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Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings

August 28, 2022

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Disclosure/disclaimer

- Presenting author-nothing to disclose
 - E. Garry, S. Vititoe, A. Weckstein, A. Baglivo, & N. Gatto are employees of Aetion, Inc., with stock options or existing equity
 - S. Leonard is an employee of HealthVerity, Inc
- The views expressed are my own and are not intended to convey official US Food and Drug Administration, CMS, or Department of Health and Human Services policy or guidance.
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Outline

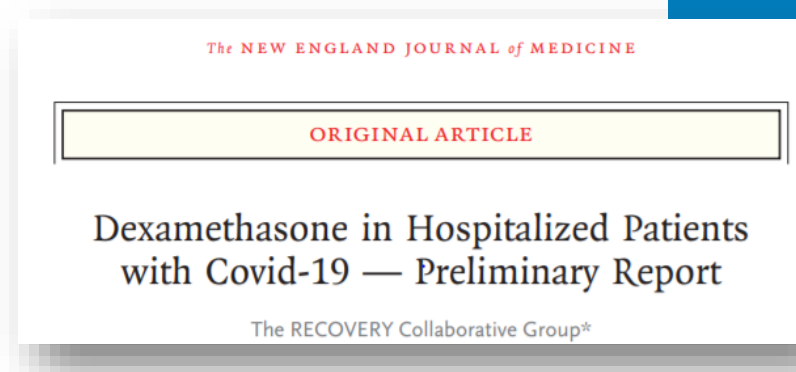
- Background and objective
- Methods
- Results
- Discussion and conclusion
- Impact

Background & Objective

Background



UK RECOVERY trial (June, 2020)



- Potential signal of harm from dexamethasone use in hospitalized COVID-19 patients not using supplemental oxygen
 - Rate Ratio 28-day mortality =1.19 [0.91–1.55]



Background

The U.S. National Institutes of Health (NIH) COVID-19 treatment guidelines advise against systemic corticosteroid use in non-hospitalized patients, who do not require supplemental oxygen, in the absence of other indications, due to lack of efficacy and safety data.

Objective

Using four large U.S. real-world data sources, examine new systemic corticosteroid use among non-hospitalized COVID-19 patients from April 2020 -September 2021, including:

- Clinical and demographic characteristics
- Utilization patterns

Four data sources

Medicare

(April 1, 2020 - August 31, 2021)

FDA Sentinel System

(April 1, 2020 - July 31, 2021)

HealthVerity

(April 1, 2020 - September 28, 2021)

Veterans Health Administration (VA)

(April 1, 2020- September 16, 2021)

Methods

**Index Date
(Day 0)
COVID-19 diagnosis***

 **Date of corticosteroid
initiation (Day T)**

Inclusion criteria Days [-183, -1]^a

- Continuous enrollment
- 65+ years [Medicare]

^a VA: Encounters in days [-365, -1]

Exclusion criteria Days [-183, -1]

- Evidence of residing in a skilled nursing facility
- Prior COVID-19 diagnosis

Exclusion criteria [-90, -1]

- Prior corticosteroid use

Assessment of baseline characteristics Days [-183, -1]^b

^b VA: Days [-365, -1]

Corticosteroid initiation Days [0, 14]

Censoring events Days [0, 14]

- hospitalization
- death
- disenrollment

Follow-up Days [T+1, T+30]

Hospitalization and death

*Non-hospitalized, non-institutionalized patients with incident outpatient COVID-19 between April 2020 and September 2021
Diagnosis code (ICD-10: U07.1) or positive SARS-CoV-2 laboratory test in outpatient setting
Date of COVID-19 diagnosis or date of lab collection = date of cohort entry



Exposure

Corticosteroids (oral or injectable)

- Dexamethasone, prednisone, prednisolone, methylprednisolone, hydrocortisone, cortisone, betamethasone, triamcinolone



Descriptive Analyses

- Demographics and clinical characteristics of COVID-19 patients and those who initiated corticosteroids
- Baseline use of inhaled corticosteroids (ICS) and other COVID-19 treatments

Among corticosteroid initiators:

- *Corticosteroid type*
- *Time between COVID-19 diagnosis and corticosteroid initiation*
- *Outpatient setting of initiation*
- *Prescriber specialty (Medicare only)*
- *Concomitant therapies (other COVID-19 therapies received)*
- *Hospitalizations and deaths in 30 days following corticosteroid initiation*

Results

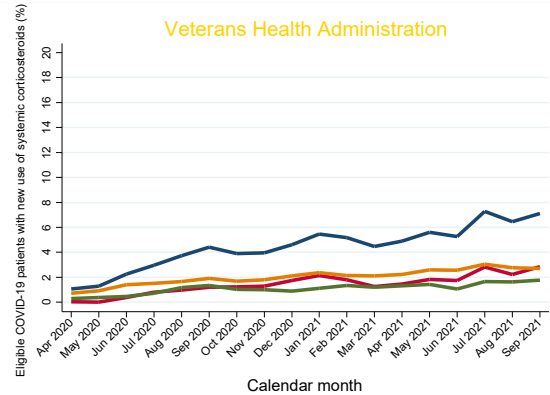
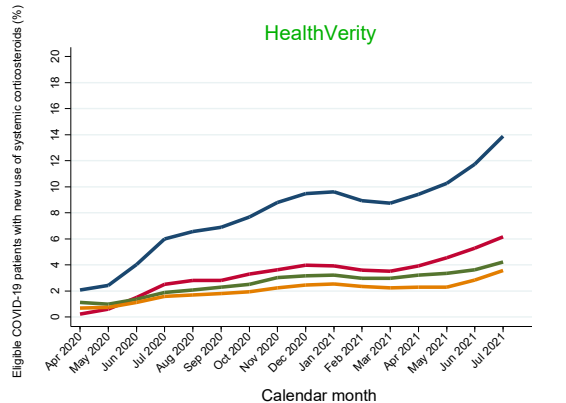
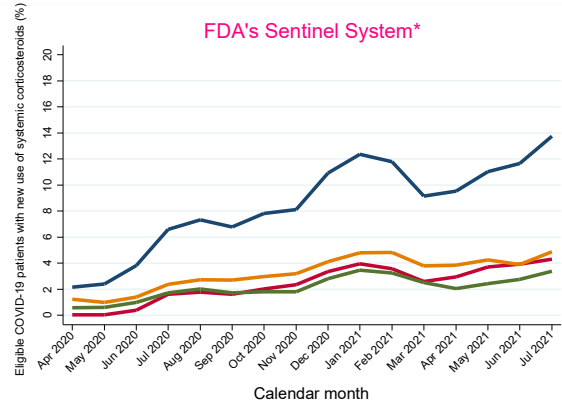
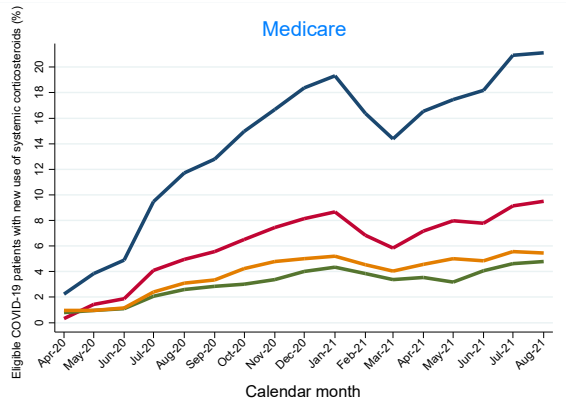
Corticosteroid use



	Medicare N (%)	Sentinel* N (%)	HealthVerity N (%)	VA N (%)
COVID-19 patients	576,885	766,105	6,320,071	224,890
Corticosteroid initiators	94,781 (16.4)	72,124 (9.4)	561,029 (8.9)	10,715 (4.7)
<i>Dexamethasone</i>	41,550 (43.8)	16,501 (28.4)	234,433 (41.8)	3,673 (34.3)
<i>Prednisone</i>	25,826 (27.3)	24,606 (42.4)	185,177 (33.0)	4,748 (44.3)
<i>Methylprednisolone</i>	20,740 (21.9)	16,637 (28.7)	142,794 (25.5)	2,537 (23.9)
<i>Other corticosteroids</i>	1,798 (1.9)	295 (0.5)	22,453 (4.0)	135 (1.3)
Time from diagnosis to corticosteroid initiation (days)				
Median [IQR]	0 [0,3]	0 [0,4]	0 [0,4]	0 [0,3]

*Individual corticosteroid dispensing, N =58,039, were assessed among N = 72,124 patients; percentages correspond to the total number of corticosteroids dispensed

Proportion of COVID-19 Patients Initiating Systemic Corticosteroids Within 14 Days of Diagnosis



— Any systemic corticosteroid (%)
 — Dexamethasone (%)
 — Methylprednisolone (%)
 — Prednisone (%)

*In Sentinel System the name of the corticosteroid was only available for pharmacy dispensing
 **In HealthVerity data, initiator proportions for August-September 2021 have been truncated as these data might be incomplete.

Demographics and select baseline clinical characteristics for patients with COVID-19 and corticosteroid initiators-I



	Medicare (April 1, 2020 - August 31, 2021)		Sentinel (April 1, 2020 - July 31, 2021)		HealthVerity (April 1, 2020 - September 28, 2021)		VA (April 1, 2020 - September 30, 2021)	
	COVID-19 diagnosis, N (%)	Initiators, N (%)	COVID-19 diagnosis, N (%)	Initiators, N (%)	COVID-19 diagnosis, N (%)	Initiators, N (%)	COVID-19 diagnosis, N (%)	Initiators, N (%)
Total^a	576,885 (100)	94,781 (100)	766,105 (100)	72,124 (100)	6,320,071 (100)	561,029 (100)	224,890 (100)	10,715 (100)
Age, years								
Mean (SD)	74.6 (7.2)	74.4 (6.9)	48.5 (19.9)	57.7 (16.7)	39.3 (21.1)	45.3 (18.3)	56.3 (16.4)	57.4 (15.3)
Sex								
Male	249,044 (43.2)	42,516 (44.9)	357,697 (46.7)	32,988 (45.7)	2,599,356 (41.1)	226,952 (40.5)	184,349 (82.0)	9,210 (86.0)
Female	327,841 (56.8)	52,265 (55.1)	408,408 (53.3)	39,136 (54.3)	3,720,715 (58.9)	334,077 (59.5)	40,446 (18.0)	1,496 (14.0)
U.S. region^b								
Northeast	104,929 (18.2)	8,864 (9.4)	139,333 (18.2)	7,284 (10.1)	1,222,537 (19.3)	60,764 (10.8)	28,306 (12.6)	756 (7.1)
Midwest	135,261 (23.5)	20,394 (21.5)	152,091 (19.9)	11,792 (16.3)	1,351,824 (21.4)	109,630 (19.5)	49,409 (22.0)	2,113 (19.7)
South	241,340 (41.8)	53,437 (56.4)	302,766 (39.5)	43,523 (60.3)	2,721,161 (43.1)	322,001 (57.4)	98,635 (43.9)	6,015 (56.1)
West	94,553 (16.4)	12,056 (12.7)	161,097 (21.0)	9,167 (12.7)	1,024,549 (16.2)	68,634 (12.2)	46,859 (20.8)	1,804 (16.8)
Smoking								
Mean (SD)	69,016 (12.0)	12,191 (12.9)	51,602 (6.7)	7,215 (10.0)	408,215 (6.5)	48,622 (8.7)	30,882 (13.7)	1,605 (15.0)
Comorbidity index								
Mean (SD)	0.8 (1.8)	0.8 (1.8)	0.5 (1.4)	0.7 (1.7)	0.3 (1.1)	0.4 (1.2)	1.0 (1.9)	1.2 (1.9)

Demographics and select baseline clinical characteristics for patients with COVID-19 and corticosteroid initiators-II



	Medicare (April 1, 2020 - August 31, 2021)		Sentinel (April 1, 2020 - July 31, 2021)		HealthVerity (April 1, 2020 - September 28, 2021)		VA (April 1, 2020 - September 30, 2021)	
	COVID-19 diagnosis, N (%)	Initiators, N (%)	COVID-19 diagnosis, N (%)	Initiators, N (%)	COVID-19 diagnosis, N (%)	Initiators, N (%)	COVID-19 diagnosis, N (%)	Initiators, N (%)
Individual Comorbidities								
Hypertension	351,427 (60.9)	59,589 (62.9)	217,346 (28.4)	30,880 (42.8)	1,205,009 (19.1)	149,645 (26.7)	98,974 (44.0)	5,315(49.6)
Hospitalized AMI	2,173 (0.4)	319 (0.3)	1,147 (0.1)	85 (0.1)	16,592 (0.3)	1,688 (0.3)	1,732 (0.8)	89 (0.8)
Hospitalized stroke/ TIA	1,890 (0.3)	261 (0.3)	1,098 (0.1)	85 (0.1)	43,297 (0.7)	4,443 (0.8)	5,879 (2.6)	266 (2.5)
Chronic kidney disease	65,747 (11.4)	10,770 (11.4)	40,355 (5.3)	5,559 (7.7)	157,909 (2.5)	15,981 (2.8)	16,854 (7.5)	820 (7.7)
Diabetes	148,235 (25.7)	24,070 (25.4)	110,730 (14.5)	14,733 (20.4)	670,671 (10.6)	73,870 (13.2)	55,968 (24.9)	2,867 (26.8)
Immunodeficiencies	44,211 (7.7)	7,055 (7.4)	35,006 (4.6)	4,399 (6.1)	252,509 (4.0)	25,583 (4.6)	13,900 (6.2)	676 (6.3)
Immunosuppressant therapies	33,600 (5.8)	5,625 (5.9)	15,702 (2.0)	2,122 (2.9)	95,182 (1.5)	11,256 (2.0)	10,102 (4.5)	610 (5.7)
Obesity	90,793 (15.7)	17,250 (18.2)	104,244 (13.6)	15,416 (21.4)	765,370 (12.1)	96,959 (17.3)	38,741 (17.2)	2,235(20.9)
COPD	41,908 (7.3)	9,892 (10.4)	26,625 (3.5)	5,581 (7.7)	111,058 (1.8)	18,012 (3.2)	18,112 (8.1)	1,575 (14.7)
Asthma	30,596 (5.3)	6,706 (7.1)	32,055 (4.2)	5,123 (7.1)	327,930 (5.2)	44,782 (8.0)	10,419 (4.6)	984 (9.2)
Baseline use of other COVID-19 treatments								
Inhaled corticosteroids	32,804 (5.7)	8,133 (8.6)	24,637 (3.2)	5,249 (7.3)	191,192 (3.0)	35,272 (6.3)	3,060 (1.4)	307(2.9)
Oral anticoagulants	64,629 (11.2)	10,555 (11.1)	23,826 (3.1)	3,277 (4.5)	95,873 (1.5)	12,771 (2.3)	14,945 (6.6)	783(7.3)
Non-oral anticoagulants	1,774 (0.3)	258 (0.3)	2,900 (0.4)	345 (0.5)	10,181 (0.2)	1,126 (0.2)	1,728 (0.8)	80(0.7)
Hydroxychloroquine	6,924 (1.2)	1,224 (1.3)	3,889 (0.5)	588 (0.8)	28,728 (0.5)	4,583 (0.8)	956 (0.4)	70 (0.7)
Oxygen	8,118 (1.4)	2,106 (2.2)	4,964 (0.6)	1,112 (1.5)	27,370 (0.4)	3,695 (0.7)	814 (0.4)	47 (0.4)

Abbreviations: AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; SD, standard deviation

a The group totals and percentages do not add to 100% because some patients were hospitalized, died, or disenrolled within 14 days after COVID-19 diagnosis or before they initiated treatment with corticosteroids in outpatient settings

b A small percentage of patients were not categorized into one of the four main regions

Corticosteroid initiators: Outpatient setting of initiation

Setting of Initiation/ administration	Medicare 94,781 N (%)	Sentinel 72,124* N (%)	HealthVerity 561,029* N (%)	VA 10,715 N (%)
Pharmacy dispensing	67,116 (70.8)	57,947 (80.3)	449,208 (80.1)	9,863 (92.0)
Administration in:	27,665 (29.1)	19,018 (26.4)	144,142 (25.7)	852 (8)
<i>Emergency Department (ED)</i>	16,676 (17.6)	11,416 (15.8)	79,701 (14.2)	543 (5.1)**
<i>Office visit</i>	6,307 (6.7)	7,607 (10.5)	34,138 (6.1)	422 (3.9)
<i>Urgent care, health clinic, or health center</i>	1,289 (1.4)	-	11,232 (2.0)	—
<i>Other outpatient setting</i>	3,393 (3.6)	34 (<0.1)	19,071 (3.4)	66 (0.6)
Health Care utilization on day of initiation				
ED visit	23,406 (24.7)	16,499 (22.9)	128,217 (22.9)	—

* A patient may have had corticosteroid dispensings (pharmacy) and/or corticosteroid procedure codes recorded on the same date

** Included ED and urgent care

In Medicare, the most common provider specialties were: Internal/Family Medicine/General Practice, Nurse Practitioner, and Emergency Medicine

Corticosteroid initiators: Concomitant COVID-19 therapies



	Medicare	Sentinel	HealthVerity	VA
Corticosteroid initiators	94,781	72,124	561,029	10,715
Time period	Day 0-T	Day 0-14	Day 0-T	Day 0-T
	N (%)	N (%)	N (%)	N (%)
Remdesivir	0	227(0.3)	498 (0.1)	21 (0.2)
Hydroxychloroquine	2,768 (2.9)	1,832 (2.5)	9,239 (1.6)	20 (0.2)
Oral anticoagulant	1,229 (1.3)	2,117 (2.9)	5,555 (1.0)	157 (1.5)
Non-oral anticoagulant	3,417 (3.6)	2,265 (3.1)	7,956 (1.4)	35 (0.3)
Azithromycin	42,468 (44.8)	35,192 (48.8)	228,498 (40.7)	3,604 (33.6)
Ivermectin	3,671 (3.9)	2,493 (3.5)	18,119 (3.2)	30 (0.3)
Monoclonal Antibodies	6,759 (7.1)	1,456 (2.0)	9,879 (1.8)	251 (2.3)
Inhaled corticosteroids	2,267 (2.4)	4,845 (6.7)	22,376 (4.0)	72 (0.7)

Corticosteroid initiators: 30-day hospitalization and death

	Medicare	Sentinel	HealthVerity	VA
	94,781	72,124	561,029	10,715
COVID-19 Hospitalization* within 30 days of initiation, N (%)	15,277 (16.1)	8,022 (11.1)	35,515 (6.3)	1,113 (10.4)
Time to hospitalization (days)				
Median [IQR]	5.0 [3,8]	--	4 [2,7]	4 [2,7]
Deaths within 30 days of initiation** N (%)				
	3,886 (4.1)	--	--	244 (2.3)
Time to death (days)				
Median [IQR]	15.0 [10,21]	--	--	15 [10, 22]

* U07.1 diagnosis code in any position ** Data available for Medicare and VA only

Discussion and conclusion

Summary

- Between 4% and 16% of patients with COVID-19 initiated corticosteroids in the outpatient setting
 - Corticosteroid use increased over time in all data sources
- More common in older people and non-VA systems
- More common in the South than in any other U.S. regions
- Over 50% initiated on day of diagnosis with COVID-19

Summary

- Most frequently received as a dispensing in **pharmacy**
- Most common concomitant therapy: **azithromycin**
- 6-16% patients hospitalized within 30 days of corticosteroid initiation
 - Highest % hospitalization seen in Medicare
- Around 4% of initiators in Medicare died

Limitations

- Inability to capture date of symptom onset and indication for corticosteroid use
- Potential for misclassifying mild to moderate COVID-19 disease
 - Limited ability to capture elements to define COVID-19 disease severity, including oxygen use

Conclusion

- Despite NIH recommendations, increasing numbers of non-hospitalized patients with COVID-19 were prescribed systemic corticosteroids, often on the day of diagnosis
- Given increasing use of corticosteroids, the potential safety signal, and the lack of efficacy data in patients with mild to moderate COVID-19 it is critical that **prescribers consider the NIH guidelines in the therapeutic management of non-hospitalized patients with COVID-19**

Impact

Research Letter

FREE

April 8, 2022

Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021

Marie C. Bradley, PhD, MPharm, MScPH¹; Silvia Perez-Vilar, PhD, PharmD¹; Yoganand Chillarige, MPA²; et al

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JAMA. 2022;327(20):2015-2018. doi:10.1001/jama.2022.4877

Updated Information on Availability and Use of Treatments for Outpatients with Mild to Moderate COVID-19 Who are at Increased Risk for Severe Outcomes of COVID-19



Distributed via the CDC Health Alert Network
Monday, April 25, 2022, 1:00 PM ET
CDCHAN-00463

The screenshot shows the NIH COVID-19 Treatment Guidelines website. The main heading is "Therapeutic Management of Nonhospitalized Adults With COVID-19". The page is part of a breadcrumb trail: Home / Management / Clinical Management of Adults / Nonhospitalized Adults: Therapeutic Management. The text "Last Updated: August 8, 2022" is visible below the main heading.

1. Bradley et al., JAMA May 24/31, 2022 Volume 327, Number 20;
2. https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_463.pdf
3. <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/>

