Saving those who can't wait

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For the terminally ill, waiting for a suitable organ for a life-saving transplant may take time. In this issue of the *ERJ*, the results of the French system for prioritising the urgently ill are reported, and this commentary compares it with other systems. http://bit.ly/2Zw0IaX

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Lung transplantation is a remarkable accomplishment. It may be the only life-saving treatment option for patients with terminal lung disease, but while some patients may experience a slow progression, others may develop a sudden acceleration and rapid deterioration. The ideal time for the transplantation is therefore not easy to determine. In addition, for a transplant to be possible, the death of another human being is necessary, and the timing of this is inherently unpredictable. Thus, a peculiarity of lung transplantation is that the patients in need are known before the actual treatment is available and it is necessary to create a waiting list.

In an ideal world with plenty of organs for all in need, the management of such a waiting list would not be problematic. Currently, however, the number of patients in need far exceeds the available number of organs, and the proportion of patients dying on the waiting list for lung transplantation is reported to vary from 5% to 30% in current allocation systems. Whenever a matching organ becomes available for transplantation, it seems reasonable to allocate the organ to the matching patient on the waiting list who is least likely to survive until the next organ might arrive (rule of rescue) [1]. This means prioritising the most critically ill patients or those who have features suggesting an unacceptably long waiting time, such as an unusual size (usually very small stature) or sensitisation against human leukocyte antigens. While the latter is commonly considered in allocation schemes for kidney transplantation, most lung allocation systems do not take such features into account, possibly due to lower transplant volumes.

The disadvantage of giving unrestricted priority to those most urgently ill is that such patients may often have lower survival rates after transplant. Thus, most urgency allocation schemes include criteria to reduce the rate of possibly futile transplants. Also, if too many patients fulfil the criteria for priority, the system might lose its discriminatory capacity, and a lack of ability to give priority to anyone would ensue [2]. Finally, factors not directly related to urgency may sometimes be included in the allocation scheme, such as geography or recipient age (table 1). Once prioritised, a patient obviously moves upward on the waiting list to the disadvantage of those who consequently are moved down. In some systems, the prioritised patient may additionally get access to organs from a larger procurement area than before. In such cases, the disadvantage for those not prioritised is shared between a higher number of patients at a higher number of collaborating centres (table 1).

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TABLE 1 International urgency criteria in lung transplantation

Country/region	Emergency criteria	Valid for	Consequence
France [4]	COPD/re-do transplantation: no priority All other indications: MV or ECMO CF: P_{aCO_2} >80 mmHg despite NIV ILD: S_{pO_2} <90% despite high flow oxygen or oxygen mask Vascular diseases: functional class IV, CI <2 L·min^{-1}·m^{-2} and pulmonary vascular resistance >1200 dyn·s·cm^{-5}	8 days (maximum 16 days)	From regional to national priority
Italy [10]	Invasive MV or extracorporeal support (except CO_2 removal systems), previously listed Age <50 years BMI between 18 and 30 kg·m^{-2}	1 week (maximum 3 weeks)	
Spain [11]	Invasive MV/ECMO, or PAH in life threatening condition despite adequate therapy	NA	From regional to national priority
Switzerland [12]	Invasive MV or ECMO Pulmonary fibrosis Pulmonary vascular diseases Age under 40 years (if donor <40 years)	4 weeks	Reordering within existing wait list
UK [13]	Tier 1: extracorporeal support, if previously listed Tier 2: COPD: P_{CO_2} >49 mmHg/pH <7.3. despite 24 h NIV or >10 L·min^{-1} O_2 or right heart failure despite therapy CF: P_{CO_2} >49 mmHg/pH <7.3 despite 24 h NIV or >10 L·min^{-1} O_2 or right heart failure or haemoptysis after embolization ILD: >10 L·min^{-1} O_2 or right heart failure despite therapy PAH: right heart failure or CI <2 L·min^{-1}·m^{-2} and CVP >20 mmHg or continuous inotropes	NA	From regional to national priority
Scandiatransplant [14]	Supranational tier 1: extracorporeal circulatory support (or ventilatory support) Supranational tier 2: patient with a rapid progression of organ failure with poor prognosis in a short time as defined by the responsible centre	3 patients per year and centre (total for both tiers)	Both tiers promote patient from national to supranational priority
Belgium [15]	Centre allocation (clinical discretion), LAS 50 or above qualifies for international urgency in Eurotransplant area	14 days	From regional to international priority
Austria [15]	Centre allocation (clinical discretion), LAS 50 or above qualifies for international urgency in Eurotransplant area	14 days	From regional to international priority
Germany [15]	National allocation by LAS, LAS 50 or above qualifies for international urgency in Eurotransplant area Rescue allocation (organs declined elsewhere) allocated by centre discretion		National and international priority
Canada [16]	Centre allocation, two urgency tiers defined by criteria		Regional priority
Australia and New Zealand [17]	Centre allocation, fulfilment of certain criteria of urgency and HLA sensitisation may be considered for national allocation		Possibly from regional to national
USA [18]	LAS (and physical distance)		Highest LAS has first priority within radius of 250 nautical miles from procurement centre

ECMO: extracorporeal membrane oxygenation; MV: mechanical ventilation; NIV: non-invasive ventilation; NA: not available; CF: cystic fibrosis; ILD: interstitial lung diseases; PAH: pulmonary artery hypertension; BMI: body mass index; P_{aCO_2}: arterial partial pressure of carbon dioxide; P_{CO_2}: partial pressure of carbon dioxide; S_{pO_2}: peripheral oxygen saturation; CI: cardiac index; CVP: central venous pressure; LAS: lung allocation score; HLA: human leukocyte antigen.

Basically, there are three systems for lung allocation: single centre allocation, national urgency tiers (usually on top of centre allocation), and numerical scoring systems. Single centre allocation means there is just one transplant centre in an organ procurement region. In such systems, whenever an organ becomes available, healthcare professionals select the matching patient on their list perceived to be most needy, usually according to clinical judgment and not according to predefined criteria, although separation into first and second priority tiers according to some criteria may occur. Such centre allocation is used in many countries, especially in countries with only one transplant centre and in systems covering large, sparsely populated areas, such as Canada and Australia.

An alternative to single centre allocation is urgency allocation that stratifies patients into tiers that give supra-regional priority. This is possible where several centres share one organ procurement system, and the tiers may be determined based on clinical judgment or by specific predefined criteria.

Whether regional or supra-regional, priority may also be determined using a numerical scoring system, such as the Lung Allocation Score (LAS). This is a continuous numerical model based on approximately 20 variables that are assumed to predict survival benefit, and it may be used both for local and supra-regional or international prioritisation [3].

To evaluate whether an allocation system actually works as intended, four basic questions should be answered:

- First, who gets priority? (*i.e.* are the most imminently urgent patients actually identified by the system, and what other criteria may be at play?)
- Second, is the system efficient? (*i.e.* does the system ensure allocation of well-matched organs within reasonable time?)
- Third, what is lost? (*i.e.* does the system reduce the overall survival after lung transplantation?)
- Fourth, what else is affected? (*i.e.* does the allocation system affect external factors, such as the actual patient selection for lung transplantation, or the number and quality of the organs accepted for transplantation?)

In the current issue of the *European Respiratory Journal*, Roussel *et al.* [4] report that since the introduction of the French High Emergency Lung Transplantation system (HELT) in 2007 until the end of the observation period in 2015, 22% of lung transplant recipients in France were given urgent status. The proportion thus prioritised is substantially higher than the 8% granted urgent status under the Scandiatransplant scheme [5], where the there is a cap on the number of patients permissible for urgent allocation. In the UK, a criteria-based system of urgency tiers, which is similar to the French system based on a preliminary report after its recent introduction, the number allocated for urgency is similar to the HELT (21% urgent and 6% super-urgent) [6]. Translating urgency to a LAS of 50 or above, in Germany this proportion was 28% [7] while the corresponding proportion is slightly lower in the USA, where 15% had a LAS >50 in 2017 [8]. It is hard to judge how well the French HELT system actually identifies urgently ill patients since no data about time on waiting list or death on waiting list is given. The defining criteria seem plausible, but it does seem likely that the system also skews the allocation in ways not directly related to urgency, for instance by excluding patients with COPD and by giving preference to younger patients. Interestingly, however, the same tendency seems to be present in other urgency allocation systems (table 2).

The authors did find that the organ matching is stretched in patients allocated by urgency, with more frequent mismatch of size, blood group and cytomegalovirus status, probably with some measurable adverse effects for the recipients. As in an earlier report of the French HELT system [9], Roussel *et al.* [4] identified a clearly reduced survival in the HELT recipients, with a hazard ratio of death of 1.4 compared

TABLE 2 Results of selected urgency allocation systems

Country/region	France (Roussel *et al.* [4])	Italy [10]	Scandiatransplant [5]	Spain [11]
Year of introduction	2007	2010	2009	1998
Lung transplant activity in 2016	384 (6 pmp)	144 (2 pmp)	143 (5 pmp)	363 (7 pmp)
Area km^2	643 801	301 338	1 320 000	505 990
Centres n	11	10	5	8
Urgency	503/2333 (22%)	28/140 (20%)	71/1033 (7%)	279/2752 (10%)
Median age of urgent patients years	44	34	40	44
ECMO/MV n (%)	38 (13%)/49 (10%)	24 (86%)/25 (89%)	32 (45%)/7 (10%)	NA/60 (82%)
Urgency tiers n	1	1	2	1
Specific criteria	Yes	Yes	No	Yes
Waiting time on urgency	NA	6 days	3 days	4 days
1-year death on waiting list urgent/elective	(6% *versus* NA)	21% *versus* NA	10% *versus* 3%	15% *versus* NA
1 year survival after lung transplant urgent/ elective	68% *versus* 78%	71% *versus* NA	81% *versus* 85%	61% *versus* 80%

ECMO: extracorporeal membrane oxygenation; MV: mechanical ventilation; NA: not available; pmp: per million population.

to the non-HELT patients. As the authors state, it has to be kept in mind that COPD patients are excluded from these data. The influence the inclusion of these might have had, however, is not reported.

There seems to be reason to believe that the HELT system may have encouraged increased utilisation of donor organs, since the data presented by Roussel *et al.* [4] also shows that urgently listed patients more frequently receive organs of presumed reduced quality. In an analysis of attributable risks, the authors show that the use of such organs contributed only 4.2% to the reduced survival of the HELT patients.

There are many very different interests to consider for those who manage the waiting list of potential lung transplantation recipients. In allocation the main motive should be that those who are in need and who have a clear benefit do get a transplant and that no one should be left behind. In times of organ shortage, complex decisions have to be made, and Roussel *et al.* [4] describe some of the consequences of 8 years of practising the HELT system for lung allocation in France. Many questions remain unanswered, but by publishing their data the authors give tentative answers to some and highlight others. In their discussion, they also provide an ethical context to the decisions that need to be made in urgency allocation. Bringing a patient in need and a suitable donated organ together for lung transplantation is indeed remarkable and the report by Roussel *et al.* [4] shows some of the complexity of this accomplishment.

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References

1 McKie J, Richardson J. The rule of rescue. *Soc Sci Med* 2003; 56: 2407–2419.
2 Stevenson LW. Crisis awaiting heart transplantation: sinking the lifeboat. *JAMA Intern Med* 2015; 175: 1406–1409.
3 Egan TM, Murray S, Bustami RT, *et al.* Development of the new lung allocation system in the United States. *Am J Transplant* 2006; 6: 1212–1227.
4 Roussel A, Sage E, Massard G, *et al.* Impact of donor, recipient, and matching on survival after high emergency lung transplantation in France. *Eur Respir J* 2019; 54: 1900096.
5 Auraen H, Schultz HHL, Hammainen P, *et al.* Urgent lung allocation system in the Scandiatransplant countries. *J Heart Lung Transplant* 2018; 37: 1403–1409.
6 Rushton S, Al-Aloul M, Carby M, *et al.* The introduction of urgent and super-urgent lung allocation schemes in the United Kingdom. *J Heart Lung Transplant* 2018; 37: S185.
7 Gottlieb J, Smits J, Schramm R, *et al.* Lung transplantation in Germany since the introduction of the Lung Allocation Score. *Dtsch Arztebl Int* 2017; 114: 179–185.
8 Valapour M, Skeans MA, Smith JM, *et al.* OPTN/SRTR 2015 annual data report: lung. *Am J Transplant* 2017; 17: Suppl. 1, 357–424.
9 Boussaud V, Mal H, Trinquart L, *et al.* One-year experience with high-emergency lung transplantation in France. *Transplantation* 2012; 93: 1058–1063.
10 Palleschi A, Benazzi E, Rossi CF, *et al.* Lung Allocation Score System: first Italian experience. *Transplant Proc* 2019; 51: 190–193.
11 Román A, Calvo V, Ussetti P, *et al.* Urgent lung transplantation in Spain. *Transplant Proc* 2005; 37: 3987–3990.
12 Swiss Allocation Rules. https://www.swisstransplant.org/de/organspende-transplantation/rechtlichegrundlagen/ Date last accessed: 21 August 2019.
13 UK Allocation Policy. http://odt.nhs.uk/pdf/lung_allocation_policy.pdf Date last accessed: 21 August 2019.
14 Scandiatransplant Allocation Guidelines. http://www.scandiatransplant.org/members/nttr/Guideline_SHLG_oct_2017.pdf Date last accessed: 21 August 2019.
15 Eurotransplant Allocation Rules. https://www.eurotransplant.org/cms/mediaobject.php?file=Chapter6_Thoracic13.pdf Date last accessed: 21 August 2019.
16 Hirji A, Zhao H, Lien DC, *et al.* Clinical judgment vs. Lung Allocation Score in predicting waitlist mortality. *J Heart Lung Transplant* 2015; 34: S245–S245.
17 Australia and New Zealand Allocation Guidelines. https://www.tsanz.com.au/TSANZ_Clinical_Guidelines_Version1.3%5B6986%5D.pdf Date last accessed: 21 August 2019.
18 USA OPTN Allocation Rules. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf Date last accessed: 21 August 2019.