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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

Defining International Critical Care Pharmacist Contributions to Sepsis and Exploring Variability

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Abstract

Purpose of Review To define international clinical pharmacist contributions to managing sepsis in critically unwell patients and explore variation.

Recent Findings Clinical pharmacists improve clinical outcomes and cost efficiencies. They provide pharmaceutical advice on selection, administration, plus monitoring of antimicrobials and supportive therapies. Logistical activities reduce drug administration times. Guideline production, patient/clinician education, prescribing error identification, plus therapeutic optimisation activities are also reported.

Summary A survey incorporating semi-structured interviews identified further antimicrobial stewardship, prescribing and digital contributions to optimise sepsis management. However, disparities associated with multidisciplinary team integration and intensive care unit service provision were found. Variability was attributed to multifaceted physical, social, financial, training and education themes. Findings empower collaborations between pharmacists and stakeholders to identify and overcome contribution barriers. Strategies to mitigate barriers and enhance sepsis contributions were envisaged by reported aspirations. These emphasised the importance of professional advocacy, interprofessional education and impactful implementation research.

Keywords Clinical Pharmacist · Intensive Care Unit · Sepsis Contributions · Barriers · Aspirations · Service Variation

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Introduction

Sepsis is a leading cause of morbidity and mortality worldwide. Sepsis is commonly cared for in the intensive care unit (ICU) setting, whereby the severity/complexity of a patient's illness presents additional therapeutic challenges compared to general ward-based patients [1–4, 5•].

Clinical pharmacists are emerging as key ICU multidisciplinary team (MDT) members to address such challenges by optimising associated patient outcomes and expenditure, whilst providing professional support [3, 4, 6•,7–24]. For individual patients, this has been demonstrated by provision of pharmaceutical care [25] (identification of prescribing errors and consulting) and formation of partnerships required for medicines optimisation (enhancement of therapy to improve efficacy) [26, 27•]. These interventional activities are reported to reduce mortality, adverse drug events and litigation costs. In addition, length of stay and expenditure is improved through cost-effectively individualising pharmacological therapy [8, 11, 12, 15–17]. ICU-wide benefits are also reported through development/implementation of medicine-related guidance, improved resource use and medicine prescribing/expenditure analytics [2–4, 6•, 7, 12, 13, 15, 27•, 28•, 29•, 30, 31•, 32].

However, the adoption of clinical pharmacists and ICU specialty contributions to sepsis is not well reported outside of Western Europe, North America and Australasia. Consequently, there is a limited understanding of the global contributions, experiences and interests of clinical pharmacists in the management of critically ill patients [15, 17, 27•, 28•, 33•]. Through a focus of sepsis, this qualitative study aims to scope current practice of ICU clinical pharmacists, including their perceived barriers and aspirations to explore variability. To better understand participants' perspectives, their characteristics and service descriptions were captured. Identifying associations may support leadership activities to acknowledge, develop and enhance the clinical pharmacist workforce in evolving ICU infrastructures [34•, 35, 36].

Methods

The study's purpose was to explore the research question "What are international clinical pharmacists' service contributions, perceived barriers and aspirations in managing sepsis in critically unwell patients?" A survey using semi-structured interview questions to illuminate subjective experiences (Table 1) was designed and piloted within the research team.

Non-probability convenience and snowball sampling occurred between May 31 and July 13, 2023. The sample size was determined by data saturation. Professional contacts of the research team were approached with a standardised invitation email. Some contacts further forwarded this email to prospective participants unknown to the research team. The invitation provided information about the study, RO's contact details, alongside instructions for providing demographic data and written consent to participate. Returned consent forms were screened to ensure each participant met the inclusion criteria: a registered pharmacist or a pharmaceutical manager associated with the provision of ICU services, plus proficiency in the English language. Consented participants were assigned a study number to ensure pseudonymisation. Interviews were conducted remotely in a setting of the participant's choice via Zoom® for a maximum of 40 minutes between June 13 and July 20, 2023. Interview questions and prompts (Table 1) were displayed and narrated to participants. Data was automatically transcribed by Zoom®. Transcriptions were checked against interview recordings by RO and made available to participants to confirm content within 7 days. No participant requested to check their transcription before analysis.

Participant data was thematically analysed using the six-stage process outlined by Braun and Clarke [37]. Transcripts were coded by RO who derived descriptive themes based on observed trends. Codes and themes were reviewed and re-defined for consolidation with S.G and SA-M. Themes were triangulated for validity with literature findings, plus SA-M's expert opinion to guard against selectivity and increase reliability. No computer-assisted analysis software was used. Researchers reflected on their reflexive influence on study processes. This was discussed within the team and acknowledged. As this was an exploratory study, no theoretical assumptions were addressed in data interpretation [37].

Results

Participants

Pharmacists from 34 countries were contacted (42 directly, 16 via snowballing). Twenty pharmacists participated (Table 2). Seventy-five percent of participants were senior clinical pharmacists possessing over 5 years of ICU experience. Participants mainly worked in adult ICUs within medium to large hospitals. Fifty percent reported that their role was dedicated to ICU duties. Within dedicated roles, 35% of participants identified as academics with 40–80% clinical time. These participants possessed over 7 years of ICU experience.

Role Requirements

Prerequisite skills and experiences to manage septic patients in an ICU setting were stipulated by hospitals

Table 1 Survey interview questions and prompts aligned to categories associated with the research question

Category	Interview Question and Prompts
Clinical Pharmacist Characteristics	Which country is your pharmacist role based in?
	Please describe your role
	How long have you worked in a pharmacy role with ICU involvement?
	What experience is required to obtain a pharmacist role with ICU involvement at your hospital?
	What qualifications are required to obtain a pharmacist role with ICU involvement at your hospital?
	Do you provide services for critically ill adult, paediatric or neonatal patients at your hospital?
Clinical Pharmacy Service Characteristics	Do you work in a private or publicly funded hospital role?
	What is the approximate bed number of the hospital where you work in your pharmacy role?
	Is there a clinical pharmacy service provided to any ICUs at your hospital?
	When managing a septic patient, how are pharmacists incorporated into the ICU MDT at your hospital?
	At the ICU patient bedside, what is your contribution to managing sepsis in your hospital? *Prompts* Patient clinical reviews, medication logistics, therapeutic drug monitoring, governance or other activities (e.g. writing guidelines, adverse drug reaction reporting/monitoring, multidisciplinary team support, antimicrobial stewardship, preventing/reducing antimicrobial resistance)
	Away from the ICU patient bedside, what is your contribution to managing sepsis at your hospital? *Prompts* Patient clinical reviews, medication logistics, therapeutic drug monitoring, governance or other activities (e.g. writing guidelines, adverse drug reaction reporting/monitoring, multidisciplinary team support, antimicrobial stewardship, preventing/reducing antimicrobial resistance)
	Are these contributions representative of other pharmacy ICU roles within your country? *Prompts* Adult, paediatric or neonatal ICU clinical pharmacist roles Private or public funded roles Differences in ICU clinical pharmacist roles between hospitals Provision of a clinical pharmacy service
Aspirations of Clinical Pharmacists to Further Contribute to ICU Sepsis Management	How do you feel pharmacists could further contribute to the management of sepsis?
Barriers Facing Clinical Pharmacists to Further Contribute to ICU Sepsis Management	What do you feel are the barriers preventing pharmacists in your country from achieving such ambitions?

in 85% of cases. Evidence of participation in hospital training programs and attainment of post-graduate qualifications was perceived to demonstrate competency. On the other hand, Asian and Polish pharmacists expressed that apart from professional registration, no additional qualifications or experience was required to work in an ICU. However, these pharmacists reported a necessity to undertake self-directed professional development to meet role demands. Developmental activities were reported to be assisted by medical colleagues or by gaining experience internationally. Mapping personal skills and experiences to professional bodies' competency frameworks was acknowledged by many participants to assist with skill progression and ICU recruitment. Twenty percent of respondents from Portugal and the USA reported that professional bodies certified ICU competency through examination.

Service Characteristics

Service characteristics and ICU clinical pharmacist adoption were associated with stakeholder perceptions, funding sector, country and institution. For example, privately funded hospitals in South Africa were reported to routinely recruit a small number of clinical pharmacists due to their cost-avoidance contributions. Whereas publicly funded hospitals and other African nations did not routinely employ ICU clinical pharmacists. This was attributed to poor speciality recognition by regulators and hospital decision-makers. European participants reported wide variation in clinical pharmacy adoption and ICU service provision. Some hospitals were reported to not employ clinical or non-clinical pharmacists. Others employed some clinical pharmacists but prioritised their duties to certain areas, such as the

Table 2 Participant and intensive care unit clinical pharmacy service characteristics

Participant Characteristics							
Demographics							
Age	*Median*			*IQR* (*interquartile range*)			
	35 years			8 years			
Sex	Male 35% (7)			Female 65% (13)			
Location							
Continent	Europe						
Country of origin	Netherlands 5% (1)	Switzerland 5% (1)	Austria 5% (1)	UK 10% (2)	Portugal 5% (1)	Belgium 5% (1)	Poland 5% (1)
Continent	Africa						
Country of origin	South Africa 5% (1)						
Continent	Asia						
Country of origin	Vietnam 10% (2)	Malaysia 5% (1)					
Continent	Australasia						
Country of origin	Australia 10% (2)						
Continent	South America						
Country of origin	Brazil 10% (2)						
Continent	North America						
Country of origin	USA 15% (3)	Canada 5% (1)					
Role descriptions							
Role and reported grades-within role	Clinical Pharmacist with associated ICU duties 50% (10). Grades included: Senior 30% (6), Specialised Senior 15% (3), Highly Specialised Senior 5% (1)	Clinical Pharmacist with dedicated ICU duties 50% (10). Grades included: Senior 10% (2), Management Lead 15% (3), Specialised Senior 5% (1), Highly Specialised Senior 10% (2), Consultant 10% (2)		Clinical-Academic Pharmacist with at least one protected research day weekly 35% (7). Grades included: PhD candidate 5% (1), PhD 5% (1), Associate Professor 20% (4), Professor 5% (1)			
ICU patients cared for	Adult 95% (19)	Paediatric 20% (4)	Neonate 10% (2)	Adult and Paediatric 25% (5)			
ICU experience	< 5 years	> 5 years	> 10 years	*Median*		*IQR*	
	25% (5)	75% (15)	30% (6)	7 years		6 years	
Role requirements							
Required experience for ICU working	Professional body stipulated 20% (4)			Hospital stipulated 85% (17)		Nil 15% (3)	

Table 2 (continued)

Participant Characteristics					
Details of required experience	5 years of rotational hospital experience, including > 1 year supervised in an ICU 10% (2)	2–3 years of rotational hospital experience 30% (6)	Local ICU training 10% (2)	Demonstratable competency 5% (1)	1.5–2 years of rotational hospital experience, plus > 0.5 years supervised in an ICU 20% (4)
Required credentials	Professional Doctorate (PharmD) 20% (4)	Master of Pharmacy (MPharm) 25% (5) (additional post-graduate Diploma or Master of Clinical Pharmacy desired)		Bachelor of Pharmacy (BPharm) and Master of Clinical Pharmacy 15% (3)	BPharm 40% (8)
ICU Clinical Pharmacy Service Characteristics					
Service descriptions					
Sector	Public 60% (12)		Private 35% (7)	Public and private 5% (1)	
Hospital bed number	Small < 100 5% (1)		Medium 100 to 499 55% (11)	Large >500 40% (8)	
ICU clinical pharmacy service, including countries service reported in	No dedicated ICU service. Non-bedside remote advice and drug logistics provided. No weekend (Sat/Sun) or out-of-hours (OOH) service 30% (6). Reported in: Austria, Belgium, Poland, Switzerland, Malaysia, Brazil	Shared service with wards. Mainly non-bedside remote advice and drug logistics provided. Some ward round attendance and non-bedside back-office activities. No (Sat/Sun) or OOH service 10% (2). Reported in: South Africa, Portugal	Devoted bedside service and non-bedside back-office activities provided. Remote advice and drug logistics (Sat/Sun) + OOH 30% (6). Reported in: UK, Netherlands, USA, Canada, Brazil	Devoted bedside service and non-bedside back-office activities provided. Reduced bedside service (Sat/Sun). Remote advice + drug logistics OOH 25% (5). Reported in: Australia, USA, Vietnam	Devoted bedside service all week. Non-bedside back-office activities excluding (Sat/Sun) provided. Remote advice and drug logistics OOH 5% (1). Reported in: Australia
Sources of variability in national ICU clinical pharmacy services					
Inter-related themes	Determinants		Recruitment	Service provision	
Sub-themes	Funding, legislation, population, workforce, perceptions		Qualifications, experience	Constituents, delivery	

emergency department. Some institutions spread clinical pharmacist duties across departments, including the ICU; whilst others facilitated a dedicated bedside ICU clinical pharmacy service. Weekend and out-of-hours provisions varied between institutions. No institutions were reported to provide a seven-day, twenty-four hour bedside clinical pharmacy service.

ICU clinical pharmacy services were reported to be affected by local infrastructures, which can be determined by themes (Table 2). Tables (Online Resource 1–2b) illustrate the codes representing the multifaceted components of these themes. As an overview, it was interpreted that patient populations trigger an ICU workforce requirement linked to stakeholder perceptions. ICU clinical pharmacist recruitment may reflect these perceptions. Perceptions may be shaped by clinical pharmacist cost-effectiveness evidence, plus stakeholders' knowledge and experience of clinical pharmacy. Education and training was deemed central to producing competent pharmacists, which reinforced positive stakeholder experiences. However, adequate numbers of ICU-competent clinical pharmacists, can be a further limiting service factor. Financial and legislative factors also shape ICU clinical pharmacy service characteristics. Combined, all factors shape ICU clinical pharmacists' scope of practice and institutional service provision.

Non-Bedside Approach

Tabulated clinical pharmacist contributions (Online Resource 3) provide greater insight into the variety of non-bedside clinical and back-office activities thematically presented in Fig. 1. Non-bedside contributions included medication supply, compounding activities and ICU stocking of empirical antimicrobials. This was felt to augment rapid and safe administration of antimicrobials. Remote clinical activities included patient medicines reconciliation and screening. This included ensuring appropriate shock treatment and antimicrobial stewardship (AMS). AMS activities principally involved providing advice on antimicrobial selection, dosing and therapeutic drug monitoring (TDM) based on patient factors. Back-office activities enhanced by electronic prescribing and medicines administration (ePMA) systems included AMS-related guidance, local antibiogram generation, education and reporting. Utilisation and development of ePMA systems to overcome inter-departmental interface issues, identify high-risk patients, capture performance and antimicrobial resistance (AMR) metrics, facilitate medication safety, support research and AMS were also reported.

The delivery of non-bedside contributions depended on ICU service provision (Table 2), which was influenced by central hospital, ICU and/or pharmacy leadership. Remote clinical advisory services were reported to be reactive to MDT requests or proactive based on clinical screening activities. MDT or inter-pharmacy communication was commonly reported via electronic entries, alongside telephone conversations. Whereas back-office activities were delivered through enhancement of ICU resources such as the ePMA system, or participation in committees. Committees could involve an ICU clinical pharmacist with a specialist interest, infection prevention and control (IPC), intensivist and microbiology stakeholders. National advocacy work and educational activities were also reported.

Bedside Approach

Comparatively, bedside contributions visualised in Fig. 1 and tabulated in Online Resource 4 were solely clinical. These were exclusive to ICU devoted or some ward shared clinical pharmacy services (Table 2). Clinical contributions at the patient bedside were more detailed in nature and consisted of components reflecting an increased scope of practice, such as prescribing activities.

Bedside medicines reconciliation contributions to optimising therapy were reported to a greater extent than non-bedside remote reconciliation approaches. As were MDT advisory activities related to medicines administration. Medication ordering and logistical activities were reported to be outsourced to pharmacy technicians in some cases. For patients in septic shock, the complexity of bedside contributions was associated with pharmacists' knowledge and skill. For example, participants with greater than 5 years' experience described tailoring of therapies to different shock states. Pharmacist pharmacokinetic/pharmacodynamic (PK/PD) skills were also reported, which were associated with antimicrobial dosing advice above manufacturer recommended limits. Compared to non-bedside clinical roles, greater emphasis was placed on sepsis identification, antimicrobial choice and dosing. This was correlated to patient, drug and microorganism characteristics. Additional TDM of an array of drugs was reported by sites affiliated to a University or on-site laboratory. ePMA systems were further reported to be used to monitor patient clinical responses and augment bedside AMS activities.

Contributions were routinely delivered on weekdays through direct MDT communication and pharmacist led interventions (particularly for time sensitive matters). Electronic ePMA entries were also reported. Greater involvement in patient care transitions was described, including communication with primary or secondary care providers, patients and/or their relatives. Pharmacist incorporated MDT sepsis outreach teams and ICU sepsis triage pathways were also reported. Prescribing activities associated with empirical antibiotic initiation, correction of TDM, medication errors and AMS activities were exclusive to management lead, highly specialised senior or consultant pharmacists under intensivist leadership. Supplementary prescribing of TDM dosage alterations based on an MDT agreed protocols was described by some pharmacists from all reported grades.

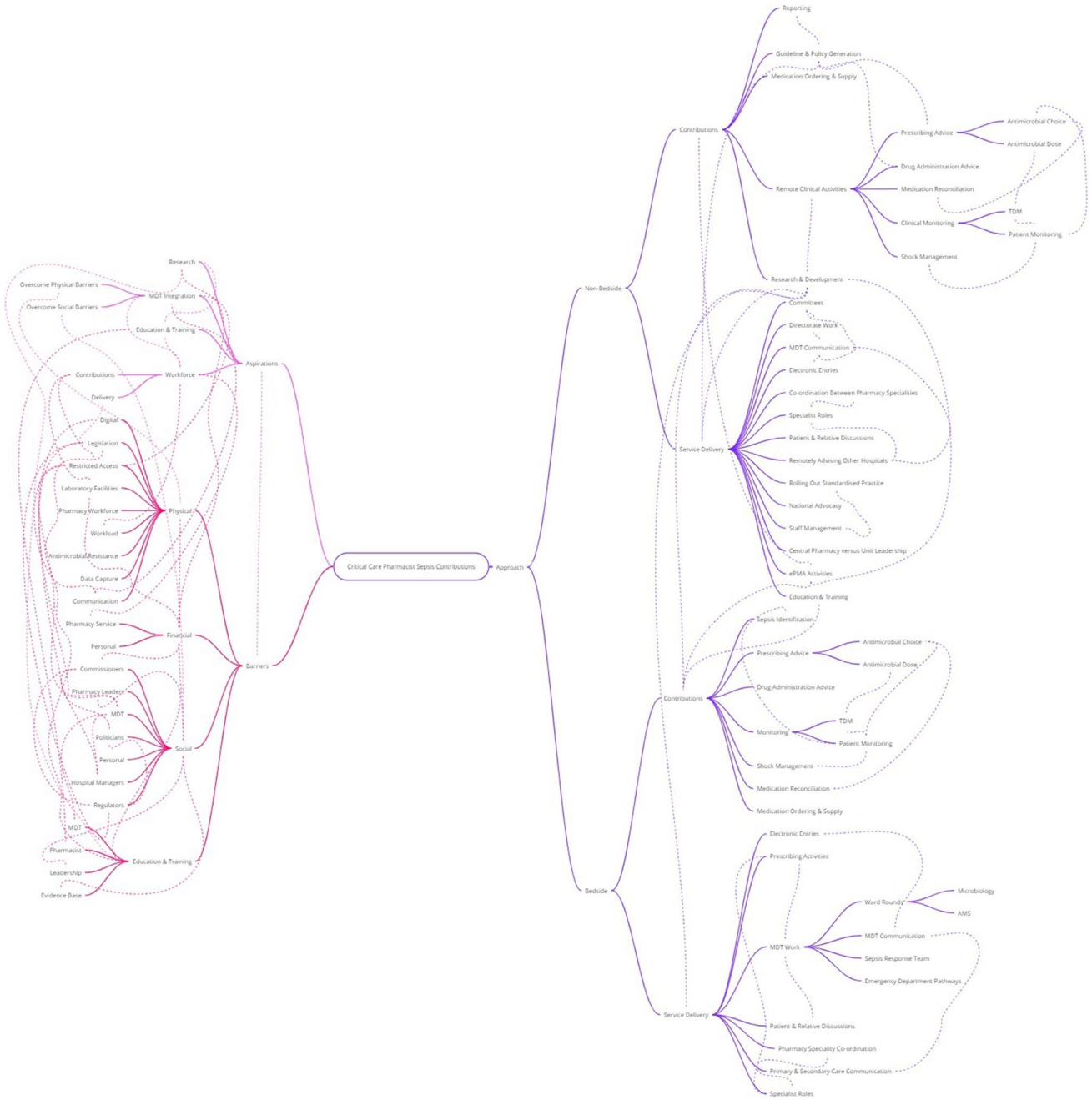

Fig. 1 Coding tree outlining thematic analysis of ICU clinical pharmacy contributions to the management of sepsis

Contribution Barriers and Sources of Variation

Tables (Online Resource 2a, b) contribute to key themes represented in Fig. 1. Physical barriers prevented pharmacist contributions, particularly for time critical interventions. This was attributed to legislation inhibiting scope of practice, plus multifactorial causes preventing physical ICU or patient record access. Causes included requirements of pharmacists' presence in non-ICU settings, understaffing triggered by financial or workforce shortages, plus direct prevention by stakeholders. For example, one pharmacist reported that their workload of "64 ICU level 2/3 beds alongside a haematology ward" prevented them from reviewing patients. Another reported that "less than 10 clinical pharmacists" were present "in the whole country". Lack of institutional ePMA systems and laboratory services was also correlated with reduced contributions. Consequently, pharmacists' contribution scope was associated with larger, well-resourced institutions due to mitigation of barriers associated with resources.

Social barriers correlated with service provision and stakeholders, triggered or compounded some physical barriers. For

example, historical practices alongside poor MDT understanding of ICU pharmacists' roles and capabilities, was communicated to lead to role contentions. In these instances, TDM activities in some institutions were reported to be exclusive to microbiologists, whereas clinical pharmacologists assumed medicine optimisation roles in others. In both cases, protected renumeration structures imposed by local government further prevented pharmacists overcoming these cultural barriers. Pharmacists themselves were also identified to contribute to social barriers, with reported resistance from non-clinical pharmacists to upskill. Moreover, it was felt that some pharmacy leaders were not interested in moving away from renumerated medication supply services. This was compounded by poor payment incentives, lack of undergraduate/post-graduate training and work balance for clinical pharmacists. Furthermore, pharmacists reported that MDT relationships could be hampered by poor social skills. This was attributed to limited mentorship and training. For example, some pharmacists were reported to act like "the antimicrobial police" and overwhelm prescribers with negative information about their practice. Some participants further communicated that their junior colleagues did not "feel safe" or have the "confidence" to make ICU interventions. Highlighting the need for local and national mentoring, leadership and education/training. Some participants also reported that traditional management progression pathways jeopardised their ability to advance their clinical or research contributions.

Contribution Aspirations

Tabulated findings in Online Resource 5 highlight the interconnection of aspirations with the mitigation of associated barriers (Fig. 1). Aspirations to overcome physical and social barriers to enhance contributions, focus on bedside MDT integration. Pharmacists providing remote clinical services as a core aspect of their non-bedside role, reported wanting to "assess patients' full clinical picture" instead of "just looking at results on a screen". Face-to-face MDT consultations were envisaged to improve relationships. One participant reported that personal contact has helped make their MDT "feel safer with a pharmacist". Improved digital infrastructures and patient record access were felt to further enhance MDT communication and collaborative contributions.

Uniformity in structured interprofessional education/training opportunities aimed at residency and specialist-stage ICU pharmacists, was felt to mitigate the formation of social barriers. Such opportunities were also envisaged to encourage higher-value MDT interventions. Improvements to the ICU clinical pharmacy evidence base and extrapolation of existing evidence to local settings were also identified. Combined with development of data capture tools to benchmark contribution cost-effectiveness, these aspirations were reported to reduce physical, social and financial barriers. Professional advocacy and leadership was also championed to overcome all barriers. For research, there was a unanimous interest in antimicrobial personalisation contributions facilitated by point-of-care devices, genomic/phenotypic markers and ePMA systems. Collectively, these aspirations were felt to help standardise the international ICU pharmacy workforce, address unmet patient needs and adapt clinical pharmacists to evolving ICU infrastructures.

Discussion

This study reviewed ICU clinical pharmacist contributions in the management of sepsis across the globe. Sources of variability associated with barriers and aspirations were captured. These were correlated with participant and clinical pharmacy service characteristics. Findings may be used to increase stakeholder awareness of ICU clinical pharmacist contributions and their delivery. This may improve understanding and consideration of how pharmacists can integrate into an ICU service. A unique insight into contribution barriers further provides an opportunity for stakeholders to reflect on the challenges faced by pharmacists in different settings. Whereas reported aspirations provide an opinion on developmental goals stakeholders can work with clinical pharmacists to achieve.

Defining Contributions

Contribution Context

Clinical pharmacists from Western countries report reducing sepsis-related mortality and improving care quality through advisory and logistical activities [1, 2, 7–9, 11–22]. Typically contributions involve: guiding drug choice and administration, identifying and managing drug interactions or prescribing errors, therapy modification based on patient/concomitant medication factors, reducing antimicrobial prescribing and administration delays, patient and clinician education, generating guidance, medication reconciliations including history taking and medication reviews. Delivery is typically reported through bedside activities such as ward round interventions, supported by back-office operations [1–4, 6•, 7–24, 26, 27•, 28•, 29•, 30, 31•, 38, 39]. Variance in pharmacist contribution outcomes exists, and is likely due to differing local practices and metrics capture. Due to a lack of comparative studies, contribution impact from bedside and non-bedside clinical roles is unclear. Although, increased scope of clinical pharmacist practice can be attributed to patient bedside locations [1–4, 6•, 7–24, 26, 27•, 28•, 29•, 30, 31•, 38, 40–42]. Study findings offer additional insights into contributions prior to and after antimicrobial prescription generation. Particularly for AMS,

prescribing and digital activities. Furthermore, identification of contributions delivered by ICU clinical pharmacists within sepsis outreach teams and ICU triage pathways is novel. Associated impact of additionally identified contributions and delivery mechanisms on patient clinical outcomes should be investigated. Empirical evidence suggests suboptimal patient outcomes when seven-day pharmacy services closer to patients' bedside are not employed [34•]. Therefore, stakeholders should consider the benefits of assisting clinical pharmacists accordingly. This could be achieved by working with pharmacists to identify and address associated barriers, whilst capturing local metrics to support service changes.

Contributions Prior to/at Time of Prescription

Reported independent and supplementary prescribing, plus digitally facilitated activities are examples of evolving clinical pharmacist roles in sepsis. Furthermore, an AMS subspeciality of contributions not previously associated with pharmacists is emerging. Associated reported activities include delabelling of patient allergies, generating antibiograms and leading TDM activities [32, 40, 41]. Although, such activities were only reported in select institutions where clinical pharmacists were well-integrated into MDTs at the bedside. Sharing stakeholder experiences of pharmacists and implementation strategies at such institutions, could offer constructive learning opportunities. In other settings, evolving contributions may contend with traditional MDT roles, preventing adoption. However, stakeholder assessment of how pharmacists' skillset could be integrated, enhanced and balanced within the MDT has demonstrated benefits. Including reductions to MDT workloads, reduced ICU workforce shortages and enrichment of patient outcomes (particularly for TDM) [2, 8, 12, 15, 17, 19, 30, 32, 34•, 36, 40, 41, 43–47]. Further research on which professional partnerships offer the best quality metrics and return on investment would be useful for commissioners. Whereas implementation research and regulatory consideration of evolving clinical pharmacist roles outlined by professional bodies, could further support adoption [8, 11, 16, 17, 19, 27•, 36, 48].

Post-Prescription Contributions

Clinical re-assessment, data review and antimicrobial modification, are common activities associated with clinical pharmacist advice. Increasingly, pharmacists reported using ePMA technology as a tool to facilitate medicines optimisation and AMS activities [8, 9, 11, 16, 17, 20, 21, 26, 32, 47]. By harnessing technological advancements, some pharmacists have demonstrated that they are well-positioned to embrace evolving ICU landscapes [6•, 10, 35]. ICUs could therefore utilise pharmacists to undertake greater clinical governance activities and metric reporting, including AMR surveillance [8, 11, 16, 17, 32, 40, 41]. Clinical pharmacist integration into sepsis response teams and emergency department triage pathways, has demonstrated reduced ICU admission rates and improved clinical outcomes [1, 2, 8, 15, 16, 18, 20–22, 24, 45, 47, 49]. Therefore, pharmacists should be considered in sepsis-related performance strategies [5•, 30, 50, 51]. Providing pharmacists with opportunities to upskill in PK/PD expertise, may also improve likelihood of antibiotic effectiveness in complex patients. Supporting pharmacists with the time and resources they need to develop this skillset and fulfill their research ambitions, may also empower ICUs to offer unique cutting-edge services [7, 8, 11, 16, 17, 27•, 36, 43–46, 52, 53–56].

Exploring Variability

Participant Characteristics

The study's recruitment strategy is subject to response and selection bias. This restricted insight into pharmacists' contributions from smaller, remote institutions and less-developed countries [28•, 29•, 33•, 34•, 57]. Despite this, participants from six continents were represented. However, findings reinforce that ICU clinical pharmacy is a sub-speciality of clinical pharmacy established predominantly in developed nations or well-resourced institutions [28•, 29•, 33•]. Clinical pharmacist contributions and associated impact has been correlated with seniority and experience [27•, 36]. Therefore, although the study sample underrepresented junior pharmacists, it offers a unique perspective to answer the research question.

Clinical Pharmacy Service Characteristics

Sepsis contributions generally consisted of World Health Organization (WHO)/Centers for Disease Control and Prevention (CDC) AMS components [32, 40, 41]. Advisory contributions based on antimicrobial dose adjustment, administration and TDM were reported by all participants. However, inconsistencies in contribution type and detail emerged between bedside and non-bedside clinical contributions. Particularly for activities relating to medicine reconciliation, sepsis recognition, [5•, 50, 51] utilisation of ePMA software and prescribing. These disparities were associated with physical, social, financial and education/training themed barriers tabulated in Online Resources 2a and 2b plus Fig. 1 [28•, 29•, 33•]. Interestingly, institutions with limited or no ICU clinical pharmacy services were reported in both Western and non-Western countries [28•, 29•, 33•]. This suggests that a greater emphasis may be placed on

social barriers in preventing clinical pharmacy adoption and expansion of practice. Advocacy of ICU clinical pharmacy services to stakeholders at such institutions by professional leaders, with endorsement from politicians could be an effective approach. This could emphasize sub-optimal clinical outcomes and increased expenditure associated with the abscence of clinical pharmacy services [1, 2, 4, 7, 8, 11, 15–17, 34•, 57]. This could be associated with local authority enforcement of a national/international consensus on ICU service standards, specifying minimal safe clinical pharmacist to patient staffing ratios [6•, 10, 17, 29•, 34•, 57–59].

Physical Barriers

Inconsistent pharmacy workforce provisions and prohibitive barriers were identified in many non-dedicated ICU clinical pharmacist services. These issues were associated with preventing timely contributions at sepsis onset, plus the breath of contributions [28•]. Reduced supply given the demand for competent ICU clinical pharmacists and provision of safe staffing levels, [29•] is associated with multiple factors [6•, 10, 38, 58, 60•, 61]. Whereas prohibitive pharmacist access to the ICU and patient records, alongside poor utilisation of ePMA resources may be associated with social barriers and health inequalities [9, 20–22, 26, 29•, 34•, 47, 60•, 61]. Legislation limiting the scope of clinical pharmacists' practice was often reported to be interlinked and compound such barriers.

Solutions to workforce issues guided by reported ambitions could include robust local staffing mechanisms. Including greater utilisation of pharmacy technicians, well-evidenced ICU clinical pharmacist business cases, on-call or twenty-four hour bedside clinical pharmacy services, increased pharmacy undergraduate engagement and incentivising ICU development pathways [6•, 10, 29•, 34•, 57, 58]. Whereas interlinked social and physical barriers could be tackled through advocacy solutions, interprofessional education and ICU pharmacist accreditation. Similar strategies have been reported to advocate national changes in legislation and stakeholder perceptions of clinical pharmacists in the UK [27•, 29•, 33•, 34•, 38, 57, 60•, 61].

Social Barriers

Negative stakeholder perceptions of clinical pharmacy have previously been correlated with role expectations, poor advocacy and lack of understanding [33•, 38, 60•, 61]. Reports from pharmacists providing routine non-bedside clinical advice, reemphasize these findings with reports that stakeholders perceived clinical pharmacy as a "non-priority service" and "threat". Participants suggested that medical jurisdiction affected their scope of practice, including their ability to attract service and/or research funding. Such experiences may further compound reluctancy of some pharmacists to seek clinical or ICU training. However, in institutions with dedicated bedside ICU roles, positive stakeholder perceptions were communicated. MDTs in such institutions were reported to respect clinical pharmacists and welcome their input, as pharmacists in these instances had proven their value. Participants expressed this created an environment to nurture trusting relationships, which enhanced their contributions [27•, 38]. Both pharmacists and stakeholders could learn from MDT structures incorporating dedicated bedside ICU clinical pharmacists. Placements at such institutions could be encouraged [28•]. This may be facilitated with the assistance of networking via professional groups or societies. Complex social barriers require root cause analysis, with solutions tailored to different stakeholders and stage of clinical pharmacy adoption [10, 33•, 34•, 38, 60•, 61]. Pharmacists could engage MDT stakeholders by instigating educational opportunities on topics of interest, deduced from common MDT queries. Whereas formal interprofessional education and advocacy strategies may improve role expectations and MDT integration [28•].

Financial Barriers

ICU funding is a historical service provision barrier and is complex in nature [35, 59]. For example, UK clinical pharmacist posts are commonly funded by different hospital stakeholders based on business case generation from local leaders [29•]. Despite recommendations [6•, 58], UK clinical pharmacy funding is exempt from national funding pathways correlated to ICU bed capacity/complexity. This is not the case for medical and nursing professions [35, 59]. Similar complexities are likely to have precipitated reported disparities in inter-institutional and sector ICU pharmacist staffing. Both staffing levels and salary factors are known to de-incentivise pharmacists to work in clinical capacities [17, 38, 60•, 61]. However, institutional AMS budgets could offer chief pharmacists an opportunity to improve their ICU workforce offering. This could be sustainable if clinical pharmacists were supported to capture and validate their contributions as part of their role [32, 40, 41, 58].

Collection and review of the financial impact of ICU clinical pharmacists are confined to a small number of studies [6•, 8, 11, 15, 16, 18]. Despite not demonstrating improvements in sepsis rates; length of patient stay, adverse event and drug/laboratory costs are considerably reduced with bedside ICU clinical pharmacists. Estimated return on these salary investment of a bedside ICU clinical pharmacist is reported 25:1 from cost avoidance. This proportion increases with rising pharmacist to ICU bed ratios. Furthermore, this ratio is likely an underestimate,

considering financials associated with mortality, plus length of stay is unaccounted in studies. Given that ICU clinical pharmacist return on investment is greater than other specialities, clinical pharmacists should be prioritised to ICU areas. Existing evidence could be extrapolated to local contexts to support buisness cases [6•, 8, 11, 15, 16, 18]. Consequently, there is a rationale to support non-ICU clinical pharmacists with funding and time to develop their expertise. Research is required to update economic evaluations to reflect evolving contributions identified by this study and undertake meta-analysis. Furthermore, improved contribution data capture methods and research study endpoints linked to commissioning requirements are required. This would support local business case generation and political advocacy to enforce regional, national or international ICU service standards [6•, 8, 11, 15, 16, 18, 28•, 29•, 62].

Education and Training Barriers

Many international pharmacists were reported to not possess clinical pharmacy specialty training. Moreover, many hospital clinical pharmacists were felt by participants to not possess the skills and experiences for ICU working. These reports were correlated with undergraduate/post-graduate training and individual contribution variation [27•, 29•, 63]. Recognition of such factors by professional bodies in some Western countries has resulted in competency frameworks, formal accreditations, and faculty staging [31•, 39, 58, 64, 65]. Implementation of these strategies globally could lead to increased workforce standardisation. This would increase stakeholder confidence in pharmacists' capabilities whilst assisting with recruitment processes. However, workforce development using accredited virtual/in-person training packages [58, 66, 67], key resource familiarisation [32, 40, 41, 53] and other upskilling strategies [29•, 36, 60•, 61] requires both local and national leadership [28•]. Consultation of some country's ICU pharmacist development models and roadmaps [6•, 31•, 34•, 39, 58, 64, 65], generation of White Papers by professional groups [68] plus integration of clinical pharmacists into ICU societies; could begin facilitating change [60•, 61]. These entities also have great potential to reduce education inequalities. This could be through improving education/training resource access via virtual mentorship and low-cost subscription schemes. Professional and research networking via virtual peer communication platforms and conferences, could also help develop an international ICU MDT community in which clinical pharmacists are part of.

Reflexivity

Study processes, findings, and their interpretations were influenced by participants and the research team. Consequently, objectivity in addressing the study research question is challenging. Research team member reflections acknowledged subtle differences in interview probing of TDM practices and pharmacokinetic associated contributions. Consequently, findings may overrepresent these contributions. Despite junior pharmacist underrepresentation, study methods were deemed to encourage participation from pharmacists with information-rich insights with central importance to the purpose of the study enquiry [27•, 28•, 29•, 69]. Furthermore, research team selection of international ICU/infection specialty clinical pharmacists from heterogenous institutions, was felt to embrace participant subjectivity as faithfully as possible.

Limitations

As this was an exploratory study, further studies are required to explore findings in greater detail with revised methodologies. For example, variation in service characteristics could be better quantified with routine ascertainment of clinical pharmacist to ICU-bed ratios. Theoretical assumptions could also be explored, which would be central to a methodology exploring the meaning behind reported experiences. This would be useful for investigating a broader range of clinical pharmacist and stakeholder perspectives.

Conclusions

In critically unwell septic patients, clinical pharmacists contribute to management through pharmaceutical care and medicine optimisation activities. Some pharmacists enhance these contributions through evolving AMS, prescribing and digitally facilitated components. These may be made prior to, at the time of, or after therapeutic prescription. Delivery of clinical contributions may be through remote or in-person means. The setting of contributions is not exclusive to the ICU bedside. Pharmacists may be positioned in back-office or other locations such as wards, depending on local service provision. Dedicated bedside ICU clinical pharmacy services, supported by back-office and clinical outreach activities, empower pharmacists to maximise their contributions to sepsis. These types of services are typically present in larger institutions, but are not always correlated with Western countries. International inconsistencies in ICU clinical pharmacy adoption, MDT integration and

subsequent ICU service provision, are responsible for contribution variability. Irregularities are interlinked with multifaceted contribution barriers. These can be categorised into physical, social, financial and training/education themes. Reported contribution aspirations have informed an opinion on proposed resolutions. Tailored solutions require both pharmacists and stakeholders to collaborate in identifying and problem-solving thematic barriers. This may include research into implementation strategies and outcomes associated with ICU clinical pharmacists' expanding scope of practice. Updating and locally extrapolating the evidence based supporting ICU clinical pharmacist contributions, is key to workforce prioritisation, standardisation and renumeration. Whereas professional advocacy, interprofessional education and leadership, are central to MDT integration and advancing clinical pharmacy roles.

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Author Contribution RO, DL and AG contributed to the study conception and design. Material preparation and literature search was performed by RO. Data collection was performed by RO, SA-M, SG, HT, MC and SK. Analysis was performed by RO, SA-M and SG. The first draft of the manuscript was written by RO and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials Not applicable.

Compliance with Ethical Standards

Ethical Approval Institutional ethical approval for the study was obtained from St George's, University of London (SGUL) Research Ethics Committee reference no. 2023.0125, which included a data protection impact assessment.

Consent to Participate Participants provided informed written consent to participate and for their personal information to be stored securely on the SGUL electronic server before deletion upon study completion. Written consent was provided by email return of a digitally completed or a scanned manually completed consent form.

Consent for Publication Participants provided informed written consent for the research team to publish anonymous quotes and analysis of their descriptions in response to interview questions.

Conflict of Interest Robert Oakley, Sarraa Al-Mahdi, Sonja Guntschnig, Ha Trinh, Marco Custodio, Sarah Korshid, Andries Gous, and Dagan O Lonsdale declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards and international/national/institutional guidelines).

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