Intensive care: who benefits? F105, 2C01

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Intensive care has saved many lives but there are still those patients who are so ill at the time of presentation that the benefit of escalating intensive care support is not clear-cut. To be fair to these patients and the others who can benefit from our services, it is vital that decisions concerning how far organ supporting measures should be pursued are made as reliably and robustly as possible. This review describes some of the prognostic features available at presentation or shortly afterwards, pertaining to five clinical scenarios associated with a perceived poor survival rate (ie, acute-on-chronic liver failure, haematological malignancy, chronic lung disease, cardiac arrest and morbid obesity).

Keywords: *intensive care; COPD; cardiac arrest; obesity; liver failure; haematological malignancy*

Introduction

Intensive care is an enormously important hospital specialty. Since its advent in the 1950s, intensive care has saved millions of lives. In the UK, approximately 120,000 critically ill patients are admitted to ICUs in England, Wales and Northern Ireland each year; 77% survive to leave hospital.[1] However within this impressive survival rate, critically ill patients fall into three broad categories, namely those who are well and so would survive anyway, those who are seriously ill and would have died but for ICU and finally those who are so ill that they would die whatever is done. The true benefit of intensive care is determined by its impact on improving survival in the second group. Combining the seven randomised trials examining the impact of intensive care, they showed that the absolute reduction in mortality was 17.4% (95% Confidence Interval (CI) 7.6-27.3).[2] This translates into a number needed to treat of 5.7; in other words having to treat six critically ill patients to save the seventh's life.

While such a large absolute risk reduction is reassuring, the triage of patients in the second and third groups (ie, those who are seriously ill and would have died but for ICU versus those who are so ill that they would die whatever is done) is fraught with difficulty and uncertainty. Decisions concerning the benefit of intensive care are based upon probabilities, the final estimate of which is largely subjective, as objective methods (eg, scoring systems) cannot compensate for all the relevant factors, some of which may indeed not be clinical. The purpose of this review is to examine the recent literature pertaining to five clinical scenarios that frequently pose the most difficult decisions about whether or not to embark on intensive care as the prognosis is often seen as hopeless. Clinical heterogeneity within these admission categories means that sensible conclusions are often difficult to draw. The clinical decisions concern patients presenting with acute-on-chronic liver failure, haematological malignancy, chronic lung disease, cardiac arrest and morbid obesity.

Acute-on-chronic liver failure

Acute-on-chronic liver failure describes an acute deterioration of liver function in patients with cirrhosis, which is usually associated with a precipitating event and results in the failure of one or more organs. Such acute decompensation is characterised by the rapid development of one or more major complications of liver disease (ie, ascites, encephalopathy, gastrointestinal haemorrhage and bacterial infection); these complications are usually the main presenting complaints. While many cirrhotic patients may present without significant physiological disturbance, some will have already declined or be at risk of declining into multiple organ failure. Such patients may be referred for intensive care support because of their high risk of short-term mortality.

A large recent pan-European study (in 12 countries, 29 university hospitals, with 1,343 patients) explored the development and progression of acute-on-chronic liver disease.[3] From an intensive care perspective, the key finding was that 28-day mortality escalated in line with increasing organ failure (**Table 1**), especially if renal dysfunction was present. Patients admitted to ICU had a 32.3% mortality compared to 4.6% for those treated on a general ward.

Pre-admission characteristics associated with a poor outcome included:

- Patients with acute-on-chronic liver failure presenting with their first episode of acute decompensation. Their mortality was almost 1.5 times higher than those with previous decompensation.[3]
- There was a direct relationship between white blood cell count (WBC) and mortality. Patients with acute-on-chronic liver failure and previous decompensation suffered a 28-day mortality of 30% with a WBC count of $6x10^9$/L; with WBC of $14x10^9$/L mortality increased to 50% and when it reached $18x10^9$/L mortality was over 60%. If this was the patient's first acute decompensation, then mortality was 50%, 80% and 100% respectively.[3]
- Ultimate non-survivors were less likely to have gastrointestinal bleeding as the indication for admission to ICU compared to survivors and more frequently had severe encephalopathy, ascites and the need for inotropic support.[4]

Infection was a common feature of acute-on-chronic liver

No. and types of organ failures		Deaths/all patients, n (%)
No organ failure		39/874 (4.5)
One organ failure		39/267 (14.6)
	Single liver failure	14/101 (13.9)
	Single cerebral failure	3/30 (10.0)
	Single coagulation failure	3/28 (10.7)
	Single circulation or lung failure	3/22 (13.6)
	Single kidney failure	16/86 (18.6)
Two organ failures		31/97 (32.0)
Three organ failures or more		33/42 (78.6)

Table 1 28-day mortality according to the number and types of organ failures in patients presenting with acute-on-chronic liver failure. Data are presented as number (%).[3]

Category of haematological malignancy	Admissions (n)	Deaths (n)	Hospital mortality (%)	Odds ratio (95% CI)
Bone marrow transplant	143	93	65.0	1.88 (1.00-3.53)
Acute lymphoblastic leukaemia	254	141	55.5	
Acute myeloblastic leukaemia	591	398	67.3	1.37 (0.86-2.20)
Chronic lymphocytic or myeloblastic leukaemia	290	165	56.9	1.02 (0.58-1.80)
Hodgkin's lymphoma	200	142	71.0	2.38 (1.30-4.36)
Non-Hodgkin's lymphoma	944	625	66.2	1.46 (0.92-2.31)
Myeloma	378	227	60.1	0.79 (0.47-1.35)
Totals	2,800	1,791	63.9	

Table 2 ICU and hospital mortality varying with category of haematological malignancy.[10]

failure, which complicates the natural history and significantly increases mortality. About 40-50% of cirrhotic patients admitted to hospital presented with sepsis and a further 20-40% developed nosocomial infections. Once on the ICU, multiple organ failure or sepsis accounted for 60% deaths at 90 days.[3] The combination of renal dysfunction and mild to moderate encephalopathy synergistically increased the chances of death; patients with alcoholic liver disease needing renal replacement therapy suffered 94% hospital mortality.[5]

Alcohol-induced decompensation of pre-existing liver disease significantly increased the risk of death in comparison with non-alcoholic decompensation. The adjusted odds ratios (OR) of 30-day mortality for patients with alcoholic liver cirrhosis, non-alcoholic liver cirrhosis, and alcoholism compared with other bacteraemias were 6.3 (95% CI 3.3-11.7), 2.4 (95% CI 0.9-6.7), and 2.5 (95% CI 1.7-3.7), respectively.[6] Patients who developed sepsis on a background of alcoholism (dependence or withdrawal) had an OR of 4.66 (95% CI 2.81-7.72) of hospital mortality.[7]

However, overall the mortality of patients with advanced liver dysfunction has declined with improved intensive care management of organ dysfunction, from which patients with cirrhosis have benefitted. In the UK, Cholongitas[4] reported a significant decline in mortality from 82% in 1989-92 to 52% in 2001-04; similar improvements have been reported in France.[8] Expeditious use of specific interventions such as transjugular intrahepatic porto-systemic shunts (TIPSS) can improve one year survival of patients with cirrhosis and variceal bleeding (86% *vs* 61%).[9]

In summary, patients presenting with their first decompensation of alcohol-induced acute-on-chronic liver failure with infection, particularly sepsis, and/or multiple organ failure, especially renal dysfunction have the worst prognosis on ICU. Their ICU mortality is closely related to the degree of organ failure rather than to the severity of underlying liver disease. While not suggesting that such patients should be declined ICU admission, awareness of their poor prognosis may help determine limits to interventions and modify expectations.

Haematological malignancy

Patients referred to intensive care with a background of haematological malignancy pose many difficulties. They are frequently younger than the other ICU patients, being on average a decade younger[10,11] and may have just presented with haematological malignancy or may be receiving active treatment of their malignancy. Two of the most important considerations are the type of malignancy, as not all haematological cancers have the same prognosis, and the reason for referral (ie, whether the admission is primarily caused by the haematological malignancy or if it is just part of the past medical history). It is also vital to appreciate (and make clear to the family and referring clinicians) that it is well established that the ICU survival of patients with

haematological malignancies does not depend on disease-related parameters but rather on the severity of the acute illness (ie, the degree of physiological disturbance); their long-term survival is associated with disease-related parameters.[12-14]

One of the largest reviews of patients with haematological malignancy was a secondary analysis of the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme (CMP) Database. This was conducted on admissions to 178 adult, general ICUs in England, Wales and Northern Ireland between 1995 and 2007 and included 7,689 eligible admissions.[10] The overall ICU mortality was 43.1% (3,312 deaths) and acute hospital mortality was 59.2% (4,239 deaths) in patients identified from their primary, secondary and ultimate primary reason for admission fields, from either of two other conditions relevant to the admission, and from the past medical history. This average hospital mortality (59.2%) is in line with contemporaneous data from the Scottish Audit Group who reported 53% mortality (379 deaths in 714 patients). This cohort comprised patients admitted directly with malignancy or its treatment but also patients with a history of haematological malignancy admitted for reasons unrelated to the malignancy or its immediate treatment.[15] If only admissions with a haematological diagnosis as the primary, secondary or ultimate reason for admission are examined, then overall hospital mortality reported by ICNARC is almost 64% with patients with Hodgkin's lymphoma faring worse (71% hospital mortality) (**Table 2**).

Poor prognostic signs present at referral include the time interval between the acute hospital admission and admission to intensive care; the acute hospital mortality was 54.1% in patients admitted immediately to the ICU compared with 70.8% if admission occurred after 20 days or more in hospital.[10] Severe sepsis was a common presenting condition (54.3%) and significantly increased acute hospital mortality (OR=1.29). As with other critical illnesses, declining physiological reserve was associated with increasing age, and in these patients mortality increased with an OR of 1.14 for every 10-year increase in age. Hampshire reported ten physiological factors which significantly decreased the chances of survival (haematocrit, systolic blood pressure, respiratory rate, heart rate, Glasgow Coma Score, sedation, PaO_2, arterial pH, urine output, serum sodium, and serum urea), all but one of which reflect organ function. The impact of organ dysfunction in patients with haematological malignancy is much more serious than other ICU patients; with only two or more organs failing, the hospital mortality of these patients exceeded 68% (**Table 3**). Although mechanical ventilation within 24 hours of ICU admission was not associated with hospital mortality after adjustment for other prognostic factors, 70.2% of intubated patients died, compared with 45.3% of non-intubated patients.

However, it is important to bear in mind that the treatment of haematological malignancy is rapidly evolving and treatment options have changed. A combination of factors has been proposed to account for the decreasing mortality rate over time.[16] Improved survival may be related to the use of more intensive chemotherapeutic regimens and the development of more potent and targeted therapies, together with new strategies avoiding early chemotherapy for chronic malignancies (eg, 'watch-and-wait' policies or immunotherapy) to reduce organ-related toxicity and epithelial and endothelial dysfunction. Improved ICU management, with the development of non-invasive diagnostic and therapeutic strategies (especially for respiratory failure) as well as advances in supportive care and the prevention of organ dysfunction contribute to lower mortality rates. Triaging patients with the highest chances of survival and then offering early ICU admission improves outcome.

Organ failures	Non survivors/ survivors (n)	Mortality (%)	95% CI
0 organ failures	196/443	39.8	35.5-44.1
1 organ failure	495/891	55.5	52.2-58.8
2 organ failures	540/778	69.4	66.0-72.6
3 organ failures	354/419	84.5	80.6-87.8
4 organ failures	166/181	91.7	86.4-95.1
5 organ failures	40/41	97.6	85.6-99.9

Table 3 Hospital mortality by number of organ system failures, mortality% (95% CI) (n=2803 admissions with a haematological diagnosis as the primary, secondary or ultimate reason for admission).[10]

In summary, one in three patients admitted to ICU primarily because of their haematological malignancy will survive to leave hospital. At presentation, the patient's outcome is determined by the degree of physiological disturbance and not by the type or progression of their haematological malignancy. Patients with two or more organ system failures do particularly badly, with a much higher mortality (68%) than other ICU patients with the same degree of organ failure.

Chronic obstructive pulmonary disease (COPD)

In the UK, about 900,000 patients are diagnosed with COPD; it accounts for over one million bed-days per year in the UK and causes approximately 30,000 deaths each year, with more than 90% of these occurring in patients aged over 65.[17] One in eight emergency hospital admissions is due to COPD and many will be referred to ICU for ventilator support. The problem for intensive care physicians is distinguishing an exacerbation in a reasonably stable patient from the exacerbation that is part of a terminal decline.

Examining patients admitted to ICUs predominantly contributing to the ICNARC CMP Database between 2002 and 2003, Wildman reported that generally intensive care physicians were unduly pessimistic about the intermediate (180-day) survival of patients admitted with an acute exacerbation of COPD.[18] Five hundred and seventeen patients (62%) actually survived to 180 days, while the clinicians' mean predicted survival was 49%. For the fifth of patients with the poorest prognosis, the predicted survival rate was 10% whereas the actual rate was 40%. In 2004, NICE issued guidance stating that the decision to proceed to invasive ventilation could be made after considering prognostic factors such as poor prior functional status, low BMI, requirement for oxygen when stable, the presence of co-morbidities and previous ICU admissions.[17] Since then however the use of non-invasive

ventilation as the first line means of support has increased, which was reflected in the updated 2010 NICE guidance.[19] This recent guidance states that when patients are started on non-invasive ventilation, there should be a clear plan in the event of deterioration and agreed ceilings of therapy.

However, prognostic factors that allow ceilings of care to be determined in a reasonable and reliable fashion remain unclear. In 2012, Messer reviewed 28 worldwide studies (four of high quality and 24 of low quality from a variety of intensive care settings) to evaluate the predictive factors associated with poor outcome at six months (182 days).[20] The only significant pre-morbid prognostic variable was duration of hospital stay prior to ICU admission (OR=3.36 if prior hospital admission was between 4-7 days inclusive). Surprisingly, pre-morbid functional status, BMI, oxygen status, previous hospital or ICU admissions (ie the 2004 NICE criteria) did not appear to be influential in determining intermediate outcome. However, some of these factors are known to affect outcome beyond six months[21,22] so the lack of significance in Messer's review may have been determined by the choice of length of follow-up. Hansen-Flaschen summarised the risks for dying with respiratory failure within one year for patients with COPD as:

- Best FEV_1 <30% of predicted
- Declining performance status, with increasing dependence on others for activities of daily living
- Uninterrupted walk distance limited to a few steps
- More than one urgent hospitalisation within the past year
- Left ventricular dysfunction and/or other chronic co-morbid disease
- Older age, depression or unmarried.[23]

Messer's review found that the predictive variables of a poor outcome present at referral to ICU included:

- Admission following cardio-respiratory arrest (OR varying between 1.83 and 4.4)
- Admission with a GCS <8 (OR=2.5)
- Dysrhythmia on admission, particularly atrial fibrillation (OR=2.37)
- An abnormally high acute physiology score (either APACHE II or COPD and Asthma Physiology Score) (>1 abnormal COPD and Asthma Physiology Score value, OR=3.06)
- Low serum bicarbonate (<20 mmol/L) or inadequate metabolic compensation for respiratory acidosis (OR=1.8).[20]

Unlike the survival curve of the general ICU cohort, the mortality of COPD patients continued as the underlying disease progressed (mortality at six months 39%, 42.7% at one year, 61.2% at three years, and 75.9% at five years).[24] Therefore identifying patients in a terminal phase is required for robust decision making about ceilings of care. Important pre-morbid factors seem to reflect the level of disability (ie, limited functional capacity with dependence upon others and oxygen), previous recent emergency hospitalisation, other co-morbidities and poor spirometry. Prognostic features at referral reflect a failure to improve during the current hospital admission or to compensate for the respiratory acidosis and severity of physiological disturbance (ie, cardiac arrest, depressed consciousness, arrhythmia, or high physiological scores). No single prognostic factor seems to take precedence and decisions probably need to be made based upon cumulative and possibly synergistic effect of several poor prognostic signs.

Cardiac arrest

The outcome from cardiac arrest is generally poor although there are signs that survival may be slowly improving (3.9% improvement following in-hospital arrests with each decade).[25] However, current UK survival rates among people who have a cardiac arrest outside hospital remain extremely poor, varying from 2% to 12%.[26] For the majority of cardiac arrest patients, there is a risk that the use of cardio-pulmonary resuscitation (CPR) may prolong death and suffering without adding to the quality of life. The challenge for physicians is to identify those patients whose outcome will ultimately be poor. Pre-arrest morbidity scores are useful, as above a certain threshold, they have very high specificity (and hence high negative predictive value). However these scores are now quite old and were not validated in all population groups. Use of CPR in patients unlikely to benefit may be due to a physician's inability to estimate the probability of survival, a desire to offer hope to patients, a fear of litigation and poor communication. Patients and relatives also have overly optimistic expectations regarding the outcome of CPR. Provision of information about CPR and expected survival rates has been shown to affect patient preferences for CPR. It is therefore important that clinicians, patients and their families have the best possible information on which to base these important decisions. Fortunately over the last five years, there have been a number of reviews, which have identified poor prognostic features.

Out-of-hospital cardiac arrest

Using data extracted from 79 studies involving 142,740 patients, predictors of survival included whether the arrest was witnessed by a bystander or emergency medical personnel, whether there was effective bystander CPR, what the initial rhythm was and whether there was pre-hospital return of spontaneous circulation (**Table 4**).[27] Although the links within the chain of survival were paramount, early CPR to restore flow and early defibrillation were crucial. For every minute of delay from collapse to CPR or defibrillation, death was 1.1 times more likely. Moreover, there was a window of opportunity for both interventions. Delay of CPR for >10 minutes rendered defibrillation ineffectual; similarly, a delay of defibrillation >10 minutes largely eliminated the benefit of

Variable	Hospital survival rates (%)
Witnessed by a bystander	6.4-13.5
Witnessed by emergency medical personnel	4.9-18.2
Effective bystander CPR	3.9-16.1
Initial rhythm ventricular tachycardia/fibrillation	14.8-23.0
Pre-hospital return of spontaneous circulation	15.5-33.6

Table 4 Survival to hospital discharge stratified by predictors of better outcome.[27]

prompt CPR.[28] Early effective CPR was crucial to a good outcome; after more than 15 minutes without CPR, the hospital mortality was reported to be 100% (**Table 5**).[29] Shockable initial rhythms carried a better prognosis; the final outcome if the initial rhythm was ventricular fibrillation was better (41%) than pulseless electrical activity (9.5%) or asystole (4%). Adrie combined five prognostic indicators to generate a predictive score for out-of-hospital cardiac arrests.[30] Unfortunately, calculating the score is cumbersome, as it requires logarithmic transformation of the raw data. However, the five parameters were:

- the initial rhythm (VT or VF versus PEA or asystole)
- the duration of 'no flow' (ie, no effective CRP)
- the duration of CPR until the return of spontaneous circulation
- the arterial lactate
- serum creatinine levels.

Non-shockable rhythm and increased other parameter values predicted a poorer neurological outcome.

Once on ICU, early prognostication is unreliable; ideally, clinical signs which have a zero false-positive rate for poor survival would be most useful. The American Academy of Neurology reviewed the literature and concluded that myoclonus status epilepticus within the first 24 hours in patients after primary circulatory arrest was the only early reliable indicator of poor outcome.[31] However after three days, absence of pupillary responses and corneal reflexes together with absent or extensor motor responses all had sufficiently low false positive rates to recommend them as reliable indicators of poor outcome. Relying on a single one of these indicators may be dangerous. Nolan reported that of the 5,487 (25.4%) patients admitted who had fixed pupils recorded at some point in the first 24 hours after out-of-hospital cardiac arrest, 321 (5.9%) survived to hospital discharge and 221 (4.1%) were discharged home.[32] However following out-of-hospital cardiac arrest, if pupils were fixed, or the lowest Glasgow Coma Score was ≤5, or the patient was still comatose 24 hours after ICU admission, the OR of hospital mortality was 4.19 (95% CI 3.75-4.68); this may be useful for guiding early discussions with the family.

In-hospital cardiac arrest

In a recent meta-analysis of 35 studies, the hospital survival rate following in-hospital CPR ranged from 0% to 32%, with an overall pooled survival rate of 17.5%.[25] Metastatic malignancy (OR=3.9) or haematological malignancy (OR=3.9), age over 70, 75 or 80 years (OR=1.5, 2.8 and 2.7, respectively), altered mental status (OR=2.2), dependency for activities of daily living (range OR=3.2-7.0 depending on specific activity), impaired renal function (OR=1.9), hypotension on admission (OR=1.8) and admission for pneumonia (OR=1.7), trauma (OR=1.7) or medical non-cardiac diagnosis (OR=2.2) were significantly associated with failure to survive to discharge.

The reported survival to hospital discharge is better for in-hospital compared to out-of-hospital cardiac arrests, with rates varying between 15% and 20%.[33] Pre-morbid sepsis, cancer, renal failure, stroke and housebound lifestyle are significantly associated with poor survival. Nocturnal cardiac arrests have half the survival rates of daytime ones, while arrests within ICU and the coronary care unit have better outcomes than those occurring in the accident and emergency departments and the general ward.[33] Primary respiratory arrests have much better survival rates, with just under half of the patients surviving to leave hospital.[34] Once the in-patient has suffered a cardiac arrest, similar factors to those for out-of-hospital cardiac arrest (whether the arrest is witnessed, effective staff CPR, initial rhythm, early defibrillation and early return of spontaneous circulation) will influence the final outcome.

Collapse to effective CPR (mins)	Survival (deaths/all patients)
<5	44% (12/27)
5-10	32% (6/19)
10-15	31% (4/13)
>15	0% (25/25)

Table 5 Prognosis at collapse; discharged home or to rehabilitation.[29]

In summary, in-hospital cardiac arrests had a better outcome so long as other serious pathologies which may have precipitated the arrest are not overwhelming. However out-of-hospital cardiac arrests had a particularly poor outcome especially if CPR was delayed, initial rhythm was non-shockable, defibrillation delayed and return of spontaneous circulation late. Once on ICU, absent corneal or pupillary responses or deep coma after 24 hours were all poor prognostic signs.

Obesity

Obesity is a major risk factor for cardiovascular disease, diabetes, obstructive sleep apnoea, and certain malignancies. Up to 25% of ICU patients are obese (15,347 with BMI ≥30 out of a cohort of 62,045 patients)[35] and this proportion will increase. Obese ICU patients are difficult to look after for three main reasons. First, their reduced mobility and higher incidence of co-morbidities such as diabetes and congestive cardiac failure leads to generalised loss of fitness and physiological de-conditioning. Second, obese patients are more challenging to manage, with difficult venous access and physiological changes that make interventions such as ventilation more problematic (ie, decreased chest wall compliance and increased gastric reflux). They are also more difficult to nurse and mobilise. Third, obese patients have higher rates of morbidity on ICU (ventilator-associated pneumonia, deep vein thrombosis, pulmonary embolism, cardiovascular complications and pressure sores).[36]

However, the effect on mortality of these risk factors is not clear. Obesity in critical illness appears to exert no clear effect on mortality, or may even decrease mortality, despite longer ICU stay and time to resolve organ failure.[37] This 'obesity paradox' may or may not be real. On one hand, obesity does induce a chronic low-grade inflammatory state[38] and obese critically ill patients do have lower early levels of Interleukin-6 in sepsis.[39] Furthermore there is a tendency not to fully dose obese patients on a true mg/kg or mL/kg basis; as a result such obese patients may be 'relatively undertreated' which in other

intensive care spheres (eg, fluids, blood transfusion, vasopressors) have enhanced survival. Finally, the general level of basic intensive care support has improved with better turning, skin care, mobilisation and care bundles. However, contrary to these positive aspects, the obesity paradox may not be real because of the retrospective nature of some of the studies, the poorer calibration of severity of illness scores in obese patients and, most importantly, the protective effect of obesity may not be supported by bedside clinical experience.[40]

It therefore appears that the obese patient while possibly having a stormier course on ICU may ultimately have similar mortality as the general ICU patient cohort. Decisions concerning whether ICU admission is worthwhile or about futility of continuing organ support need to be made on factors other than the patient's BMI.

Conclusion

Triaging patients for ICU admission is fraught with difficulty and uncertainty. Due to the severity of physiological disturbance at referral, declining admission can have very serious consequences for the patient. Being aware of adverse prognostic features presenting premorbidly or at referral helps justify and explain why the patient's care should not be escalated to full organ support. The rapid development of additional organ failure or failure of neurological recovery allows expectations to be managed. While evidence must guide our clinical practice, individual decisions encompass much more than just following bald facts from an evidence base. However, with patients and families increasingly questioning clinical decisions, it is vital that intensive care physicians have good knowledge of the important prognostic indicators and use them as foundations for decision making.

Conflict of interest

None declared.

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