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CONCEPTS

The Practice of Emergency Medicine

Emergency department implementation of monoclonal antibody infusion for the treatment of coronavirus disease 2019: A template for rapid deployment

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Abstract

Monoclonal antibody (mAb) therapy can improve coronavirus disease 2019 outcomes when infused early in select patients. We sought to rapidly create and implement a program for emergency department (ED) mAb infusion to aid care. Using multiple strategies and actions—education, selection criteria, screening tools, rapid testing, compounding, and delivery—we infused 832 ED patients with a mAb. The screening tool identified 94.5% of these patients as potential candidates. Length of stay was nearly identical for patients who tested positive for coronavirus disease 2019 versus those requiring testing. Mild adverse reactions occurred in 2.3% of mAb infusions, and severe reactions occurred in 0.5% of infusions. We highlight a strategic approach for using the ED as a key coronavirus disease 2019 therapeutic site for this intervention and with high utility and low disruption.

KEYWORDS
casirivimab, coronavirus disease 2019, emergency department, etesevimab, imdevimab, monoclonal antibodies, severe acute respiratory syndrome coronavirus 2

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1 | INTRODUCTION

In late 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the first monoclonal antibody (mAb) therapy available to patients with mild to moderate infections with the severe acute respiratory syndrome coronavirus 2 virus. Bariola et al[1] demonstrated that mAb therapy administered within 10 days of coronavirus disease 2019 symptom onset in patients with mild to moderate coronavirus disease 2019 improved outcomes at 28 days. The authors observed a 60% reduction in hospitalizations and deaths in patients treated with the singular mAb bamlanivimab compared with untreated patients.[1] The authors also noted that earlier therapy (within 4 days of symptom onset) may be more beneficial compared with mAb therapy later in the disease course (ie, 5–10 days after symptom onset).[1]

Since that first mAb, newer mAb combinations (2 antibody preparations) now have EUAs targeting the same group of patients with coronavirus disease 2019—those early in disease course, not yet requiring oxygen, and with other at-risk factors for coronavirus disease 2019 complications. Additional studies by Dougan et al[2] have continued to demonstrate the efficacy of mAb therapy on hospitalization and mortality rates. Given these options and the public health benefit of therapy, expanding easy access to mAb infusions is important for public health.[3] We describe our experience with the implementation of an emergency department (ED)–based mAb infusion program across the 28 EDs in our 40-hospital health system.

1.1 | Clinical setting

The University of Pittsburgh Medical Center (UPMC) is a large, integrated health system that serves western and central Pennsylvania, western Maryland, and areas of New York state via 40 hospitals and >8000 total inpatient beds. Hospitals serve urban, suburban, and rural communities and span from small, community-based hospitals to large quaternary referral centers. UPMC EDs serve >1.2 million patients yearly.

When the FDA issued the first EUA for mAb therapy for coronavirus disease 2019, UPMC designed and implemented a system-wide group of outpatient therapy sites to deliver authorized mAbs. These initial sites included infusion centers, senior care facilities, and at-home infusions. These sites treat patients with ≤10 days of symptomatic severe acute respiratory syndrome coronavirus 2 infection diagnosed via polymerase chain reaction (PCR) testing. The initial infusion site dispersion covered our geographical service area, including western and central Pennsylvania, Maryland, and New York, seeking to serve all with ease of travel and with full treatment capabilities.[3] The goal was to quickly begin delivering therapy to those who met EUA criteria—spending weeks to months developing and initiating a mAb protocol and infrastructure would have denied an important care opportunity to many. We also sought to provide care that allowed us to "learn by doing,"[3,4] ensuring that we could seamlessly collect data that could inform care moving forward.

Despite these outpatient options, a key potential opportunity existed in each ED, where many patients with or suspected of having coronavirus disease 2019 seek care at the key early stages of illness. Developing and rapidly employing an ED mAb program required swift, multifaceted action, including clinician and nursing education; collaboration with pharmacy for compounding and delivery; a screening tool development to identify potential candidates; and buy-in, cooperation, and teamwork from the leadership through the staff.

1.2 | Why deliver in the ED?

Although most patients with this infection receive care only outside the hospital and are eligible to receive mAb therapy at an infusion site, others will seek emergency care. This means the ED has a clustering of patients who could benefit from severe acute respiratory syndrome coronavirus 2–targeted mAbs. We recognized that targeting the ED care intervals could ease therapy for a patient (by not requiring a trip to another location) and limit delays for mAb therapy by using this window of opportunity at a capable setting. By expeditiously treating these patients, we sought to decrease the number of patients who would develop severe (requiring hospitalization) coronavirus disease 2019, benefiting both the patients and assisting in unburdening the hospital inpatient units and intensive care units. These reasons spurred us to create the ability to deliver infusions of mAb at 28 EDs across our system.

1.3 | Challenges of providing coronavirus disease 2019 therapies in the ED

Developing a process for ED mAb therapy for the treatment of coronavirus disease 2019 involved many challenges—it required ED physician or APP, nurses, pharmacists, and leadership to quickly adopt an unfamiliar therapy for the treatment of an unfamiliar disease—and multiple potential barriers existed to initiating this therapy in the ED. First, mAbs are not currently a class of drug typically administered in the ED. This means that ED physician or APP lacked familiarity with this treatment option, notably the indications, exclusions, and adverse effects. Second, the logistics of ordering, compounding, and infusing a drug only available through an EUA in the ED is a new challenge. This task started with a glaring, but basic, gap—no preexisting mAb ordering process using the electronic health record (EHR) existed. Third, nursing staff also lacked familiarity with mAb infusions. Finally, concerns regarding competing priorities and potential increased ED length of stay (LOS) attributed to testing and infusion time were commonly cited as potential barriers to implementation.

We share our approach to addressing these barriers and we share the steps taken to rapidly develop, implement, and grow a mAb infusion program for in-ED care, recognizing the need for prompt action to address the pandemic and to meet our goals of care and learning.
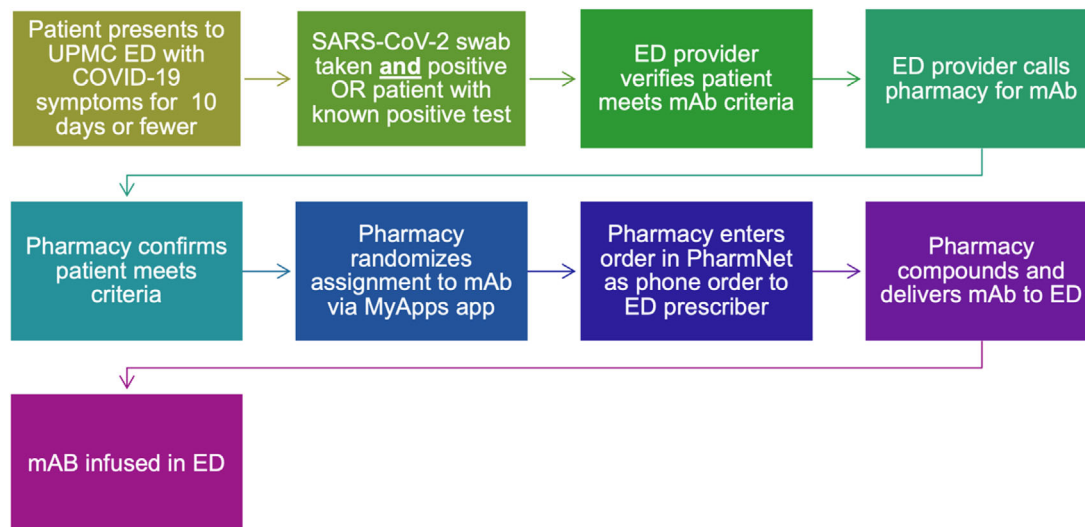
FIGURE 1 Flowchart depicting the workflow for ED mAb infusions from patient presentation to time of infusion. For clarification, MyApps is the UPMC homepage for accessing health care related applications (EHR for ED physician or APP, nursing, pharmacy, intranet, digital libraries). COVID-19, coronavirus disease 2019; ED, emergency department; EHR, electronic health record; mAb, monoclonal antibody; SARS Cov-2, severe acute respiratory syndrome coronavirus 2; UPMC, University of Pittsburgh Medical Center

2 | OUR STRATEGY FOR DEPLOYMENT

We describe our strategy for deployment from ED physician or APP and nursing education through screening and testing and, finally, to the infusion specifics. This process began with a multifaceted approach to educating ED physician or APP, leadership, and nursing staff. We collaborated with information technology specialists to develop appropriate EHR orders and ordersets as well as a screening tool. Finally, we developed, in conjunction with our pharmacy staff, a protocol for specific mAb formulation assignment and infusion. We summarize the workflow process of ED mAb infusion in Figure 1 and fully detail the process in the next sections.

2.1 | Raising awareness and educating staff

ED physicians, advanced practice PA/NP, and nursing staff lack familiarity with mAb infusions, as these are rarely given in this setting. We deployed multiple communication strategies to raise awareness and educate all staff. We targeted education detailing the EUA clinical criteria for eligibility, the common features of those who did not qualify, and the beneficial impact of therapy, including the most current data on outcomes and any effects of the infusion. We employed both ad hoc and regularly standing meetings with ED leadership and staff, and we added online electronic meeting forums for question-and-answer sessions. This effort required intense and prompt action—in days, not weeks—and a dedicated multidisciplinary team of messengers and experts. As an ancillary tool, we update our system intranet page (called *Infonet*)—the repository for all coronavirus disease 2019 policy and advice—daily with the latest information, education, and frequently asked questions. We promoted this site as the definitive, easy-access resource for staff

that would allow an asynchronous and "just-in-time" place for staff seeking insights. We also sent individual emails from key leaders with harmonized content to all ED staff. Finally, ED leaders met with all staff to educate and respond to any concerns.

2.2 | Screening and identification of patients who are infected

We recognized the importance of timely identification of potential mAb candidates as vital to expediting testing and infusions while maintaining ED throughput. As part of the implementation process of our ED mAb infusion program, we implemented a series of screening questions as part of the patient intake on ED arrival. The goal is to identify potential mAb candidates from the onset of their visit to expedite their testing and treatment. This also serves as a reminder to ED physician or APP to consider mAb therapy for these patients. We created an icon adjacent to the patient's name on the computer-based ED tracking board that denotes a positive screen. The screening form triggering the icon is a series of 4 questions (Figure 2) using a preexisting 30-day interval, deployed for many threats and clinically relevant in coronavirus disease 2019. A "yes" reply to any of the first 3 questions triggers a positive screen. A "yes" to the fourth question about international travel triggers a follow-up question and, depending on the country of travel, will flag the screen as positive or negative. The travel screen is regularly updated. We did not implement nursing-driven testing protocols and allow the ED physician or APP to determine the need for testing. A positive screen is not a requisite for testing, and an ED physician or APP can test patients with atypical symptoms (eg, gastrointestinal symptoms) or a negative screen for whom the ED physician or APP holds a suspicion of coronavirus disease 2019.

FIGURE 2 Coronavirus disease 2019 screening form to identify potential patients who could benefit from coronavirus disease 2019 testing and monoclonal antibody therapy. COVID-19, coronavirus disease 2019

In the early 2020 months of the pandemic, the supply of rapid and reliable PCR testing for severe acute respiratory syndrome coronavirus 2 limited ED testing to those patients with more severe symptoms and who usually required higher levels of inpatient care. By the time of the first EUA for severe acute respiratory syndrome coronavirus 2–targeted mAb in November 2020, rapid PCR testing availability increased. By January 2021, system-wide demand for PCR testing declined, allowing PCR testing capabilities with a 1-hour turnaround time in our EDs. Given the use of nasopharyngeal sampling for other respiratory pathogens in the ED, adding this capability was not a challenge or unfamiliar to our teams.

2.3 | Patient selection and eligibility once known to be infected

The EUA specifies eligibility criteria for patients to receive mAb therapy, starting with a known positive severe acute respiratory syndrome coronavirus 2 test (either obtained in the ED or from an outside facility), mild to moderate symptoms for ≤10 days, and ≥1 qualifying features specified by the FDA. Qualifying conditions include certain age groups and body mass indexes, chronic kidney and/or liver disease, cardiovascular disease, tobacco/substance abuse, diabetes, immunosuppression or sickle cell disease, neurologic and neurodevelopmental disease, and medical device dependence.

Exclusion criteria include new or worsening oxygen requirement, severe coronavirus disease 2019 symptoms, and/or need for inpatient/intensive care unit level care related to coronavirus disease 2019. Patients being placed in overnight observation or admitted for a different condition do not exclude themselves from mAb therapy. If a patient meets the aforementioned criteria, the ED physician or APP may discuss the treatment option with the patient, review the FDA fact sheet, and answer any questions. If questions arose about a positive test from an outside facility, the patient underwent a retest in our ED to ensure compliance with EUA criteria.

A challenge with the EUA inclusion and exclusion criteria is that it is regularly revised and updated as more data and research become available. We used the UPMC *Infonet* (see section 2.1) and orderset updates to keep ED physician or APP abreast of the most up-to-date criteria and recommendations.

2.4 | Creating ED ordersets

Given the novelty of the coronavirus disease 2019 virus, our EHR lacked the orders needed for rapid testing and specimen prioritization as well as for the appropriate precautions these patients require. Therefore, we created ordersets using a multidisciplinary team of physicians, pharmacists, programmers, quality improvement specialists, and representatives from coding/billing. Two ordersets were integral to the process. The "ED Suspected COVID" orderset clearly identified patients under investigation to every other ED physician or APP involved in their care, from registration staff to all ancillary services. The "ED COVID Testing" orderset included a specific mAb subphase with the eligibility criteria within the order; the use of this orderset prioritized specimen collection and testing for the laboratory.

2.5 | Drug availability and infusion

Unlike many other medications dispensed in the ED, mAb infusions require compounding before delivery. All drug preparation occurs in a hospital pharmacy to minimize risk of errors and comply with compounding standards. We ensured prioritization of compounding and delivery by having a designated pharmacy professional assume responsibility for all requests. We targeted infusion times of ≤31 minutes depending on mAb product, allowing for better efficiency and less impact on overall ED care capabilities and throughput. We also monitored ED length of stay (LOS) and set a priori comparisons with other

common ED evaluations and treatment times, such as abdominal pain or migraine headache.

2.6 | mAb assignment

A unique challenge that arose with ED mAb infusion involved developing a method of assigning a mAb product to a patient that ensured efficient delivery and supply chain management, especially given that 2 products are approved under the EUA. Once a physician or other independent ED physician or APP identifies an eligible patient and choses mAb therapy (and with the agreement of the patient), we chose to have any ED (physician, advanced practice ED physician or APP, or nurse) call the ED pharmacist or centralized hospital pharmacist. We used telephone contact with a designated pharmacist to eradicate the need for the ordering ED physician or APP to know current mAb supply or to enter specific formulations in the orderset. This also expedited the process as the pharmacist was aware of the patient as soon as the ED physician or APP decided to order. The pharmacist then reconfirms eligibility as a safety and fidelity measure.

Each eligible patient is randomly assigned an authorized 2 antibody preparation mAb treatment—either bamlanivimab–etesevimab or casirivimab–imdevimab–via an assignment application that links the site mAb inventory to the current patient encounter and randomizes the mAb infusion. This randomization is not at a decision to treat at a patient level or to determine if mAb therapy will occur; it is part of the therapeutic drug exchange distribution process for similarly authorized and chosen products (in contrast to the common convenience or haphazard methods that may be used when >1 authorized or approved products exist). This means that the specific mAb product a patient receives is randomly selected (a ED physician or APP does not choose one vs the other) based on supply and under the assumptions both products are of equal efficacy under the EUA. If the ordering ED physician or APP has any concerns about the assigned mAb product, the pharmacist can discuss and resolve these concerns including using a specific product. Our committee overseeing quality improvement efforts and the institutional review board both agreed that the process met all safeguards. Of note, we had previously offered the single antibody preparation, bamlanivimab, before the FDA rescinded its EUA in April 2021.

After mAb assignment, the pharmacist enters the order for mAb and associated infusion reaction rescue medications into the EHR, compounds the mAb, and dispenses the medication. In addition, a record is automatically created upon randomization in the UPMC Clinical Data Warehouse, which tracks those who receive the infusions.[1]

A total of 8 smaller community UPMC hospitals do not have pharmacy support 24 hours a day. If we identify eligible patients at those EDs during the hours when the pharmacy is not available, options include holding the patient in the ED or in a Clinical Decision Unit until the morning or referral to 1 of 18 outpatient infusion centers throughout the system for next-morning infusion. The latter happens with a single electronic order that is reviewed promptly by 8 am by a designated pharmacy team member, with infusion scheduling occurring within hours.

Finally, our process allows for quick and efficient for adoption of new mAb drug combinations of the same class as they become available and as the landscape of the pandemic shifts, for example, the delta variant.

2.7 | Infusion specifics

Patients must havea 22-gauge intravenous or larger secured catheter for infusion. The casirivimab–imdevimab preparation is a 23-minute infusion that delivers 120 cc of fluid, whereas the bamlanivimab–etesevimab preparation is a 31-minute infusion delivering 160 cc of fluid. Vital sign recordings occur just before, at the midpoint, and after the infusion is complete. We require observation of each patient for 1-hour post infusion with reevaluation and final disposition at the discretion of the ED physician or APP. An infusion reaction and extravasation management guideline assist ED physician or APP.

Nursing documentation includes the vital signs noted previously with a final vital sign assessment before discharge after the 1-hour observation period. Nursing staff record the start and stop times of the infusion and any adverse effects. All nurses receive education on potential adverse reactions and alert the physician or advanced ED physician or APP to confirm any preexisting reaction treatments ordered or directs any therapy changes.

At discharge, patients receive standard coronavirus disease 2019–specific instructions (information on the virus, symptoms, at-home symptomatic therapy, quarantining, and social distancing) as well as the FDA fact sheets for the antibodies infused, the latter automatically added to the discharge instructions with mAb ordering.

3 | PERFORMANCE DATA

On December 16, 2020, we infused the first ED mAb dose. Since then, 832 total ED patients received a mAb infusion during an emergency care interval, with 800 infusions since March 1, 2021, through May 26, 2021. This represents 22.8% of mAb infusions at UPMC (with 2809 non-ED infusions) during this same time period. In addition, 18 (2.2%) of the mAb infusions were patients aged between 12 and 17 years. Figure 3 provides a flow representation of these data.

The triage screening tool identified 786/832 (94.5%) of ED patients as potential mAb candidates during the initial intake process. Clinical judgment allowed for added testing in patients with negative screens but clinical suspicion to avoid missing potential candidates.

In total, 890 patients had ED mAb therapy requested by treating physicians: 832 (93.5%) received the infusion, 56 (6.3%) refused infusion after randomization, and 2 (0.2%) developed new O_2 requirements and thus were no longer eligible. Reasons for refusal after randomization are unclear, but no patient was "prerandomized" before obtaining consent, and no ED physician or APP requested a change of assigned therapy. All randomization occurred after consent for receiving an authorized monoclonal preparation. In addition, we have no reported
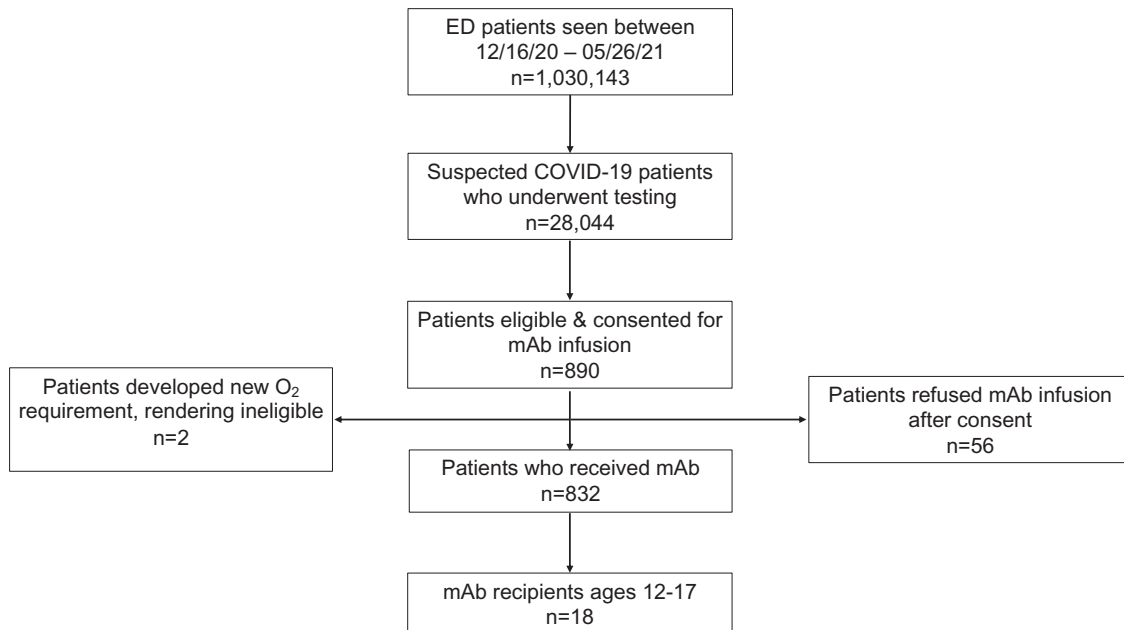
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FIGURE 3 Flow model illustrating mAb infusion statistics in the context of suspected cases of coronavirus disease 2019 and overall ED volume, where n equals the number of patients in each category. COVID-19, coronavirus disease 2019; ED, emergency department; mAb, monoclonal antibody

TABLE 1 Mean and median LOS for patients receiving mAb therapy versus other ED patients (December 16, 2020–May 26, 2021)

	LOS (minutes)	
Visit type	Mean ($\pm$95% CI)	Median
Infusion only (known coronavirus disease 2019 positive), n = 446	329 (282.2–375.8)	283
Coronavirus disease 2019 test and infusion in ED, n = 107	432 (411.4–452.6)	286
All ED visits (December 16, 2020–May 26, 2021), n = 1,030,143	232.3 (231.9–232.6)	189

CI, confidence interval; ED, emergency department; LOS, length of stay.

cases of a patient inappropriately receiving a mAb infusion when they did not meet eligibility criteria.

The need for ED coronavirus disease 2019 PCR testing did not alter the median LOS compared withpatients who presented to the ED with known positive coronavirus disease 2019 tests (Table 1). The LOS data include patients who waited overnight in the ED to receive mAb in the morning.

3.1 | Complication/reaction data

In our experience, symptoms possibly related to the infusions were rare, occurring in 2.3% (n = 48) of patients; most potential infusion-related symptoms were mild and often common symptoms of coronavirus disease 2019, including fever, shortness of breath, headache, and flushing. More severe symptoms that resulted in the infusion being discontinued or in the administration of additional medications directed at allergic reactions occurred in 0.5% of patients (n = 5). In 4 patients, infusion discontinuation occurred because of new or worsen-

ing shortness of breath or generalized pruritis and at discretion of the ED physician or APP or patient request. One patient had shortness of breath and trouble swallowing that led to the administration of intramuscular epinephrine, steroids, and an H1/H2 blocker.

Patient outcome data after ED mAb infusions, including the use of the hospital for care and/or death after infusion, are reported separately with all-system infusion observations.

4 | LESSONS LEARNED

We learned that rapid action is possible, but it requires intense organization, strict schedules, and prompt evaluation/reevaluation/"honing as needed" actions. This contrasts with the much slower traditional approaches.

We also learned that an intense effort had clear uptakebenefits when done as planned. This meant that our teams rapidly began using the training and tools, and the short feedback cycles helped us gain a quick foothold in care. We also learned that structured

observations to inform care was possible with this frameworkand in the ED.

The size and preexisting infrastructure of our health system allowed us to use our already robust network of EDs, ED staff, pharmacists, and our supply chain to implement this therapy. In addition, the ability to centralize and standardize the ED mAb program over our health system and the large catchment area it serves proved crucial to successful implementation and afforded us the ability to implement on a large scale. To our knowledge, no other health system is delivering ED mAbs on this scale.

Although the coronavirus disease 2019 pandemic is unique, the lessons may apply to the next infectious threat and any time-sensitive therapy. We "learned by doing," identifying and addressing barriers quickly.

Our program can serve as a template for other hospitals and health systems to build their ED approach, and we hope that our experiences, as well as those of others who implement similar programs, can be shared and further entrench the role of EDs in acute care opportunities.

5 | CONCLUSION

We share our template for rapid ED mAb deployment as part of an effort to deliver this transformative therapy in a timely, structured, patient-centered manner. Our insights can inform future efforts. We conclude that it is possible to act promptly and use the ED as a key coronavirus disease 2019 therapeutic site for this intervention and with high utility and low disruption. This approach may also serve well for future time-sensitive and new ED care opportunities.

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REFERENCES

1. Bariola JR, McCreary EK, Wadas RJ, et al. Impact of monoclonal antibody treatment on hospitalization and mortality among non-hospitalized adults with SARS-CoV-2 infection. *Open Forum Infect Dis.* 2021;8(7):ofab254.
2. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate covid-19. *N Engl J Med.* 2021;383:2041.
3. Bariola JR, McCreary EK, Khadem T, et al. Establishing a distribution network for COVID-19 monoclonal antibody therapy across a large health system during a global pandemic. *Open Forum Infect Dis.* 2021;8(7):ofab151.
4. Angus DC. Optimizing the trade-off between learning and doing in a pandemic. *JAMA.* 2020;323(19):1895.