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Outcomes of emergency laparotomy in patients on extracorporeal membrane oxygenation for severe respiratory failure: A retrospective, observational cohort study

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ABSTRACT

Purpose: There is a paucity of literature to support undertaking emergency laparotomy when indicated in patients supported on ECMO. Our study aims to identify the prevalence, outcomes and complications of this high risk surgery at a large ECMO centre.
Materials and methods: A single centre, retrospective, observational cohort study of 355 patients admitted to a university teaching hospital Severe Respiratory Failure service between December 2011 and January 2017.
Results: The prevalence of emergency laparotomy in patients on ECMO was 3.7%. These patients had significantly higher SOFA and APACHE II scores compared to similar patients not requiring laparotomy. There was no difference in the duration of ECMO or intensive care unit (ICU) stay post decannulation between the two groups. 31% of laparotomy patients survived to hospital discharge. Major haemorrhage was uncommon, however emergency change of ECMO oxygenator was commonly required.
Conclusion: Survival to hospital discharge is possible following emergency laparotomy on ECMO, however the mortality is higher than for those patients not requiring laparotomy, this likely reflects the severity of underlying organ failure rather than the surgery itself. Our service's collocation with a general surgical service has made this development in care possible. ECMO service planning should consider general surgical provision.

1. Introduction

Veno venous extracorporeal membrane oxygenation (VV ECMO) is increasingly utilised to support severe respiratory failure (SRF) [1]. In recent years, the number of cases, centres and indications has increased along with the survival rate [1]. A proportion of these patients present with associated septic shock and multiple organ failure and are at risk of developing intrabdominal complications which may require emergency laparotomy while on ECMO [2,3]. It is thought that ECMO per se, may be an additional risk factor for abdominal complications and the need for emergency laparotomy due to the high risk of ileus and gastroparesis in patients receiving ECMO [2,4-6].

There is however limited data available on the indications, risks and outcomes of patients on ECMO undergoing emergency laparotomy. In addition, there is little precedent in adult patients to guide decision making or perioperative management [5,6]. A recent study by Glowka and colleagues has addressed this deficit by examining the outcomes of 11 patients undergoing bedside decompressive laparotomy for the treatment of abdominal compartment syndrome during ECMO [7]. The study finds that survival to hospital discharge is possible following such intervention but is limited to bedside laparostomy and does not examine the broader indications for emergency laparotomy in theatre. As part of the United Kingdom (UK) based National Emergency Laparotomy Audit (NELA), preoperative risk assessment of patients is now a national standard of care [8] and both by objective risk prediction score or by clinical judgement, the decision to proceed with an emergency laparotomy on an unstable patient already in multiorgan failure might be considered inappropriate.

Following the H1N1 influenza pandemic in 2009/10, the national specialised commissioning for NHS England set up a dedicated regional referral service for adult respiratory VV ECMO in England. Local

Abbreviations: SRF, severe respiratory failure; NELA, national emergency laparotomy audit; MaxSOFA, maximum sequential organ failure score; DDAVP, D-amino D-arginine vasopressin; TIVA, total intravenous anaesthesia; SAPS II, Simplified Acute Physiology Score II.

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hospitals refer to five regional tertiary intensive care units (ICU) that provide consultant delivered triage, assessment and retrieval on ECMO. Our institution is one of these centres and it is collocated with a general surgical service. Our study aims to identify the prevalence of patients undergoing emergency laparotomy on ECMO and to understand the outcomes and the associated morbidity, in order to inform future practice.

2. Materials and methods

2.1. Study design, participant characteristics and data source

A single centre, retrospective, observational cohort study. All patients admitted on either venoarterial (VA), venovenous (VV) or veno venoarterial (VVA) ECMO between December 2011 and January 2017 were identified from a prospectively completed SRF database (Excel; Microsoft, Redmond, WA). All adult (>18 years) patients who underwent a primary or relook laparotomy in theatre, for any indication, whilst on ECMO were included, those who underwent other general surgical procedures or laparotomy before or after their ECMO run were excluded. The electronic health record (ICIP; Philips, Eindhoven, The Netherlands) was used to identify patient data for analysis including risk prediction scores and data on diagnoses, course of treatment and hospital outcomes. CT abdomen scan reports were gathered from the picture archive and communication system (GE Healthcare Centricity, Chicago, IL), and operative notes were identified from electronic patient records. Outcome data was obtained from the ICU information management team.

2.2. Study setting and characteristics of the service

The SRF service based at Guy's and St Thomas' university teaching hospital in London receives referrals from across south east England. Referrals to the service are triaged by a consultant and if accepted, a retrieval team will travel to assess the patient. Patients may subsequently be retrieved on conventional ventilation or on ECMO. Our centre's preferred method for ECMO cannulation is bifemoral in the first instance, however all cannulation routes are used if required. The circuits used are heparin bonded and in addition our standard procedure is to administer heparin by infusion for a target activated partial thromboplastin time ratio (APTTr) of 1.5–2 provided the patient is not actively bleeding.

2.3. Outcomes and definitions

Primary outcomes were: prevalence of emergency laparotomy on ECMO; indications for laparotomy; mortality risk prediction score and actual mortality rate; survival to hospital discharge. Secondary outcomes of interest were: operative mortality; timing and mode of death postoperatively; factors associated with requirement for laparotomy on ECMO; duration of ECMO run and duration of ICU stay post decannulation compared with those ECMO patients not undergoing emergency laparotomy; whether a preoperative CT scan was performed and if so did the findings reflect the operative findings; type of operation performed and postoperative abdominal status (open or closed); need for return to theatre; preoperative anticoagulation management; prevalence of major haemorrhage; requirement for ECMO oxygenator change perioperatively; factors associated with survival to discharge.

Major haemorrhage was defined as: loss of more than one blood volume within 24 h (70 mL/kg, >5 L in a 70 kg adult), 50% of total blood volume lost in <3 h, or bleeding in excess of 150 mL/min [9].

2.4. Statistics

Data analysis was both descriptive and inferential. Continuous variables were compared with Independent Samples *t*-test or Mann Whitney *U* test. Discrete binomial variables were compared with Chi squared test or Fishers Exact Test. Significance level was assessed at 0.05. SOFA score was treated as skewed data with medians, range and interquartile range used and comparative analysis performed using a Mann Whitney *U* test. APACHE II score passed tests of normality (Kolmogorov Smirnov) and was therefore analysed using mean and standard deviation and compared with Independent Samples *t*-test. Multivariate logistic regression was used to assess for covariance and independent predictors of discrete dichotomous outcomes. Analysis was conducted using SPSS Statistics for Macintosh (IBM Corp., Version 24.0. Armonk, NY) and Excel for Office 365/2016 (Microsoft, Redmond, WA).

3. Results

355 patients were established on ECMO during the study period. The initial mode of ECMO was 329 patients on VV ECMO, 16 patients on VA ECMO and 10 patients on VVA ECMO. Patient demographics are described in Table 1.

3.1. Prevalence of emergency laparotomy

13 out of 355 patients underwent emergency laparotomy whilst on ECMO giving a prevalence of 3.7%. The median number of days from ECMO cannulation to operation was 4 (IQR 1–5). The median predicted mortality using P POSSUM risk scoring [10] was 91% (IQR 83% - 95%). Median lactate level immediately preoperatively was 5 mmol/L (IQR 2.4–10.8). Seven patients (54%) returned to theatre for a relook laparotomy. Multivariate analysis was unable to identify significant risk factors for patients who would require a laparotomy. Operative indication, predicted mortality and operative findings of the patients undergoing emergency laparotomy are described in Table 2.

3.2. Outcomes

All patients survived laparotomy (intraoperative mortality was 0%). Two inoperable cases were closed and returned to ICU for end of life care. Five further patients (54%) died during their ECMO run, mode of death in four cases was withdrawal of therapy and in the fifth case, cardiac arrest (pulseless electrical activity rhythm). Median number of days survival postoperatively in this group was 5 (IQR 1–10). Of the six patients who were successfully decannulated from ECMO (ECMO survival 46%), two subsequently died giving a hospital mortality rate of 69% overall. In both cases mode of death was withdrawal of active therapy in ICU following further organ failure. The 30-day mortality rate was 62%. Four patients (31%) survived to hospital discharge, two to a short term rehabilitation facility and two patients were discharged home. The outcomes of the laparotomy cohort compared to those ECMO patients not undergoing laparotomy are set out in Table 3.

Multivariate logistic regression was undertaken to identify factors potentially associated with survival to discharge amongst the whole ECMO cohort. The model contained five independent variables (age, laparotomy (categorical), APACHE II score, admission SOFA score and MaxSOFA score) with the final model retaining all five variables to significance. The final model was highly significant, $X2\ (5, N = 353) = 58.31$, $P \langle 0.01$), demonstrating a good differentiation between those patients who did and did not survive to discharge. The model explained between 15.2% (Cox & Snell R2) and 23.1% (Nagelkerke R2) of the variance in survival to discharge and correctly classified patients in 79.9% of cases, with a sensitivity of 95.6% and a positive predicative value of 81.5% for survival from critical care. MaxSOFA score and APACHE II score at admission to the SRF service were the only two independent predictors of survival (see Table 4). For each point added to the MaxSOFA score, the chance of dying prior to discharge increased by a factor of 1.20, and for each point added to the APACHE II score, the chance increased by a factor of 1.11, with all other factors being equal.

Table 1
Demographics of patients established on ECMO during the study period.

Variable at admission to SRF service	Laparotomy cohort ($N = 13$)	Patients not undergoing laparotomy ($N = 342$)	P value
Gender (% female)	30.8	43.6	0.408
Mean age (SD) (years)	48.6 (12.5)	44.8 (14.1)	0.574
Mean APACHE II score (SD)	21.7 (3.3)	18.6 (4.9)	0.024
Median SOFA score on day of admission to SRF service (range / IQR)	11 (4–17 / 6)	7 (0–18 / 7)	0.003
Median MaxSOFA score during admission (range / IQR)	15 (12–20 / 5)	11 (2–22 / 7)	<0.001

SRF – Severe Respiratory Failure; APACHE II – Acute Physiology And Chronic Health Evaluation II score; SOFA – Sequential Organ Failure Assessment score; MaxSOFA refers to the highest SOFA score recorded at any point during the patient's stay in ICU after admission to the SRF service.

Cox regression was unable to identify significant predictors of overall survival duration (X2 (5, $N = 355$) = 5.713, $P = .335$). There was no significant difference in overall survival based upon the laparotomy incidence (Log Rank Mantel Cox, $P = .744$).

3.2.1. Perioperative management

Of the 13 ECMO patients who underwent laparotomy, seven were receiving the standard treatment of systemic heparin infusion for circuit anticoagulation at the time of decision for theatre. The other six were not receiving this treatment. Six of the seven patients treated with systemic heparin had the infusions stopped a median of 3 h preoperatively (IQR 2.25–3.75). The seventh patient underwent laparotomy whilst still on systemic heparin infusion. The median APTTr at operation was 1.6 (IQR 1.4–2.2) and the median international normalized ratio (INR) at operation was 1.2 (IQR 1.1–1.5). Two patients were treated for intraoperative major haemorrhage. Table 5 describes the quantity of blood products required in the perioperative period, which is taken as the time from decision for surgery until 24 h postoperatively. Eight patients (62%) required an ECMO oxygenator change postoperatively, seven (88%) of these were emergency changes for rising transmembrane pressure and mechanical failure, and one (12%) was an elective change from VA to VV configuration. Median number of days to circuit change was zero (range 0–4, IQR 1.5). There were no intraoperative oxygenator emergencies or failures.

4. Discussion

The prevalence of emergency laparotomy in our large ECMO referral centre population demonstrates that acute intrabdominal pathology requiring operative management is not a rare occurrence (almost 1 in 25 patients). As the number of cases and centres offering ECMO support increases, so might the requirement for surgical management. Our study

Table 2
Details of patients undergoing emergency laparotomy on ECMO.

Patient no.	Mode of ECMO	Indication for ECMO	Presenting compliant leading to surgical referral	Pre-operative CT abdomen findings	Predicted mortality (%) (P-POSSUM)	Operative findings	Operation performed	Abdominal status post-operatively
1	VV	Trauma	Abdominal distension	Liver laceration	78	Avulsed hepatic vein	Vascular repair; abdominal packing	Bogata bag
2	VV	H1N1 influenza	Abdominal distension	Free air; ischaemic bowel	93	Ischaemic bowel	Subtotal colectomy; small bowel resection; ileostomy	Bogata bag
3	VV	H1N1 influenza	Abdominal distension; lower GI bleed	Dilated large bowel	92	Haemorrhagic caecum	Extended right hemicolectomy; ileostomy	Closed
4	VV	Rhabdomyolysis	Abdominal distension; rising lactate	Small bowel intramural gas	83	Ischaemic small bowel	Small bowel resection; jejunostomy	Bogata bag
5	VV	Sepsis	Abdominal distension; rising lactate	Generalised mural thickening of small and large bowel	29	All bowel viable	Laparostomy	Bogata bag
6	VV	H1N1 influenza	Abdominal distension; falling ECMO flows	Ischaemic bowel	90	Patchy small bowel ischaemia	Small bowel resection; ileostomy	Closed
7	VV	H1N1 influenza	Abdominal distension; rising lactate	Not performed	91	Extensive ischaemia	Inoperable	Closed
8	VV	Bacterial pneumonia	Rising lactate	No evidence of bowel ischaemia	97	Ischaemic liver; bowel viable	Exploratory laparotomy	Closed
9	VA	STEMI	Abdominal distension; falling ECMO flows	Widespread intramural gas	95	Ischaemic bowel	R hemi-colectomy; extensive small bowel resection	Bogata bag
10	VVA	STEMI	Abdominal distension	Not performed	98	Infarcted small bowel; caecum peri-perforation	R hemi-colectomy; small bowel resection; ileostomy	Vac dressing
11	VV	Trauma	Ischaemic bowel on admission CT scan	Widespread bowel ischaemia	91	Ischaemic bowel	R hemi-colectomy; extensive small bowel resection; jejunostomy; ileocolostomy	Closed
12	VV	Sepsis	Abdominal distension; clinical peritonitis	Possible intramural gas; dilated bowel; free fluid	49	Extensive ischaemia	Inoperable	Closed
13	VV	Bacterial pneumonia	Abdominal distension; falling ECMO flows	Mural thickening of large bowel	97	All bowel viable	Laparostomy	Vac dressing

(ECMO – Extracorporeal Membrane Oxygenation; P-POSSUM – Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; VV – venovenous; VA – venoarterial; VVA – veno-veno-arterial; STEMI – ST segment Elevation Myocardial Infarction)

Table 3
Outcomes of laparotomy cohort compared to ECMO patients not undergoing laparotomy.

Variable	Laparotomy cohort (n = 13)	Patients not undergoing laparotomy (*n* = 342)	*P* value
Mortality during ECMO run (%)	7 (54)	55 (16)	0.543
Hospital mortality rate (%)	9 (69)	86 (25)	0.001
Median length of ECMO run (days) (range / IQR)	10 (2–22 / 9)	7 (0–229 / 8)	0.307
Median length of stay ICU post decannulation (days) (range/IQR)	10 (2–23 /10)	7 (0–23 / 8)	0.330
Patients discharged from hospital alive (%)	4 (31)	256 (75)	0.014

ECMO – Extracorporeal Membrane Oxygenation.

has attempted to understand the outcomes of patients on ECMO requiring laparotomy and the associated morbidity, in order to inform future practice.

The patients who underwent emergency laparotomy were not significantly different in age or gender from the total ECMO cohort, but they were more severely ill on admission to the SRF service as demonstrated by significantly higher SOFA and APACHE II scores. They also experienced more organ failure over the course of ICU stay with significantly higher MaxSOFA scores. This finding would support the hypothesis that shock and multiorgan failure are associated with developing intraabdominal pathology in this population. The most frequent presentation of pathology was abdominal distension and raised arterial lactate. We undertook a multivariate regression analysis to identify factors potentially associated with survival at discharge. Only the MaxSOFA and APACHE II scores were significantly associated with this outcome. However, given the small number of patients this analysis is more exploratory and no definitive conclusion can be drawn.

CT abdomen scans were performed in 11 of 13 cases and generally demonstrated intrabdominal pathology with ischaemic bowel. The CT findings were broadly in keeping with operative findings. Two patients were taken to theatre on clinical suspicion due to elevated lactate and abdominal distension without imaging and were found to have extensive pathology. CT scanning can be logistically demanding, especially in patients who are on ECMO and have both ECMO related instability (e.g. access insufficiency) and overall haemodynamic instability. Although in this series, CT scans had a close correlation with clinical findings, patients with a clinical perception of intraabdominal pathology but "negative/normal" CTs did not receive a laparotomy and hence the negative and positive predictive value of CT abdomen in this population cannot be reported. The operative management most often required at laparotomy was bowel resection with the abdomen left open in just over half the cases necessitating subsequent return to theatre. Just under half the cases were closed and required no further operations.

All patients survived the initial laparotomy and those who died did so a median of five days later and mainly due to withdrawal of therapy. The overall mortality rate is significantly higher in the laparotomy cohort than for those ECMO patients not undergoing laparotomy, however the duration of time spent on ECMO and the length of ICU stay post decannulation are not significantly different. Coupled with the finding that there was no significant difference in overall survival based upon the laparotomy incidence but rather on MaxSOFA score and APACHE II score, this suggests that undergoing emergency laparotomy itself does not cause mortality. Survival depends on the underlying pathology and severity of organ failure. The finding that approximately one third of patients survive to hospital discharge supports the assertion that undertaking emergency laparotomy in these patients is appropriate.

P POSSUM was the risk prediction score most commonly employed for emergency laparotomy at the time of these cases [11]. It was found to over predict hospital mortality in this cohort by a factor of 1.3, however there were also two notable outlying scores. We suggest that MaxSOFA score might be a better tool for risk prediction in this population. Although the 30-day mortality rate for laparotomy on ECMO of 62% compares poorly with the National Emergency Laparotomy Audit (NELA) rate of 10.6%, it is likely that the population on ECMO are significantly sicker and it would be useful to compare the mortality rate by SOFA score.

There is little precedent in the literature to guide the perioperative management of patients supported on an ECMO circuit undergoing emergency laparotomy [2]. In this series, the majority of patients were not on heparin infusions or had heparin infusions stopped at least two hours preoperatively. Additionally, procoagulants were electively administered prior to theatre in some patients. It is possible that this strategy may have resulted in a lower rate of intraoperative massive haemorrhage and blood product requirement than might otherwise have been expected. It is noteworthy that there was a high rate of requirement for emergency change of ECMO oxygenator in the immediate postoperative period. It is possible that the lack of heparin and use of procoagulant drugs and blood products predisposed to circuit thrombosis. It is reassuring that there were no intraoperative oxygenator failures or emergencies such as air emboli. We suggest that preparations for theatre include the ready availability of a replacement ECMO circuit. The intraoperative management of these cases involves close collaboration between the anaesthetic team, the ECMO consultant who is present in theatre, the perfusionist and the surgical team. Specific anaesthetic technical details of note in addition to routine monitoring, include the requirement for total intravenous anaesthesia (TIVA) and depth of anaesthesia monitoring given the absence of lung ventilation and perfusion as a route of drug administration. The ECMO circuit is known to sequester propofol and opioids [12] requiring increased doses of agents and close attention to depth of anaesthesia and analgesia which is described in previously published work [13]. From a surgical perspective,

Table 4
Logistic regression predicting likelihood of survival to discharge of patients on ECMO during the study.

	B	S.E.	Wald	df	Sig.	Odds Ratio	95% C·I. for odds ratio	
							Lower	Upper
Age	−0.016	0.011	2.203	1	0.138	0.984	0.964	1.005
Laparotomy	0.628	0.604	1.082	1	0.298	1.874	0.574	6.121
SOFA on admission	0.049	0.039	1.600	1	0.206	1.050	0.973	1.133
MaxSOFA score	−0.189	0.046	16.744	1	0.000	0.828	0.757	0.906
APACHE II score	−0.103	0.032	10.166	1	0.001	0.903	0.847	0.961
Constant	5.294	1.051	25.352	1	0.000	199.118		

Rows: B = Log odds; S.E = Standard Error of Co-efficients; WALD = Wald Chi-Square Co-efficient; Df = degrees of freedom; Sig = Significant, level set at 0.05; C.I = confidence interval.
Variable(s) entered on step 1: Age; Laparotomy; SOFA on Admission - refers to the Sequential Organ Failure Assessment score on admission to the Severe Respiratory Failure service (SRF); MaxSOFA - refers to the highest SOFA score recorded at any point during the patient's stay in ICU after admission to the SRF service; APACHE II Score – Acute Physiology And Chronic Health Evaluation score measured at admission to the SRF service.

Table 5
Quantity of blood products and anticoagulants used in the perioperative period.

Variable	Count
Median units RBC (IQR)	5 (3−11)
Median units FFP (IQR)	4 (0−12)
Median pools of platelets (IQR)	3 (2–5)
Median units of cryoprecipitate (IQR)	2 (0–4)
Use of Tranexamic acid 1 g (no. of separate cases)	7 (54%)
Use of Vitamin K 10 mg (no. of separate cases)	5 (38%)
Use of DDAVP (no. of separate cases)	1 (8%)
Use of Factor VIIa (no. of separate cases)	1 (8%)

RBC – Red Blood Cells; FFP – Fresh Frozen Plasma; DDAVP - D-amino D-arginine vasopressin.

aseptic preparation should exclude the ECMO cannulae in the groins from the operating field and surgical technique requires particular attention to the potential for venous air embolism and bleeding as well as the potential for ECMO flow insufficiency during intraoperative changes in intrabdominal pressure.

Comparison of our study with the data from the only other published large cohort of adult ECMO patients undergoing laparotomy is of interest. Glowka et al. examined decompressive laparotomy for the treatment of abdominal compartment syndrome during ECMO in a cohort of 175 patients [7]. They found a laparotomy prevalence of 6.2% and a survival to hospital discharge rate of 27% which are comparable with our data. They also conclude that the Simplified Acute Physiology Score II (SAPS II) can be used to predict mortality in a similar way to our suggestion that MaxSOFA score is an appropriate risk prediction tool. However the two study populations differ in mode of ECMO and the nature of laparotomy, with Glowka et al. examining a majority of VA-ECMO cases undergoing bedside decompressive laparostomy for abdominal compartment syndrome in those patients too unstable to transfer, where as our study has examined emergency laparotomy for all indications, including abdominal compartment syndrome, undertaken in theatre with a majority of VV-ECMO cases. The implication of this is that ECMO is frequently complicated by intrabdominal pathology of varying aetiology but that by undertaking operative management, survival to hospital discharge is possible.

The retrospective, observational design and the small numbers of patients in this study limits the conclusions that can be drawn. The retrospective nature of the study does not allow for the identification of those patients with indications of acute abdomen who may have under gone CT abdomen scans but were not operated on for comparison. Other patients may well have been too unstable to transfer to theatre and hence are also not identified for comparison. These questions might be tested in future prospective studies on this population but to date we report on the largest cohort of patients undergoing emergency laparotomy on ECMO in the biggest combined ECMO and general surgical centre in the UK.

5. Conclusions

Acute intrabdominal pathology requiring laparotomy occurs in patients on respiratory ECMO and the incidence and absolute numbers may well increase as ECMO indications expand. Most patients present with features of acute abdomen and are found to have bowel ischaemia requiring resection. Survival to hospital discharge is possible however the mortality is higher than for those patients not requiring laparotomy, this likely reflects the severity of underlying organ failure rather than the surgery itself. Our service's collocation with a general surgical service has made this development in care possible. We suggest that ECMO service planning should consider access to general surgery.

Ethics, consent and permissions

This study was registered with and approved by the institutional governance department (Audit Reference 7144). The study was not referred to the Research Ethics Committee as it qualified as a service evaluation as set out in the UK NHS Health research Authority definition. Consent to participate was not sought as the data used was collected for routine clinical care and no patient identifiable information was recorded.

Data statement

The anonymised datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CM, KA, LC, AS, MG, NB and DW were responsible for the conception and design of the study. CM had principle responsibility for data collection and undertook descriptive data analysis and interpretation. KA was responsible for all inferential statistical analysis and also undertook data collection. CM wrote the first draft of the manuscript of which KA was a major contributor. The draft was subsequently revised by LC, NB, DW, MG, AS with CM responsible for re-drafting and editing the final manuscript. All authors read and approved the final manuscript.

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Competing interests

DW served as a board member for Astellas; lectured for HealthCare 21, Astellas, Pfizer, Sage, Johnson & Johnson, and Bioproducts; received support for the development of educational presentations from Astellas; and received funding from Pfizer (board member), Astellas (board member), and Sage, Healthcare21, Johnson & Johnson, and Bioproducts speaker bureaus. The remaining authors declare that they have no competing interests.

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