%)
Total Length of Stay in ICU, days, mean (range)	0.8 (0.0, 2.0)	2.2 (1.0, 10.0)	1.9 (0.0, 10.0)	8.2 (1.0, 28.0)	3.0 (0.0, 7.0)	5.4 (0.0, 28.0)
Any Respiratory Support	0 (0%)	4 (16%)	4 (12%)	6 (75%)	9 (56%)	15 (63%)
Low flow Nasal Cannula ^d	0 (0%)	2 (8%)	2 (6%)	1 (13%)	3 (19%)	4 (17%)
HFNC/CPAP/BIPAP ^d	0 (0%)	1 (4%)	1 (3%)	4 (50%)	5 (31%)	9 (38%)
Mechanical Ventilation or ECMO ^d	0 (0%)	1 (4%)	1 (3%)	1 (13%)	1 (6%)	2 (8%)
Treatments during Hospitalization						
Insulin	9 (100%)	25 (100%)	34 (100%)	8 (100%)	11 (69%)	19 (79%)
Metformin	0 (0%)	0 (0%)	0 (0%)	3 (38%)	5 (31%)	8 (33%)
Glucocorticoids	0 (0%)	4 (16%)	4 (12%)	6 (75%)	10 (63%)	16 (67%)
Remdesivir	0 (0%)	2 (8%)	2 (6%)	5 (63%)	9 (56%)	14 (58%)
Anticoagulation ^e	1 (11%)	5 (20%)	6 (18%)	6 (75%)	12 (75%)	18 (75%)

Death during hospitalization	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	1 (4%)
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^aUnless otherwise specified, options under each characteristic were not mutually exclusive.

^bIncludes diagnoses made at admission or discharge according to the H&P and discharge summary, respectfully

^cNon-DKA diabetes-related complications included hypoglycemia or hyperglycemia with or without ketosis but not acidosis

^dCategories are mutually exclusive and represent highest level of respiratory support needed during the hospitalization.

^eIncludes prophylactic and therapeutic indications in setting of COVID-19 illness