SUPPLEMENTARY DIGITAL CONTENT

A tale of two waves: changes in the use of non-invasive ventilation and prone positioning in critical care management of COVID-19.

Appendix 1 – Example Standard of Care Guidelines

Example of 1 Page from an ICU Covid-19 Guideline at the start of the pandemic (March 2020)

Daily Reviews for the ICU Patient with suspected/confirmed Covid-19	Critical Care Manchester
Airway	Check and record tube size and position (especially after proning/deproning) Is there a cuff leak? Check cuff pressure (usually kept at 30cmH$_2$O)
Breathing	Physical examination balancing the risks of staff exposure: visual assessment first, with percusssion/palpation/auscultation if patient deteriorating or clincial concern. Ask the nursing staff about secretions: amount, quality. Mechanical ventilation: - SIMV VC+ is our standard mandatory mode. RR 20/min initially. - Target oxygen saturations: 90% in acute respiratory failure. - Check SpO$_2$ alarm settings: lower limit 87%, upper limit 98%. - Tidal volume: aim 6ml/kg ideal body weight in controlled ventilation (see overleaf) - Is the height and ideal body weight accurately recorded? Don't assume – check! - I:E ratio (normal is 1:2, start at 1:1.5, progress to 1:1 or inverse ratio in severe hypoxia) - Assess static compliance, PEEPi, plateau and driving pressure. - Record the PaO$_2$/FiO$_2$ ratio (<40 = mild, <26.7 = moderate, <13.3 = severe) - Is the patient recruitable? Does static compliance increase with increasing PEEP? - If recruitable: use the PEEP ladder (see overleaf), if not: set PEEP 8-10. Investigations: trends in ABGs and pH, when was the last CXR? SEE TOP TIPS FOR COVID-19 IN ICU FOR WHEN TO PARALYSE & WHEN TO PRONE Muscle relaxants: record duration of infusion/boluses and when last given If proned: - Review duration of prone ventilation, record dates/times of prone episodes - Plan position changes and note time for re-supination SEE EMERGENCY GUIDELINE FOR MANAGEMENT OF SEVERE ACUTE HYPOXIA

Circulation	Review 3 lead ECG – are there arrhythmias/ectopics? 12 lead only if good indication.
	Assess volume status and fluid overload, review lactate and CVP.
	Physical exam if patient deteriorating or clinical concern.
	
	Review of investigations:
	- Troponin measurements with routine bloods (risk of myocarditis in Covid-19)
	- BNP (if concerns for heart failure) – check on admission for all patients.
	Consider echocardiography – to assess fluid status and/or if Troponin/BNP elevated.
	
	Management of shock:
	1. Consider the cause (SHIT):
	   a. Septic
	   b. Hypovolaemic
	   c. Iatrogenic (eg. sedation bolus/interruption of vasopressor)
	   d. Thoracic (eg. cardiogenic, tension penumothorax, PE)
	2. Caution with fluid bolus therapy – wet lungs worsen ventilatory failure. Consider assessing fluid responsiveness first: tidal vol challenge or passive leg raising.
	3. Target MAP 60-65mmHg provided UO acceptable (see below)
	4. Noradrenaline 1st choice vasopressor: (4mg/50mls -> 8mg/50mls -> 16mg/50mls)
	5. Other vasopressors/inotropes after discussion with critical care consultant
	6. Do not give hydrocortisone as a treatment for septic shock

Appendix 2. Baseline Characteristics and Pre-ICU Care Stratified by Survival

	All (N=210)	ICU Survivors (n=135)	ICU Non-Survivors (n=75)	P value
Age, (years), mean (SD)	57.6 (13.8)	53.9 (13.3)	64.1 (12.2)	<0.01
Male sex, n (%)	139 (66.2%)	93 (68.9%)	46 (61%)	0.29
Female sex, n(%)	71 (33.8%)	42 (31.1%)	29 (39%)	
Body mass index (kg/m^2), n (%)				
<18.5	1 (0.48%)	1 (0.7%)	0 (0%)	
18.5 - 25	44 (21.0%)	26 (19.3%)	18 (24%)	
25 - 30	78 (37.1%)	48 (35.6%)	30 (40%)	0.71
30 - 35	61 (29.0%)	43 (31.9%)	18 (24%)	
35+	18 (8.6%)	12 (8.9%)	6 (8%)	
Pre-hospital dependency, n (%):				
Able to live without assistance in daily activities	162 (77.1%)	110 (81.5%)	52 (69%)	
Minor assistance with some daily activities	27 (12.9%)	14 (10.4%)	13 (17%)	0.14
Major assistance with majority of/all daily activities	21 (10.0%)	11 (8.1%)	10 (13%)	
Pre-ICU care				
APACHE II, median [IQR]	15 [8, 22]	13 [6.5, 19.5]	18 [11, 25]	<0.01
APACHE II probability of death (%), median [IQR]	22.6 [2.7, 42.5]	17.9 [5, 30.8]	31.2 [5.9, 56.4]	<0.01
Airway on arrival to ICU, n (%):				
Own Airway	165 (78.6%)	102 (75.6%)	63 (84%)	
Endo-tracheal tube	41 (19.5%)	29 (21.5%)	12 (16%)	0.23
Tracheostomy	4 (1.9%)	4 (3.0%)	0 (0%)	
Treatment limitation at ICU admission, n (%)	40 (19.0%)	10 (7.4%)	30 (40%)	<0.01

APACHE = acute physiology and chronic health evaluation

Appendix 3- ICU Care Stratified by Survival

Maintained own airway for entire ICU admission	All (N=100)	ICU Survivors (n=66)	ICU Non-Survivors (n=44)	P value
NIV/HF during ICU admission, n (%)	86 (86%)	56 (85%)	30 (68%)	0.06
With treatment limitation	32 (32%)	8 (12%)	24 (55%)	<0.01
Without treatment limitation	54 (54%)	48 (73%)	6 (14%)	
Duration of NIV (hours), mean (SD)	91 (73)	91 (58)	90 (95)	0.96

Management of patients requiring invasive ventilation	All (N=106)	ICU Survivors (n=65)	ICU Non-Survivors (n=41)	P value
Intubated prior to ICU admission, n (%)	41 (38.7%)	29 (45%)	12 (29%)	0.15
Intubated during ICU admission, n (%)	65 (61.3%)	36 (55%)	29 (71%)	
Total intubated ≤ 24hours of ICU admission, n (%)	74 (69.8%)	54 (83%)	20 (49%)	<0.01
Total intubated >24 hours of ICU admission, n (%)	32 (30.2%)	11 (17%)	21 (51%)	
NIV prior to intubation, n (%)	57 (53.8%)	31 (48%)	26 (63%)	0.72
With treatment limitation initially in place on admission	2 (1.9%)	0 (0%)	2 (5%)	-
Without treatment limitation in place on admission	55 (51.9%)	31 (48%)	24 (59%)	-
NIV duration prior to intubation (hours), median [IQR],	19 [7, 61]	10 [4, 21]	50 [23, 124]	<0.01
Time to intubation if own airway on admission (hours), median [IQR],	24 [12, 65]	19 [10, 46]	41 [17, 124]	0.01
Neuromuscular blockade Infusion, n (%)	77(72.6%)	44 (68%)	33 (80%)	0.52
Cumulative duration per patient (hours), median [IQR]	111 [46, 185]	96 [45, 163]	139 [52, 230]	0.12
Prone Ventilation, n (%)	58 (54.7%)	28 (43%)	30 (73%)	<0.01
Duration of each episode (hours), median [IQR]	19 [15, 23]	19 [16, 22]	19 [14, 23]	0.97
Cumulative duration per patient (hours), median [IQR]	43 [22, 76]	34 [22, 60]	63 [24, 93]	0.11
Number of episodes per patient, median [IQR]	2 [1, 5]	2 [1, 4]	3 [1, 6]	0.19
Time from Intubation to first pronation, (hours), median [IQR]	41 [5, 111]	42 [5, 156]	34 [5, 89]	0.74
Inhaled nitric oxide therapy at any point, n (%)	6 (5.7%)	2 (3%)	4 (10%)	-
Transferred for Extracorporeal membrane oxygenation, n (%)	3 (2.8%)	3 (5%)	0 (0%)	-
Successful extubation, n (%)	28 (26.4%)	28 (43%)	0 (0%)	-
Overall duration of invasive ventilation (days), mean (SD)	20.7 (19.6)	24.2 (23.0)	15.0 (10.5)	<0.01

Tracheostomy management	All (N=39)	ICU Survivors (n=32)	ICU Non-Survivors (n=7)	P Value
Failed extubation before tracheostomy, n (%)	10 (26)	9 (28)	1 (14)	-
Day of ICU admission performed, mean (SD)	19.7 (.1)	20.5 (9.1)	16.3 (8.9)	0.29
Successful decannulation, n (%)	30 (77)	30 (94)	0 (0)	-
Days to decannulation after insertion, mean (SD),	21.9 (16.5)	21.9 (16.5)	-	-

NIV= Non-Invasive Ventilation, HF= High Flow Oxygen

Appendix 4 - Ventilatory Parameters

Exploratory analysis undertaken at Day 1, 5 and 10 post intubation. All Values based on the mean of lowest PF per patient using available patient data for each calendar day.

|	All Patients	Wave 1	Wave 2
Positive End Expiratory Pressure (cmH$_2$O), mean (SD)			
Day 1	11.3 (2.4)	11.6 (2.6)	10.9 (1.7)
Day 5	10.5 (2.3)	10.6 (2.3)	10.5 (2.3)
Day 10	9.9 (2.6)	9.6 (2.6)	10.4 (2.4)
Peak Airway Pressures (cmH$_2$O), mean (SD)			
Day 1	26.8 (4.7)	26.8 (4.3)	27.0 (5.4)
Day 5	26.5 (4.8)	26.1 (4.2)	27.2 (5.8)
Day 10	26.1 (6.5)	24.2 (6.5)	29.2 (5.2)
Actual Respiratory Rate, mean (SD)			
Day 1	22.7 (3.3)	22.9 (3.2)	22.4 (3.4)
Day 5	24.2 (3.9)	24.0 (4.1)	24.4 (3.8)
Day 10	24.0 (4.1)	23.1 (3.8)	25.2 (3.8)
Tidal Volume (ml/Kg/IBW), mean (SD)			
Day 1	7.0 (1.2)	7.0 (1.2)	7.1 (1.3)
Day 5	7.0 (1.5)	7.1 (1.6)	7.0 (1.3)
Day 10	7.1 (1.7)	7.4 (1.6)	6.6 (1.7)
PaO2/FiO$_2$ Ratios (mmHg), mean (SD)			
Day 1	137 (56)	142 (55)	131 (57)
Day 5	129 (54)	138 (60)	124 (51)
Day 10	147 (74)	168 (74)	119 (65)

PaO$_2$ = Partial Pressure of Oxygen in arterial blood.

FiO$_2$ = Fraction of Inspired Oxygen

Calculated as the mean of the lowest PaO$_2$/FiO$_2$ Ratio per Patient per calendar day

IBW = Ideal Body Weight (Devine's formula)

Appendix 5 - FiO$_2$ Response to Proning at 12 hours stratified by wave and survival in IMV Patients
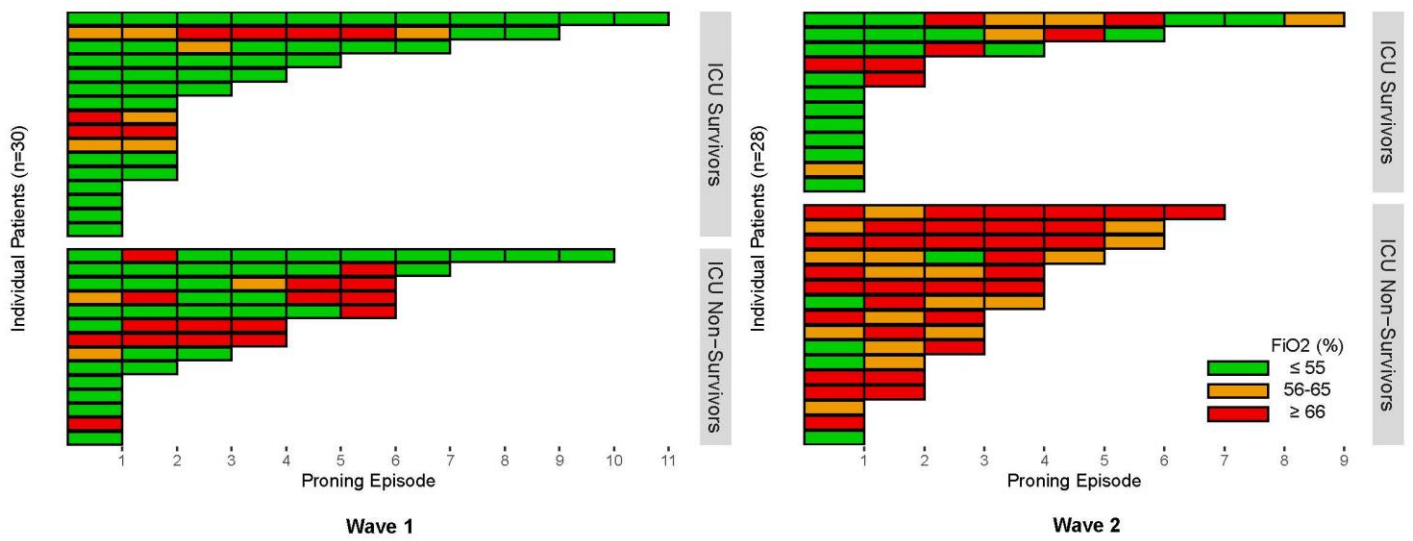
Graphical illustration of the outcome of each proning episode for all patients in the study. Individual patients are arranged on the y-axis according to ICU survival status and the number of the proning episodes they received. Each block represents a proning episode and the blocks are arranged sequentially in time for each patient. The blocks are colour coded according to the FiO$_2$ outcome observed 12 hours after proning was commenced (see manuscript).

Appendix 6 - Exploratory Analysis of Patients with high BMI ≥35kg/m^2

	BMI < 35	BMI ≥35	p value
Proportion of Patients requiring Intubation, n, (%)	85 (51%)	21 (47%)	0.61
Proportion of Patients requiring Tracheostomy, n, (%)	29 (17%)	10 (23%)	0.52
Total duration of Mechanical Ventilation, days, mean, (SD)	20.4	21.8	0.75

Subgroup exploratory analysis. Examining whether patients with a very high BMI (≥35kg/m^2) were more likely to require intubation, tracheostomy or a longer duration of invasive mechanical ventilation.