

Practical considerations for solid organ transplantation during the Coronavirus-2019 (COVID-19) global outbreak

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Abbreviations:

CXR	Chest radiograph
DDIs	Donor derived infections
DORSCON	Disease Outbreak Response System Condition
HCWs	Healthcare workers
ICU	Intensive care unit
MERS	Middle East Respiratory Syndrome
MELD	Model for End-stage Liver Disease
MOH	Ministry of Health
PCR	Polymerase chain reaction
SARS	Severe acute respiratory distress syndrome
TxID	Transplant Infectious Diseases
VA-ECMO	Venous-arterial Extracorporeal Membrane Oxygenation
WHO	World Health Organization

Abstract

The current COVID-19 pandemic has not only caused global social disruptions but has also put tremendous strains on healthcare systems worldwide. With all attention and efforts diverted to containing and managing the COVID-19 outbreak (and understandably so), essential medical services as well as transplant services are likely to be affected. Closure of a transplant programs in an outbreak caused by a highly transmissible novel pathogen may be inevitable due to patient safety. Yet program closure is not without harm, patients on the transplant waitlist may die before the program re-opens. By adopting a tiered approach based on outbreak disease alert, and having hospital based guidelines based on best available evidence, life-saving transplants can still be safely performed. We had recently performed lung transplant and liver transplant safely during the COVID-19 era. We present our guidelines and experience on managing the transplant service as well as the selection and management of donors and recipients.

Introduction

Since the emergence of a novel coronavirus (now called SARS-CoV2, causing the disease COVID-19) in Wuhan, China, in Dec 2019, there has been an exponential increase in the global number of confirmed cases. There are now more than 200,000 cases in more than 100 countries. The ongoing COVID-19 outbreak has outstripped the 2003 Severe Acute Respiratory Distress Syndrome (SARS) in scale and worldwide extent, leading the World Health Organization (WHO) to officially declare it a pandemic on 11th Mar 2020¹. The evolution of COVID-19 and the containment efforts to combat this are reminiscent of SARS. The potential for healthcare systems to be crippled by this pandemic is real and looming. Essential medical services may be affected, as hospitals commandeer resources to care for COVID-19 patients and suspects². During SARS, cities experiencing community transmission, such as Singapore and Toronto, closed their transplant programs temporarily^{3,4}. While SARS came under control after a few months, allowing transplantation to resume, the current COVID-19 outbreak may be long-drawn. Organ transplantation is an essential medical service and cannot be put on hold indefinitely or for a prolonged period of time without compromising patients on the waiting list. Thus, while the medical community is largely focused on fighting this outbreak, we the transplant community have to evaluate how best to continue providing transplant care during these trying times.

Here in Singapore, evidence of local transmission occurred shortly after the first imported cases were diagnosed. Fortunately, they were part of several chains of transmission that could be identified⁵. Having survived the tragedy of SARS, our hospital had swung into crisis mode early, freeing the negative-pressure isolation ward of its usual patients (e.g. those with tuberculosis, carbapenem-resistant

Enterobacteriaceae) and reducing the number of elective surgeries to create empty beds. Strict infection prevention protocols were implemented, and compliance audits were started. The heightened level of operations and the desire to maintain transplant as an essential service prompted us to develop internal guidelines on the selection, and management of donors and recipients for transplantation in the setting of COVID-19. Shortly after that, a brain-dead donor was identified. We implemented these guidelines and performed a deceased-donor lung and a liver transplant. The aim of this article is to share our experience in developing guidelines to continue provision of organ transplantation services in this challenging time.

The setting

Singapore's first patient with COVID-19 was imported case that was diagnosed at our hospital. Local transmission occurred within 2 weeks and several local chains of transmission were identified⁵. Through media reports, this sequence of events has been played out many times in different countries. In certain countries, even the earliest cases have not had travel links^{2,6}. The ability to identify the local chains of transmission is attributed to the Singapore Government establishing a Ministerial taskforce that, under the auspices of the Infectious Diseases Act, performed extensive contact tracing of infected and exposed individuals.

On 19th Feb 2020, the local Ministry of Health (MOH) issued a statement allowing living donor transplants to proceed, while temporarily banning all non-urgent deceased donor transplants⁷. Urgent transplants included all lung transplants, heart transplants for patients on mechanical or extra-corporeal circulatory support, and liver transplants for patients with acute liver failure (Table 1). As the epidemiologic curve of incident

COVID-19 cases in Singapore flattened towards the end of February 2020, MOH allowed non-urgent deceased donor transplants as well, provided the earlier criteria were met (communication with MOH, Singapore on 3rd Mar 2020).

Principle considerations

First and foremost, SARS-CoV2 and the disease COVID-19 is still being defined. We do not know what is the (1) risk of transmission from a positive donor to a recipient, (2) impact of a recipient become infected with COVID-19 and how that influences transplant outcomes, and (3) effective treatment (if any) for COVID-19. With that in mind, the underlying principle (to allow safe transplants to continue) would be based on any available evidence and adopting best practices to exclude COVID-19 in the donor and the recipient, while maintaining a smooth operational workflow that also protects healthcare workers (HCWs).

Measures to exclude COVID-19 in donors and recipients

Our COVID-19-specific guidelines for donor and recipient assessment are described in Table 2. The differences in criteria for living donors and deceased donors stem from the time-sensitive nature of donation after brain death. The 14-day lead-up period for living donor transplantation is based on estimates that the incubation period is approximately 5.1 days and that less than 1% will develop symptoms after 14 days of active monitoring or quarantine⁸. However, it would not be acceptable or practical to keep a brain-dead donor alive for that duration. The need for extensive testing has to be balanced against the need to expedite the evaluation process to free up intensive care unit (ICU) resources and allow a timely donation process that is acceptable to the

donor family. Any COVID-19 suspect or case would automatically be excluded from donation. Donors with any potential risk of exposure to known COVID-19 transmission routes (or case definition for a suspect case), such as recent travel history outside of Singapore, or possible relationship to any of locally-identified COVID-19 clusters, are excluded. Donors would also undergo objective testing with SARS-CoV2 polymerase chain reaction (PCR) from a respiratory specimen. Sequential testing also improves the sensitivity of the test, improving the confidence of ruling out COVID-19. For deceased donors, an additional computed tomography (CT) chest was performed even if SARS-CoV2 PCR test is negative. This was based on published reports that CT imaging findings of viral pneumonia from COVID-19 pre-dated PCR tests from respiratory samples, allowing for an earlier diagnosis⁹⁻¹¹.

The criteria for potential transplant recipients are described in Table 2. In brief, they should not be suspected of, or infected with COVID-19. For patients requiring an urgent transplant, respiratory and febrile illnesses should be extensively evaluated to exclude COVID-19. For medically non-urgent transplants, a thorough history is taken from the recipients for the presence of respiratory symptoms and/or fever, as well as contact and travel history. Lastly, a COVID-19 test is performed as a final step to exclude presence of asymptomatic COVID-19 infection before proceeding on to surgery. For potential living donor transplant donors and recipients, we recommended an interim COVID-19 test at day -7 to proactively identify asymptomatic infection in the candidate that would allow the termination of the 14 day lead-up process to transplant.

Informed consent for transplant during COVID-19 global outbreak

Extra effort was made to counsel the recipients on the risks of proceeding with transplant given the evolving COVID-19 situation. We elaborated the additional steps and precautions adopted by the institution to exclude SARS-CoV2 in both donor and recipient. We emphasized that COVID-19 may not be fully excluded despite these measures and that the natural history, and management of COVID-19 infection in transplant recipients is not known. Ultimately, these have to be weighed against choosing to stay on the transplant wait-list and the risk of drop-out.

Infection Control Precautions

Hospital-wide infection prevention precautions were introduced in mid-January 2020. HCWs were also subject to mandatory twice-daily reporting of body temperature, and a moratorium on future travel to affected countries. HCWs returning from affected areas were placed on a 14 day stay-home notice. HCWs who were unwell were directed to the staff clinic for prompt evaluation. All HCWs had to (at a minimum) wear a surgical mask in all clinical settings. HCWs in the isolation ward managing patients with, or suspected of having COVID-19 wore full personal protective equipment (PPE), including N95 masks, face shield, long-sleeved gown, and gloves. Strict guidelines were laid down for surgeons and anaesthetists in the operating room with regard to the use of appropriate PPE during procedures. Relevant to transplant, full PPE was used for aerosol-generating procedures such as intubation and extubation or surgery to the respiratory system. N95 mask was worn if the Cavitron Ultrasonic Surgical Aspirator (CUSA) was used. The radiology unit screened all requests for investigations, creating a special workflow with segregated areas for patients with worrying clinical and epidemiological features¹².

The SingHealth Duke-NUS Transplant program implemented its own business contingency plans. Those currently on, or consulting for the inpatient transplant service were not allowed to attend to COVID-19 cases or suspects. A roster for an active and backup team(s) was drawn up where possible. For example, transplant coordinators were divided into two teams. This allowed the continuation of services if any team member became exposed to, or infected with COVID-19, necessitating the need to isolate the HCW and team members. As the donor team might need to travel to another hospital for organ procurement, donor and recipient teams were formed without overlap to further reduce the risk of transmission amongst HCWs. When necessary, the back-table reconstruction was performed by the donor team in a separate operating room, prior to delivery of the organ to the recipient team. These measures taken by the hospital and transplant team were reviewed at various levels and deemed to allow safe provision of transplant care.

Post-operative care

Recipients would be nursed strictly in a single room, with droplet and standard precautions. They would be monitored closely for the development of infective symptoms and tested for COVID-19 promptly, if indicated. In the unfortunate event that the recipient becomes positive for COVID-19, they will be managed in accordance to hospital policy. All efforts will be made to establish if this was a donor-derived infection (DDI), hospital-acquired, or community-acquired. Hospital and MOH-sanctioned epidemiology teams would be engaged to perform the necessary contact tracing.

Additional considerations

A key consideration prior to proceeding with transplant surgery is the availability of operating theatre and ICU beds, as these resources may be diverted to the caring for patients with COVID-19. In addition, reduction of suitable blood donors and blood bank stores may compromise the success of transplant surgery in a coagulopathic patient. These factors may influence recipient selection and the decision to proceed with transplant.

Case description

A donation after brain-death donor was identified at another hospital. The cause of death was a cerebrovascular accident. Collateral history from the next-of-kin established that the potential donor did not have respiratory symptoms prior to admission. The donor fulfilled MOH's requirements for deceased donor evaluation, and fulfilled our criteria described in Table 2. We identified potential lung and liver recipients, who were called in to the hospital and evaluated. They too met our inclusion criteria and provided informed consent to proceed.

The recipient of both lungs was a middle-aged patient with post-infective bronchiectasis but had no other comorbidities or prior chest surgery. Intra-operative blood transfusion requirements was reduced with the use of Venous-arterial Extracorporeal Membrane Oxygenation (VA-ECMO) and intra-operative blood salvage device. The liver recipient was a middle-aged patient with hepatocellular carcinoma and a low physiologic model for end-stage liver disease (MELD) score. The patient was assessed to be a low-risk candidate and was expected to require minimal

blood transfusions during surgery. Both recipients are negative for COVID-19 at the time of writing on post-operative day 15.

Discussion

Closure of a transplant program during an outbreak of a highly-transmissible novel pathogen may be inevitable because little is known about the pathogen. Invoking the tenet *Primum non nocere* in this setting means we have to consider the potential of transplant causing harm by (1) introducing a DDI, and (2) placing them at increased risk should they subsequently become infected with COVID-19 while immunosuppressed.

Detailed reviews of DDIs have not reported transmission of Coronaviruses to guide evaluation or testing^{13,14}. Since there is no known treatment for COVID-19, there is nothing that can be given empirically or prophylactically to prevent its transmission. Therefore, the only way to prevent COVID-19 DDI is by excluding infection in the donor. This may be achieved through history taking and confirmatory testing¹⁵.

A detailed history of the donor or from family members or witnesses (in the case of a deceased donor) may shed light on the donor's exposure to the pathogen. The policy of containment and extensive contact-tracing in Singapore has allowed the identification of many chains of transmission. In addition, MOH provides a daily press release with details on newly diagnosed patients with COVID-19 and sites of potential clusters⁵. This dynamic list of COVID-19 clusters is used at the Emergency Department when screening attendees, and by organ procurement coordinators. Despite that, there exist many unlinked or yet-to-be linked cases. This implies that

history taking alone is not fool-proof in excluding COVID-19 and diagnostic tests are required to complete the evaluation.

PCR assay for SARS-CoV2 is now available at many centres. While a negative result may be used to rule out COVID-19, we do not know many of the parameters, such as the Negative Predictive Value (NPV). Even amongst pathogens such as HIV, Hepatitis B and C that have established tests with a high NPV, window period transmissions have been recorded¹⁶. Further, a recent report of a negative tests in a symptomatic patient that on repeat testing became positive is concerning, even though this may well be due to sampling or testing issues¹⁷.

We also considered testing for SARS-CoV2 RNAemia in potential donors. RNAemia was documented in 15% of 41 patients in an early series from Wuhan¹⁸. RNAemia was seen in both patients that had milder symptoms, and those that required intensive care. Whether RNAemia translates to infection in solid organs such as the liver is unknown. Moreover, the period of RNAemia in relation to symptom onset was not described in the report by Huang et al¹⁸. The pervasiveness of SARS-CoV2 in tissue and body fluids is also not fully defined. A unique feature of SARS-CoV2 is its binding to Angiotensin-converting enzyme 2 (ACE-2) receptor and that it might demonstrate tropism to tissues with increased ACE-2 expression, although this hypothesis has not been confirmed¹⁹. We know from the report by Chen et al that amongst 9 pregnant women with COVID-19 that underwent delivery by caesarean section, there was no vertical transmission – SARS-CoV2 was not identified in the amniotic fluid, cord blood, neonatal throat swab and breast milk²⁰.

Presently, the MOH guideline stipulates that a donor must have 3 sequential negative throat swab PCR tests for SARS-CoV2. These tests should ideally be taken at least 12h apart, and within 24-48h prior to organ donation. Our institution introduced the need for a CT chest as an added precaution after noting reports that CT chest findings pre-dated a positive PCR result and could be used to identify patients with COVID-19⁹⁻¹¹. In this case, we were sufficiently confident the donor did not have COVID-19, given the clinical course in the intensive care unit, the negative PCR tests and a negative CT chest.

Presently there is little guidance on management of the recipient should he or she get infected with COVID-19. Historical reports of other coronaviruses (SARS and Middle East Respiratory Syndrome (MERS)) suggest that they may be lethal in transplant recipients due to their immunosuppressed state. The liver transplant recipient described by Kumar et al died from SARS³. Of the two renal transplant patients of AlGhamdi et al who acquired MERS, one perished²¹. There has been a report of a kidney transplant recipient recovering from COVID-19 after treatment with reduced immunosuppression and low dose methyl-prednisolone therapy but little else can be concluded from the report²². Of note, that these were community acquired infections and not DDI. By virtue we are dealing with a pandemic, the patient, transplanted or not, is similarly at risk of succumbing to COVID-19 either as a patient with end-stage organ failure, or immunosuppressed after transplant. The caveat here is that robust hospital infection control processes have to be in place to ensure there is no hospital-acquired infection.

While halting transplantation may be in the interest of patient safety, it is also not without its harms. During SARS, deferring cancer treatment and postponing diagnostic testing led to what has been called the “collateral damage” of SARS⁴. The same applies to withholding life-saving transplants for these patients on the waiting list who may risk dropping out to due progression of disease or death. This must be balanced against the challenges posed by COVID-19.

At the time of writing, both lung and liver recipients have not come down with an illness compatible with COVID-19. In conclusion, the known and unknown risks of transplantation are certainly increased amid this COVID-19 pandemic. However, these risks may be mitigated if the locale practices an effective containment policy, due diligence is made to exclude COVID-19 in both donor and recipient, and there are robust infectious control processes within the hospital. As more data emerge, it is likely that we will gain more knowledge to make the process even safer.

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Table 1: Impact of disease outbreak alerts on transplantation programs

DORSCON Alert ²³ (Transmission risk)	Extent of COVID-19 Transmission	Deceased Donor Transplant Program	Living Donor Transplant Program
Green (Low)	Transmission predominantly within Hubei Province, China	Nil restrictions	Nil restrictions
	Rare cases exported outside of China	Organ donors with positive travel history to affected region may be rejected upon advice from TxID.	To defer transplant for 14-28 days if organ donors had positive contact history or travel history to affected areas.
Yellow^a (Moderate)	Increased transmission to multiple provinces and municipalities in China	Although restrictions not imposed, to proceed with transplant with caution.	Nil restrictions. Thorough screening of donor and recipients through clinical history taking expected.
	Increasing number of exported cases outside of China Imported case to Singapore; no local transmission. No case fatality.	Active screening ^c and exclusion of donors and recipients at risk of COVID-19 (based on history taking).	Active screening ^c of donors and recipients who are at risk of COVID-19 (based on history taking). To defer transplant for 14-28 days if screen positive.
Orange^b (Elevated)	Widespread transmission within China	Some restrictions placed on transplant program. To proceed with <u>extra caution</u> ^d .	Although no restrictions imposed, to proceed with <u>extra caution</u> ^d .
	Significant number of exported cases outside of China, in a few WHO region. Reports of community	Medically non-urgent transplants may be put on hold. Precautions under DORSCON yellow apply. In addition,	Living donor program transplant load expected to dip. Precautions under DORSCON yellow apply. In addition,

	transmission outside of China.	diagnostic testing to exclude COVID-19 is mandated for both donor and recipient.	diagnostic testing to exclude COVID-19 is recommended for both donor and recipient.
	Local transmission WITHIN Singapore. Severe cases of COVID-19 reported.		
Red (Very high)	Widespread transmission.	global	Transplant surgeries are likely affected due to diversion of resources to combat COVID-19. Suspension of non-urgent transplant likely.
	Ongoing transmission in Singapore.	community	Medically urgent transplants to be considered on a case by case basis in consult with TxID. This is also dependent on available resources and restrictions imposed based on situation.
	Risk of increased number of severe infections.		Medically urgent transplants to be considered on a case by case basis in consult with TxID. This is also dependent on available resources and restrictions imposed based on situation.
	Disruption of schools and businesses.		Precautions under DORSCON orange apply.
			Precautions under DORSCON organ apply.

Abbreviations:

DORSCON: Disease Outbreak Response System Condition; TxID: Transplant Infectious Diseases; WHO: World Health Organization

^a DORSCON alert was raised to yellow on the 21st Jan 2020.

^b DORSCON alert was raised to orange on the 7th Feb 2020.

^c Donors would have to be screened for respiratory symptoms AND travel history to affected areas or CONTACT with COVID-19 cases or suspects through history taking.

^d Decision to proceed with transplant is based on medical indication, and availability of resources. Medically urgent cases are given priority. Enhanced infection control precautions are put in place; restrictions are placed on the number of visitors, and healthcare workers attending to the transplant recipient.

Table 2: Donor and recipient selection criteria, and additional precautionary measures for transplant

	Living donor transplant program	Deceased donor transplant program
Donor selection criteria and instructions	<p>In addition to fulfilling criteria for routine pre-transplant workup, <u>ALL</u> of the following apply:</p> <ul style="list-style-type: none"> - <u>Absence of respiratory symptoms for at least 14 days</u> prior to planned transplant - <u>No travel history outside of Singapore for at least 14 days prior to planned transplant</u> - Respiratory specimen (e.g. nasopharyngeal or oropharyngeal specimen) test <u>negative for SARS-CoV2 PCR (x2)^a</u> prior to proceeding with transplant - Donors should not be COVID-19 suspects - Normal CXR <p>The following precautions / advice are recommended:</p> <ul style="list-style-type: none"> - Minimise hosting contacts with travel outside of locale (e.g. overseas family / friends) - Avoid congregational / large group meetings (where possible) prior to planned transplant - When participating in group activities, to wear a mask - Practise social distancing. - Inform transplant coordinators if respiratory symptoms or febrile illness develops 	<p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Those with ANY travel history outside of Singapore in the last 28 days; - COVID-19 suspects / cases at the time of evaluation <p>In addition to fulfilling criteria for routine pre-transplant workup, <u>ALL</u> of the following apply:</p> <p>(a) SARS-CoV2 PCR (x3 specimens)^b test negative AND (b) CT Chest with no evidence for viral pneumonia^c</p> <p>Patients with negative SARS-CoV2 PCR, and CT chest findings not suggestive of viral pneumonia may be considered as potential organ donors on a case by case basis in consult with TxID.</p>
Recipient selection	In addition to fulfilling criteria for routine pre-transplant workup, <u>ALL</u> of the following apply:	In addition to fulfilling criteria for routine pre-transplant workup:

criteria and instructions	<ul style="list-style-type: none"> - <u>Absence of respiratory symptoms for at least 14 days</u> prior to planned transplant - <u>No travel history outside of Singapore for at least 14 days prior to planned transplant</u> - Respiratory specimen (e.g. nasopharyngeal or oropharyngeal specimen) test <u>negative for SARS-CoV2 PCR (x2)^a</u> prior to proceeding with transplant. - Should not be COVID-19 suspects 	<p>For patients requiring a medically urgent transplant, <u>ALL</u> of the following apply:</p> <ul style="list-style-type: none"> - Should not be COVID-19 suspects - Should be worked up for any respiratory symptoms / fever, and COVID-19 ruled out prior to proceeding with transplant - In the absences of respiratory symptoms, respiratory specimen (e.g. nasopharyngeal or oropharyngeal specimen) must still test <u>negative for SARS-CoV2 PCR (x1)</u> prior to transplant
	<p>The following precautions / advice are recommended:</p> <ul style="list-style-type: none"> - Minimise hosting contacts with travel outside of locale (e.g. overseas family / friends) - Avoid congregational / large group meetings (where possible) prior to planned transplant - When participating in group activities, to wear a mask - Practise social distancing - Inform transplant coordinators if respiratory symptoms or febrile illness develops 	<p>For medically non-urgent transplant, <u>ALL</u> of the following apply:</p> <ul style="list-style-type: none"> - <u>Absence of respiratory symptoms for at least 14 days</u> prior to planned transplant - <u>No travel history outside of Singapore for at least 14 days prior to planned transplant</u> - Respiratory specimen (e.g. nasopharyngeal or oropharyngeal specimen) test <u>negative for SARS-CoV2 PCR (x1)</u> just prior to proceeding with transplant. - Should not be COVID-19 suspects
Post transplant inpatient care for donor	Routine post surgical care Standard precautions ^d	N.A.
Post transplant inpatient care for recipient	Recipient to be nursed strictly in a single room with droplet and standard precautions. Additional contact precautions for those who are colonized with multi-drug resistant organisms.	
	If febrile illness develops, to work up as appropriate ^e .	

Instructions to appointed full time carer(s) Have a dedicated full time carer.

During the pre-transplant period, the potential carer should, in the pre-transplant period, adopt lifestyle restrictions that apply to the recipient. It is advisable that during the observation period for the recipient (as described above), the appointed full time carer(s) remain free of respiratory symptoms. If they are unwell at any time before or after the transplant, they should inform the transplant coordinator, seek medical help / advice, practise social distancing and appoint an alternative carer for the potential recipient while they recuperate.

Advice to carers:

- Minimise hosting contacts with travel outside of locale (e.g. overseas family / friends)
- Avoid congregational / large group meetings (where possible) prior to planned transplant
- When participating in group activities, to wear a mask
- Practise social distancing
- Inform transplant coordinators if respiratory symptoms or febrile illness develops
- Observe good personal hygiene
- Be up to date with their yearly influenza vaccination

Instructions to household member(s) Advice to household members

- Observe good personal hygiene.
- Be up to date with yearly influenza vaccination
- For household members who are not the recipient's full-time carers: To wear a mask when they participate in group activities prior to and post transplant

Abbreviations: PCR: Polymerase chain reaction; CXR: chest radiograph; CT: Computed tomography; TxID: Transplant infectious diseases

^aThe first specimen should only be obtained after the first 7 days of the 14-day observation period for respiratory symptoms; the final specimen should be collected after a 14-day symptom-free period

^bSpecimens collected for SARS-CoV2 must be collected at least 12h apart and the final SARS-CoV2 PCR must be performed within 24 - 48h of organ procurement.

^cPatients with viral pneumonia other than COVID 19, (e.g. rhinovirus, RSV, etc) will be considered for suitability of organ donation on a case by case basis.

^d Since the outbreak of COVID-19, droplet precautions are instituted in all clinical care areas outside of isolation facilities.

^e During the COVID-19 pandemic, COVID-19 has to be considered as a cause for unspecified febrile illness / respiratory tract infection. SARS-CoV2 PCR and CT Chest to be considered as part of workup if appropriate.

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