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MAJOR ARTICLE

Ushering in Antifungal Stewardship: Perspectives of the Hematology Multidisciplinary Team Navigating Competing Demands, Constraints, and Uncertainty

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Background. The social, contextual, and behavioral determinants that influence care in patients at risk for invasive fungal diseases (IFD) are poorly understood. This knowledge gap is a barrier to the implementation of emerging antifungal stewardship (AFS) programs. We aimed to understand the barriers and enablers to AFS, opportunities for improvement, and perspectives of AFS for hematology patients at a major medical center in Australia.

Methods. Semistructured, face-to-face interviews were conducted with 35 clinicians from 6 specialties (hematology, infectious diseases, pharmacy, nursing, radiology, respiratory), followed by thematic analysis mapped to a behavioral change framework.

Results. Access to fungal diagnostics including bronchoscopy was identified as the key barrier to rational prescribing. Collective decision making was the norm, aided by an embedded stewardship model with on-demand access to infectious diseases expertise. Poor self-efficacy/knowledge among prescribers was actually an enabler of AFS, because clinicians willingly deferred to infectious diseases for advice. A growing outpatient population characterized by frequent care transitions was seen as an opportunity for AFS but neglected by an inpatient focused model, as was keeping pace with emerging fungal risks. Ad hoc surveillance, audit, and feedback practices frustrated population-level quality improvement for all actors. Antifungal stewardship was perceived as a specialized area that should be integrated within antimicrobial stewardship but aligned with the cultural expectations of hematologists.

Conclusions. Antifungal stewardship is multifaceted, with fungal diagnostics a critical gap and outpatients a neglected area. Formal surveillance, audit, and feedback mechanisms are essential for population-level quality improvement. Resourcing is the next challenge because complex immunocompromised patients require personalized attention and audit of clinical outcomes including IFD is difficult.

Keywords. antifungal stewardship; antimicrobial stewardship; aspergillosis; invasive fungal diseases; surveillance.

Antifungal stewardship (AFS) is of growing interest to hospitals worldwide that manage patients at risk for invasive fungal diseases (IFD) [1–4]. Invasive fungal diseases are associated with a high mortality/morbidity, high treatment costs, and few therapeutic options (only 4 classes of antifungal drugs) [5–7] against a backdrop of rising global antifungal resistance [8, 9]. Taken together, these observations have stimulated guideline development, with AFS emerging as a subspecialty of antimicrobial stewardship (AMS) but with inherently different complexities [1, 10]. Clinical recommendations from both high- and low-income settings [2, 4, 11, 12] as well as more recent guidelines on AFS from the United Kingdom and United States have been disseminated, but without a behavioral lens [1, 10]. Increasing evidence from the AMS antibiotic domain suggests that AMS interventions are less likely to be effective if they fail to address the social, emotional, and contextual barriers of inappropriate antibiotic prescribing, which have stubbornly persisted despite the omnipresence of antibacterial resistance [13, 14]. Although clinical guidelines specific to AFS are evolving, there remains an opportunity to shape them with the voice of the stakeholder.

It is recognized that AFS has several differences to antibiotic stewardship [1, 10]. Antifungal stewardship is largely confined to the hospital sector where patients with significant immunocompromise are managed; antifungal drugs are usually restricted on hospital formularies due to their high cost and specialty focus; durations of antifungal courses are often longer; clinician confidence is poor; quantitative metrics such as antifungal consumption and cost have dominated evaluation of AFS programs [3]; insensitive fungal diagnostics make

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empirical treatment common, but this is guided by patient and institutional risk. However, patient-level risk assessment is linked to knowledge of local (ie, institutional) epidemiology [15], with both domains incomplete due to the absence of fungal surveillance, audit, and feedback mechanisms in the majority of hospitals [16, 17].

Lessons from antibiotic stewardship highlight the need to engage early and widely with stakeholders [13, 18]. We undertook an in-depth qualitative study of the multidisciplinary hematology team to understand the challenges and opportunities related to managing immunocompromised patients at high risk for IFD [19]. We focused on the hematology unit because it has the highest consumption of antifungal drugs in our center, consistent with multicenter experience elsewhere [20]. We examined key elements of AFS, including fungal diagnostics, guidelines, audit, and feedback, but kept the interview structure intentionally flexible to allow the probing of other issues raised by respondents.

MATERIALS AND METHODS

Study Design and Setting

This was a qualitative descriptive study, with data collection performed through semistructured interviews. The study was conducted at the Alfred Hospital, a 638-bed quaternary, university-affiliated center, with trauma, heart/lung transplantation, allogeneic hematopoietic stem cell transplantation, cystic fibrosis, burns, hyperbaric medicine, and human immunodeficiency virus state-wide services. An embedded model of AMS operates under the immunocompromised host service, with a dedicated infectious diseases (ID) physician and registrar performing regular ward rounds on a referral basis for patients admitted under the hematology service. There is no formal AFS program, and the ID service works in collaboration with the hematology and pharmacy services separately to a well established hospital-wide AMS program present for over 15 years [21]. Antifungal drugs are prescribed according to institutional guidelines for prophylaxis, but empiric or targeted therapy requires preprescription authorization by infectious disease physicians.

Participants and Interviews

Through purposive and snowballing sampling, key stakeholders from hematology, ID, respiratory medicine, radiology, nursing, and pharmacy were included. One investigator (M.R.A.-R.) sent out e-mail invitations to participants. Individuals were contacted and interviewed face-to-face at a mutually convenient time. Collection of data from a variety of professional groups at different time points ensured participant triangulation, greater validity, and consistency of key themes. Verbal and written informed consent was obtained from all participants before interviews. The majority of interviews were conducted by 1 investigator (S.Fi.), with interviews of the respiratory medicine physicians conducted by M.R.A.-R. All interviews were audio recorded and transcribed verbatim by a professional service. Any identifying data revealed during the semistructured interviews were deidentified for analysis.

Interview Methodology

An interview guide, available in Supplementary Appendix 1, was kept flexible so that themes emerging during the interview process could be explored in greater depth. This study had ethics approval (Alfred Health Ethics Committee Project no. 305/18).

Analysis

One investigator (E.W.) performed open, axial, and thematic coding using NVivo software (QSR International), which was then validated by 2 investigators (T.P., D.A.) to identify dominant themes. Themes were further discussed at an expert consensus meeting involving M.R.A.-R., T.P., K.C., and A.Y.P. Analysis was continuous and themes were derived inductively from the data given the lack of qualitative studies related to AFS.

Themes were assigned deductively to domains in the behavior change wheel (BCW), which has been proposed as a means of understanding and thereby influencing behavior in AMS [13, 22]. The BCW is an interrelated framework incorporating the COM-B behavioral change model and 14 theoretical domains. At the hub is "COM," representing capability (psychological, physical), opportunity (social, physical), and motivation (reflective, automatic), which interact to produce behavior. This hub is encircled by intervention functions and an outer ring of policies that support potential interventions. The BCW allows implementation designers to appropriately select interventions informed by behavioral theory [22, 23].

RESULTS

Of the 36 invitees, 35 healthcare professionals participated in semistructured interviews conducted from July 2018 to December 2018. These included 24 doctors (7 hematology, 10 ID, 5 respiratory, 2 radiology), 8 pharmacists, 3 senior nurses, including 2 associate nurse unit managers, and 1 nurse unit manager. The doctors included consultants, who are specialist physicians, and registrars in specialty training. The interviews totaled 14 hours and 23 minutes, lasting on average 25 minutes (range 7.46 minutes to 1 hour, 6 minutes), and involved 18 female and 17 male participants.

Dominant and cross-cutting themes inductively identified from the data are shown in Table 1. Three barriers were identified for discussion: fungal diagnostics; competing demands; and ad hoc surveillance, audit, and feedback mechanisms, along with 1 enabler—tackling complexity with collaboration, culture, and communication. Shown separately in Table 2 are stakeholder perceptions of AFS and their suggested solutions to the barriers. Subthemes were mapped to the COM-B domains shown in Supplementary Table 1.

Table 1. Dominant Themes and Subthemes as Barriers and/or Enablers to Antifungal Stewardship

Theme	Subthemes	Quote
Fungal diagnostics	Rational prescribing linked to fungal diagnostics.	Q1 I suppose you want to ensure that you've got the appropriate antifungal agent and that, I think, involves ensuring that the appropriate diagnostic tests have been performed. Because often with fungal disease we know we can get a lot of answers from imaging without necessarily culture, So I suppose we want to guide the appropriate diagnostic tests to perform. And then helping provide advice both for prophylactic use of antifungal agents as well as ongoing therapeutic use. So it's the diagnostic tests, the prophylactic and the therapeutic arms-ID Registrar_28. Q2 We don't have a diagnosis and then the management is much more empirical… we are going to potentially include high cost drugs without a diagnosis and then everyone gets very uncertain about what should be done then. -Hematologist_3 Q3 It's the diagnosis that's the major issue…the radiological changes are, I think, inconsistently reported, so it depends on the radiologist who reports it…the inability to get tissue diagnosis is a problem. And probably thirdly, the inadequate diagnostic tests with respect to galactomannan and PCR. -Hematologist_19 Q4 In terms of resources, for example, the availability of bronchoscopy on an as-needs basis, an urgent basis is difficult to attain at times. I think there are certain bronchoscopy lists during the week and if you cannot get your patient on to one of those lists, you have a very difficult time in getting a diagnostic test performed in a timely manner…There have been barriers to [interventional radiology] in terms of getting that in a timely manner and interventional radiologists understanding the importance of getting a tissue diagnosis for these patients-ID Registrar_25 Q5 I feel like sometimes where it can fall down a little bit is from the teams getting access to bronchoscopies if the bronchoscopy lists are very full. And then it will really go down to a discussion between the three units around clinically how urgent is the result for treatment or does the patient need treatment started in the absence of results. -Nurse Q6 There are some days where you'll get it the next day and then there are some days where they seem to wait for ages until they get too sick to get the bronch. -Hematologist_8
Competing demands, system inefficiencies, and poor communication	Access to fungal diagnostics affected by patient and system-level constraints.	Q7 In the ideal world if there was a seven day a week bronchoscopy service and more machines able to run HRCTs particularly for patients who are in ICU. Because we often find that patients who are getting investigated for fungal infections are also in that position where we are also looking for influenza and those sorts of things. And unfortunately unless they are really clinically deteriorated, the CT scan will get put to the end of the day because the isolation delays their service so much, which can sometimes be problematic….most patients in isolation fall to the end of the list end of the day. -Nurse_1 Q8 I think it's more complicated than just strict manpower…Because we're talking about unwell patients going to bronchoscopy, there's always that element of risk and trying to overcome the feeling from a proceduralist that this is a high-risk procedure to do when we think it's important but perhaps the proceduralist thinks that it's less than necessary-Hematologist_8 Q9 Then also those ones are deemed high-risk and you might have another discussion really about risks benefits and sometimes they'll say look we need tissue and you will just very cautiously try but you do have to have a bigger discussion around those cases. -Radiologist_6 Q10 We perceive our role differently to how the referring physicians perceive our role. I think we are perceived to be the bronchoscopy rather than providing an opinion and some potential collaborative management advice. So to talk firstly about bronchoscopy, it's not a test that you want to do in someone who is particularly unwell or hypoxic and I don't think that is understood or appreciated. So things would be better if the referrals were made urgently, at the time the infiltrate was noted, not three or four days later on the consultant ward round at Thursday at 5 pm when the consultant says, "We need a bronchoscopy now". So I think a timely, early referral in a stable patient, would be critical. - Respiratory Physician_18 Q11 One is the timing of the referral is usually very late in the week at which point in time, it is much more difficult to put patients on to a bronchoscopy list, especially if they need to be isolated…we are happy to do it, but the timing of it is very poor in terms of logistically organising the list, and that's a problem. - Respiratory Physician_17 Q12 I'm concerned that those referrals often come very late in the process…after the CT is done, it will be potentially sometimes more than 24 hours before they refer to us for a bronchoscopy; and then…they want it straight away…Unfortunately one of the reasons why the CT scanning is delayed is because the patients are put into isolation…an isolated patient will wait until the end of the day and sometimes they are bumped… On occasion, I've wanted to cancel that final patient (in isolation) and that's the patient that often has the highest clinical needs … So I think if there was any way we could facilitate a quicker turnover process for the clean so you could do two iso patients on the list, that would help. -Respiratory Registrar_16 Q13 The large bronchoscopic workload at this institution…is actually quite different to most other institutions where most of the workload is sampling for cancer…a large part of the workload is also to service lung transplantations. So, we have a gigantic load relative to most other hospitals. -Respiratory Physician_14 Q14 the [theatre] turnaround time can be four plus times the amount of time it takes to actually do the procedure, which is highly inefficient. - Respiratory Physician_14

Table 1. Continued

Theme	Subthemes	Quote
Complexity the hallmark	Patient, treatment, and environmental factors.	Q15 So we have a fantastic antimicrobial stewardship service but we've got huge challenges in that space as well even by doing all of that. So I think it's one part of a comprehensive program for best practice around antimicrobials. But, particularly in a place like The Alfred, with the complexity of patients that don't always fit into a set guideline or protocol, it can be challenging. But I do think from the antifungal side, it's clearly a type of infection that has very serious outcomes for a patient and for some of the most vulnerable at-risk groups in the hospital, and the cost implications to a hospital are also very significant in terms of antifungal costs. So patient outcomes, costs, both are factors that we should be having as most comprehensive program around to improve as much as we can. -ID Physician_13
		Q16 The haematology population it's reasonably unique…a lot of patients on trials…are here at The Alfred for their last shot, which is two-fold in complexity. One is they are heavily pre-treated so often they are very immunosuppressed coming into treatment, But secondly. The stakes are higher because it's recognised that this is really a last line of therapy. - ID Physician_30
	Guidelines: utility, limitations, incomplete evidence base	Q17 So we've got risk ramifications around different haematological malignancies, whether they've been transplant patients, whether they've had steroids, there is all sorts of stratifications of who needs what and for what length of time. Do they need it while they are immunosuppressed? Do they need it when they are counter-covered? Who needs what? So basically a cut off point. The clinical pharmacists here also have cheat sheets for our registrars when there is changeover of units. That makes it really simple and really clear in conjunction with the guideline – when do you start, when do you stop?- Nurse_3
		Q18 I always say guidelines are guidelines. They are not a prescriptive set of rules that we must adhere to … you have to be able to modify your treatment and your management based on what is actually happening to the patient…studies have shown that when it comes to actually managing patients with fungal infections that we do deviate from guidelines – clinicians do that quite a lot. But I think that's a reflection also of the complexity of the patients that we're dealing with and the fact that the diagnostic tests for fungal infections are not great. - ID Physician_31
		Q19 Guidelines are good for most patients most of the time, but they're not good for every patient…so guidelines always need interpretation within the clinical context to which they are applied. Hematologist_7
		Q20 Yeah, I guess the times where we would go against it, would be if there's significant drug-drug interactions or other patient-related factors that mean it's not safe or applicable to go by what the guidelines are saying. So those would be the major reasons- Hematologist_8
		Q21 And we use a lot of antifungals in prophylaxis. And one of the struggles that we have it the gap between evidence and practice. We clearly have patient groups who we clearly have good evidence in, talking about our AML inductions. But there are other groups like the ALL patients, that I look after a lot of, where we know there are high rates of fungal infection but that we don't have good data in terms of prophylaxis we've got to use. So that's one aspect. The other aspect of course is in treatment of fungal infections in our patient population. And the complexities of it now because of near universal application of prophylaxis in our high-risk patients that we don't see many patients that have got a typical aspergillus infection. We're seeing more and more patients who have something unusual, which makes management a bit harder than just putting more voriconazole. Hematologist_8
		Q22 The evidence for antifungal prophylaxis is not strong, but its reasonable. But in the setting of transplantation, it's used too broadly and that does have some implications. For instance…the prophylaxis does have significant toxicity and that leads to issue with toxicity of some of the other drugs. -Hematologist_19

Table 1. Continued

Theme	Subthemes	Quote
Blind spots of an inpatient focused stewardship model	Transitions between inpatient and outpatient settings. Patients surviving with significant immunocompromise. Staying agile in the face of microevolutionary changes and their impact on risk. Limitations of ID input by invitation.	Q23 And a lot of the care is moving to outpatients, so if the only involvement that ID can have is with inpatients they're going to lose all that. A lot of this stuff is just coming out of clinical trial and it's in compassionate use at the moment. But it's going to move into mainstream quite soon. Venetoclax is just the tip of a massive mountain of stuff that's going to be quite complex for patients to manage in almost every outpatient…They are lingering on for years…We've got leukaemia patients being able to survive through multiple lines of treatment now that there are multiple lines of treatment. -Pharmacist_21 Q24 The biggest change that's coming into practice is there is a new field of leukaemia management just exploding …with small molecule inhibitors, things that…can still have other downstream effects. The thing that a lot of them have in common is massive interactions with azoles…another thing…is that they don't put the patients in CR [complete remission] or if they do it's quite slow. And so, the patients can be quite profoundly neutropenic for quite a reasonable period of time, just kind of grumbling along and that involves us using a lot more (liposomal amphotericin) and people trying to make an educated guess and patients being exhausted, being near palliative for years. -Pharmacist_21 Q25 The challenge that we face is that more and more there are novel drugs coming into practice that have Cytochrome P450 interactions. So, we can't necessarily go by what the guidelines say because it wouldn't be safe to do so. Some of the novel cancer inhibitors, for example, have Cytochrome P450 interactions, so we can't use an azole and an antifungal in that context, so we may have to use a non-azole-based technique. - Hematologist_8 Q26 I think what we're lacking is like a follow up role especially outpatients who are on prophylactic antifungals…no one is keeping an eye on their levels, do they need to drop it, should they have stopped it. -Pharmacist_9 Q27 I'll be interested to know what the outpatients guys experience is because while we are here, it feels to me like it falls to the pharmacists around ensuring levels are done consistently. I don't know how well that goes in the community…we see [patients] coming in with subtherapeutic levels and how long has it been? Is it as per the recommendation and the guidelines around checking or where does that fall? -Nurse_2 Q28 I think the ID Team probably have the biggest role there. But only when we involve them because if we don't involve them in the patient care then they have no idea what is going on. - Hematologist_2 Q29 I think there are teams that start treatment on their own, without referring to ID. Sometimes we get referred a few weeks into treatment, when it's not really working; and that's bad. That's a big flaw. - ID Physician_5

Table 1. Continued

Theme	Subthemes	Quote
Collaboration, culture, and communication as enablers	Balancing patient and population-level imperatives. ID expertise and collaboration as enablers. Lack of knowledge/ self-efficacy as an enabler	Q30 It's a complicated relationship between Haematologists and ID. I think we are dependent on ID for needing their advice, particularly as the complexity of a lot of the infected issues we deal with grows. I think equally there are clearly points of contention between ID and Haematology…we perhaps err towards over treatment… compared with ID maybe wanting to narrow spectrum and restrict treatment more. But that's a long-standing thing. But I think in general we have a collaborative approach with ID.- Hematologist_8 Q31 When you're giving a recommendation, you always need to be balancing that decision with what the ecological impact of that antimicrobial decision is. I think it's extreme in the case of a sick, young haematology patient. And I think this is a bit of a challenge with stewardship… And this is the ongoing discussion, not only at this hospital but every hospital that has a haematology service, it's a very common ID Haematology issue. Haematologists often and you know, want to use anything and everything to save that individual's life, and the ID physician of course wants to as well, but has to bring the perspective of well that might be excessively broad-spectrum for what we require here. -ID Physician_13 Q32 I think the strengths are we do have a good collaboration with infectious diseases and that we have good awareness of the issues of fungal infections. I think weaknesses, sometimes access to diagnostic procedures can be challenging – things like bronchoscopy. It can take time…- Hematologist_8 Q33 [The ID service] are aware of our patients and they round on the wards, they come to our unit meetings, they know who is sick, so they are part of our team. -Hematologist_7 Q34 I think it's good that the majority of people will make treatment decisions in conjunction with the ID team. Because I think they probably know what the best agents to use when and where are. And so I think the fact that we talk to them and we communicate with them is good. - Hematologist_27 Q35 I do rely heavily on the ID physicians because they have broader knowledge about antifungals and different fungal infections and so forth…In haematology patients, there are some special issues about drug interactions such as Vincristine, organ impairments and so forth. But again, I usually rely on the ID physicians to advise us about those things. - Hematologist_10 Q36 Like I say, the ID registrar for our immunosuppressed patients, they are here every day, they are talking to all of the clinical haem [registrars]…The clinical pharmacists are all really good and I think we are quite lucky [as] sometimes there is sort of some significant drug interactions with some of the chemotherapy agents our patients have, that prompts further discussion around is this the appropriate antifungal agent for this patient and also do they need it or not. Same with clinical trials where they'll be really specific for what the trial sponsors say they have to have. -Nurse_2 Q37 Personally, for me the strengths are the people in ID who are absolute experts. -Pharmacist_15 Q38 I think it's a very well established program which is great and importantly it has buy in from all the different care groups…I think that's really important because obviously you need to have the trust, you need to have the willingness of that team for you to be involved in the care. - ID Physician_11 Q39 I think the strengths are, the clinical teams try to work together as much as possible. - Pharmacist_24 Q40 We've got the benefit of having an excellent pharmacy service in here, which guides us well. - Hematologist_20 Q41 We usually have a consultant that's with us and having their experience is useful because fungal infections are a bit tricky both in terms of diagnostics as well as duration of treatment and things like that… So the strengths are that people here have experience. - Microbiology registrar 5

Table 1. Continued

Theme	Subthemes	Quote
Ad hoc surveillance, audit and feedback	Antifungal costs the default barometer for AFS performance.	Q42 Patient-level care is very good…meaning we're responsive and we see patients. But I think taking a step back from that is how do we know we're good? Well, we don't, because unless you audit, you don't know what your practice is. -ID Physician_31
	Weak audit and feedback loops increase motivation for better processes.	Q43 It would be good to have a systematic way of looking at where the antifungals are used because we still don't have a feel as to what propulsions are being used for prophylaxis and treatment… then we would know if and where we could improve. -Pharmacist_15
		Q44 That's what I would say would be a suggestion for improvement I think. Auditing what we do, looking at what we do, looking at how often we are getting unnecessary drugs, how often we are giving things that are too broad spectrum, how often we are using things that are quite expensive and unnecessary. I think that would be a good thing to do. -Hematologist_27
		Q45 We have in the past, done many antifungal audits…but my understanding is more on an ad hoc basis rather than a systematic, ongoing behaviour. -Hematologist_7
		Q46 I don't have much of an understanding. I think that certain people in the Infectious Diseases Unit would audit incidents of IFI and trends…but I haven't seen it or am not sure. -Pharmacist_22.
		Q47 (Re antifungal practice), We don't usually get much direct feedback formally on those things to the actual department. They may be presented or discussed within the ID unit but they are not generally fed back to us on a formalised regular basis. It if is, it's ad hoc. -Hematologist_3
		Q48 So the audit process is kind of limited to how much dispensing of antifungals occurs…generally having this ongoing system of audit and feedback doesn't seem to happen on an ongoing basis. -ID Registar_25.
		Q49 Pharmacy-wise, all we can audit is use, overtime and cost but it's not always the best.-Pharmacist_1
		Q50 (Re antifungal practice), I couldn't tell you with respect to the diagnosis monitoring that side of it, I don't know how that data is looked at. From a pharmacy side, maybe it's a good thing is the high cost drugs, they are monitored quite closely. So that gets reported through our executive and governance structure so there is a report at the end of the month that will say, " you've used an extra $200 000 worth of Posaconazole. What's the reason for that?" So that's how we monitor it. It's not official auditing. - Pharmacist_24
	Population-level audit and feedback needed but difficult in practice.	Q51 [IFD] are difficult to monitor in hospitals… Because of that, we tend not to audit these infections in any systematic way. The problem is that we're unable to benchmark ourselves against anyone else… – ID Physician_31
		Q52 So the way I would now look at antifungals is I first do a dispensing report, which gives me all the names of all the people that had a particular product…but then to get any further information I would then go into individual histories, retrospectively and look at what they've used, really look at what they've used and really look at clinical notes and it's not often easy…-Pharmacist_15
		Q53 Because what we want to do is also find out whether we are getting outcomes that are worth putting the patients through the procedure. We don't necessarily get that feedback… actually looking at whether it was of any value. -Respiratory physician_17
		Q54 (Re clinical audit), No, which is something we need to do and we're actively looking at doing. We do have a bronchoscopy-computerised database, but as of yet, we haven't been doing a regular safety audit, which we absolutely need to do. - Respiratory Physician_29
		Q55 (Re radiology reporting), there is no quality control method…for most things, a specialist report is the final opinion. -Radiologist_4.
		Q56 The only time I see those (fungal) cases is when I am reporting them myself or when the clinician comes and asks me. So, there is no follow up for that group for me. I guess it would be nice to have that follow up to confirm what you suspected was right. -Radiologist_6

Abbreviations: AFS, antifungal stewardship; AML, acute myelogenous leukemia; CT, computerized tomography; HRCT, high-resolution CT; ID, infectious diseases; ICU, intensive care unit; IFD, invasive fungal diseases; IFI, invasive fungal infection; PCR, polymerase chain reaction.

Table 2. Stakeholder Perceptions, Opportunities, and Solutions for Antifungal Stewardship

Challenge	Opportunities/Solutions	Quote
Data for action	AFS is multifaceted, improving all aspects is important Expand from patient-level service provision to a systems- level approach including audit and feedback to drive quality improvement.	Q57…the concept of antifungal stewardship, they just think that people are policing their prescribing, but actually it starts with assessing how likely somebody is to have an invasive fungal infection and getting the diagnostic tests done…and then obviously prescribing. -ID Registrar _25 Q58 So you would have to find the right people to be the stewards doing [AFS]. So if you've got a steward which maybe doesn't have the best skills with respect to communication or developing relationships with treating teams, that can run into trouble I think. But the other thing that I think they would need to embrace would be the whole package, not just the drug treatment, it would be things such as the diagnosis. So they would need to take responsibility for ensuring that the diagnostic tests are better implemented. - Hematologist_19 Q59 (Re current antifungal practice), I think it's been dependent on that referral process so the team referring, rather than having a more holistic view of what is happening within that group of patients. I think it has been looking more from a service provision rather than a population, quality program, and trying to understand who is on certain antifungals or other drugs at that time and seeing if there are ways to improve overall practice, not just for a specific patient…AMS programs are very well embedded in most hospitals throughout Australia. In fact, they are mandated. For the hospital to be accredited, they have to be providing AMS services. So there are ways to adapt and graft an AFS process onto an AMS and we have been involved in implementation of stewardship programs in hospitals both public and private and so on, and so there is a lot of lessons that we've learnt through that, that can easily inform how you approach the same process for AFS. -ID Physician_11 Q60 Where we probably want to go now in terms of best care and management is probably a team effort with data collection, outcomes, reporting and auditing to assess practice and looking for trends or things that aren't following our set guidelines. So, I think we've got the guidelines in place, that are international guidelines, they are fitting. But there are so many nuances to these patients and I don't think we've necessarily got the post intervention sort of follow up and auditing and feedback loop in place enough. -ID Physician_13
Integrating AFS within antimicrobial stewardship	Strengthening an existing embedded stewardship model	Q61 Re AFS: Perhaps integrated into some other system. I think if it was integrated maybe within the broader context of antimicrobial stewardship, it would be useful. I think that looking at aspects of appropriate prophylaxis, for example. At the moment it falls heavily on the Haematology Unit. And perhaps antifungal stewardship could look at showing that all patients are on appropriate prophylaxis and flag those who discussion needs to go into what prophylaxis they receive, as well as when we are treating people, we are using empiric antifungals at times. And having defined treatment time courses and timelines for working up a diagnosis and flagging that these patients are on antifungals and there needs to be consideration of where to from here. Hematologist_8 Q62 I'm all for AFS. But I guess it depends on what the role of that group will be. I still think this shoe will fit under AMS…I guess it depends what the model will look like in the end and how much manpower it needs to run…from a pharmacist side, it probably doesn't need a lot more… I think any program that will make things better across the board is great. But I don't know if it really needs its own. - Pharmacist_24 Q63 I think it would benefit from having [AFS] within the structure of antimicrobial stewardship with the appropriate people… Well I think it's also confusing because I'll give you an example. When I came here coming from a place where you did a lot of things and we all did multiple things, I came here and they said, "So and so is our ID Pharmacist" and I thought, that's great. So I'd go and say, "Well Ceftriaxone isn't being used properly" and they'd say, "Oh no I only look after this group of drugs". I can understand people specialise but I think that's confusing for end users. -Pharmacist_15 Q64 It depends on what the program is designed to achieve. If you are thinking about say for example, therapeutic drug monitoring… and someone is going to follow them, liaise with the haematologists about what to with the next dose… then yes. But if it's going to sort of be didactic about what can't be used…that aspect is generally sort of detrimental. - Hematologist_10
Processes and targets	Early respiratory referral promotes planning and better respiratory engagement. -Outcome metrics -Bronchoscopy access -Improving usability of guidelines	Q65 The current state is "bronchoscopy please" and the concept needs to be more protocolised in that, if the patient has an infiltrate and they are immunosuppressed, the referral needs to be right away, so that we can provide more considered, and timely and safe response. There is nothing worse than doing a bronch on someone and they end up intubated, which is a real thing. - Respiratory Physician_18 Q66 Very happy for our referrals registrar to be contacted as soon as there is a possibility of a bronchoscopy…because then the place can be at least theoretically reserved for that patient, two or three lists down the track. - Respiratory physician_14 Q67 I think the main outcomes are the microbiological yield from the procedure and also where there has been a change of management as a result of the [bronchoscopy]. We would also be interested in the duration from referral to bronchoscopy. - Respiratory Physician_14 Q68 What we want to do is also find out whether we are getting the outcomes that are worth putting the patients through the procedure. - Respiratory Physician_17 Q69 (Re bronchoscopy access), having increased access and capacity overall would alleviate the entire problem - Respiratory Physician_14 Q70 (Re bronchoscopy referral), we'd definitely appreciate a phone call as opposed to the text message referral because a phone call helps communicate the acuity of the situation. - Respiratory Registrar_16 Q71 (Re improving guideline usability) It would be more useful if we have those recommendations incorporated into our chemo guidelines, that would be quite nice, Then when doctors look at our chemo guidelines they'd know which antifungal to prescribe for this particular chemo regimen. Some of our guidelines do have a statement saying antifungal required but not all of them have that. -Pharmacist_23

Table 2. Continued

Challenge	Opportunities/Solutions	Quote
Scope	Supporting an expanding immunocompromised outpatient population with frequent care transitions. -An expanded model of stewardship is a resource intensive proposition.	Q72 The BMT (bone marrow transplant) patients have 50% chance of readmission for management of various issues and will or will not be on antifungals for prophylaxis of treatment at the time, and so if we are doing any stewardship it should always have been across the whole thing, inpatient and outpatient. - Pharmacist_21 Q73 For the immunocompromised patients, they are so complex and challenging, that I don't think anyone would be confident to be giving a recommendation just by looking at a note and looking at a few labs. So there is the challenge of how to do AMS in complex immunocompromised host patients. And so, I think that's where we are at, at the moment, is thinking how do we best provide that sort of stewardship service across the spectrum of the patients but knowing that they need a bit more intensive time and sometimes we will often need review of the patient themselves. -ID Physician_13

Abbreviations: AFS, antifungal stewardship; AMS, antimicrobial stewardship; BMT, bone marrow transplant; ID, infectious diseases.

Diagnostic Delays and Uncertainties Are a Barrier to Rational Prescribing

Improving fungal diagnostics was seen as vital to effective stewardship by providing evidence for appropriate treatment, rather than resorting to inappropriate and costly empirical antifungal use (Q1–Q3). There was widespread frustration among treating clinicians regarding access to fiber optic bronchoscopy and the availability of rapid fungal diagnostics (Q3–Q6). Patient isolation added another level of complexity, compounding delays in diagnostic investigations, including medical imaging and bronchoscopy (Q7). Environmental factors including logistics (eg, theater turnaround times) or resources (eg, access capacity) was not the only barrier to invasive investigations, with patient-related factors (eg, acuity) also highlighted by the interdisciplinary team (Q8–Q10).

Competing Demands Exacerbated by System Inefficiencies and Poor Communication

Respiratory physicians raised several barriers to delivering a timely bronchoscopy service. These included late referrals, which made planning bronchoscopy lists difficult (Q10–Q12); a high elective bronchoscopy workload compared with other institutions, largely due to "an increasing number of lung transplants with extraordinary survival rates" (Respiratory Physician 14, Q13); with capacity further squeezed by system inefficiencies including long theatre changeover times between patients, exacerbated by theatre cleaning requirements for patients in isolation (Q12, Q14).

The responses from treating clinicians and the respiratory team highlighted a lack of mutual understanding and communication. Treating physicians are unaware as to why there are delays in bronchoscopy; respiratory physicians are unaware as to why the referrals come so late in the week. In response, respiratory physicians strongly advocated early referral and welcomed the opportunity to contribute their clinical expertise as "an opinion and some potential collaborative management advice" (Respiratory Physician 18), rather than only being perceived as proceduralists (Q10).

Tackling Complexity With Collective Decision Making, but With Blind Spots

A complex interplay of patient, treatment, and environmental factors (Q15, Q16) was frequently highlighted as a challenge for guideline adherence, rapid diagnosis (Q8, Q9, Q12), and appropriate prescribing (Q18–Q21). Guidelines were useful for junior prescribers unfamiliar with antifungal prophylaxis protocols (Q17) but had well recognized limitations (Q18–Q20). Antifungal prophylaxis was singled out for its incomplete evidence base and implications on management, especially when breakthrough IFD may be due to non-*Aspergillus* moulds (Q21, Q22). Patients "lingering on for years" (Pharmacist 21) with significant immunocompromise due to novel chemotherapies (Q23, Q24) presented a unique challenge due to limited antifungal prophylaxis options (Q25), especially in ambulatory care where stewardship was weak (Q23, Q26, Q27). The current inpatient-focused model did not address the needs of a growing population frequently transitioning between inpatient and ambulatory care settings (Q23, Q26, Q27). Many respondents noted that despite accessibility to ID, they were being underutilized, with some hematology teams failing to refer inpatients for consultation (Q28, Q29). Balancing patient- and population-level priorities was a perennial, but low-grade, tension between hematology and ID (Q30, Q31), who readily deferred to ID for antifungal management (Q32–Q36). Overseeing all of this was a culture of collective decision making among the interdisciplinary team, with ready access to ID, which was highly valued (Q32, Q33, Q36, Q37–Q41).

Ad Hoc Surveillance, Audit, and Feedback

All professional groups agreed that regular audit of antifungal practice was beneficial for better understanding local practice, trends, and clinical outcomes (Q42–Q44). In the absence of any formalized process, confusion prevailed as to whose responsibility it was (Q45–Q47). Antifungal drug costs and consumption were preferentially reported (Q48–Q50) because surveillance and audit of IFD are difficult to perform in practice (Q51, Q52). Respiratory physicians were interested in

understanding the risk-benefit associated with subjecting vulnerable sick patients to bronchoscopy (Q53, Q54). For radiologists, the need to improve reporting accuracy and efficiency was vitally important, given their high after-hours case load, where "close to 50% of our work is done after 5 pm" (Radiologist 4), and feedback was important because "then you are learning and improving" (Radiologist 6), but did not occur in practice (Q55, Q56).

Perceptions of Antifungal Stewardship and Strengthening an Existing Model

Respondents recognized that AFS is a multifaceted program that goes beyond "policing prescribing" to encompass risk assessment and diagnostics delivered in a culturally sensitive manner (Q57, Q58) (Table 2). A more systems-level approach to AFS was seen as the next phase (Q59, Q60), recognizing that the current model "has been looking more from a service provision rather than a population, quality program" (ID Physician 11), where antifungal practice has been "driven by individuals rather than by systems" (Hematologist 19). Perceptions of service provision were generally positive, which paradoxically served to dilute any additional perceived benefits of AFS. Some believed that AFS was informally operating at some level already, "our unit are pretty heavily involved … we give them a good service and there are lots of protocols and so forth. So I think there is AFS… It's already happening" (ID Physician 2), and "Better diagnostics is a big unmet need… I don't think we have a great problem with stewardship" (Hematologist 20). Integration with AMS was the preferred option, "either together or underneath the banner of AMS" (Pharmacist 22, Q61–Q63), and potentially less confusing to end-users (Q63), provided it was adequately resourced "because if everybody is trying to do it on top of their existing jobs, it's going to fall apart" (Pharmacist 26). Antifungal stewardship delivered by people with good interpersonal skills was important, because "if you've got a steward which maybe doesn't have the best skills with respect to communication or developing relationships with treating teams, that can run into trouble I think" (Hematologist 19, Q58). Concerns were raised among hematologists that AFS may result in additional bureaucracy: "I've no real desire to see more people walking around with clipboards, giving us work to do" (Hematologist 20) or onerously restrictive practices: "if it's going to sort of be didactic about what can't be used…. that aspect is generally sort of detrimental" (Hematologist 10, Q64). Threats to prescriber autonomy were noted by ID, who understood that hematologists "want to be able to maintain autonomy and maintain, not control, but maintain that relationship they have with the patient and for processes like AFS not to interfere with that relationship and not to interfere with their autonomy" (ID Physician 11). Again, respondents circled back to the weaknesses of the current referral-based model, but offered solutions to improve care (Q65–Q71) (Table 2) while recognizing the challenges ahead (Q72, Q73).

DISCUSSION

Navigating AFS in the high clinical stakes environment of the immunocompromised hematology population is complex and nuanced. The need for process change was dominant, with respondents zeroing in on improved diagnostic processes to guide prescribing; data-driven quality improvement that includes a growing ambulatory population and monitoring emerging fungal risks in response to microevolutionary changes in cancer treatment. Stakeholders knew the barriers and enablers of AFS, preferring integration of emergent AFS within established AMS as well as offering solutions for an achievable vision of timely quality care. Antifungal stewardship was perceived as multifaceted, going far beyond "policing prescribing" to encompass several interdependent and mutually reinforcing properties (ie, risk assessment, fungal diagnostics, data for action supported by formalized surveillance, audit, and feedback mechanisms) within a truly complex system. Although the underlying logic of a complex system is likely to be different across settings [24], the themes identified by stakeholders are universal.

Respondents identified opportunities for improvement within structural (guidelines), process (diagnostics, therapeutic drug monitoring, adherence, outpatients), and outcome (surveillance, audit, and feedback) measures that are common to both AMS [10] and AFS [4]. They believed that effective AFS needs to embrace the "whole package," with fungal diagnostics singled out as central to rational prescribing. However, improving access to bronchoscopy means dealing with system inefficiencies. These are compounded by late referrals and patient factors including isolation, which is a common scenario in immunocompromised patients that results in slow turnover between cases due to theatre cleaning requirements. In reality, the challenges of timely bronchoscopy, expansion of AFS to ambulatory care, and formal audit and feedback mechanisms each require dedicated redesign thinking to solve [25], but this must be addressed for meaningful process change to occur.

Surveillance, audit, and feedback of antifungal practice and outcomes was ad hoc, with confusion rife among ID, pharmacy, and hematology regarding whose responsibility this was. The difficulties of IFD surveillance and clinical audit meant that the reasons behind fluctuations in antifungal usage were hidden, with antifungal drug costs becoming the default barometer for AFS, corroborating a recent systematic review of hospital-based AFS program [3]. As a result, the strong motivation to use data for action went unfulfilled, with concerns raised about missing emerging fungal threats and tightening antifungal practice (ie, through de-escalation, therapeutic drug monitoring, adherence) in an ambulatory population who were "exhausted and near palliative for years." For surveillance and audit of invasive mold diseases, our use of machine learning of chest imaging has facilitated a clearer understanding of our outcomes and gaps in practice at a population level [16], with prospective multicenter validation underway (ClinicalTrials.gov NCT03793231).

However, although audit and feedback are key behavior change techniques, they are only moderately effective unless combined with goal setting and action planning [26], pointing to synergistic interventions that should be considered for effective and enduring AFS.

The overarching principle of AMS—to optimize patient outcomes through judicious use of antimicrobials—also holds for AFS, but with distinct differences compared with antibiotics. Where the antibiotic stewardship model is typically ID providing remote advice, away from the bedside, this is not true for complex immunocompromised patients. Our embedded model of stewardship includes bedside ID advice, ID attendance at weekly hematology unit meetings, and activities that promote collaboration, including guideline development and research. Opportunities for interaction have built positive working relationships aided by open communication channels that are now regarded as a core competency in AMS [27]. Although the locus of control in antibiotic stewardship rests with the individual prescriber [28], for antifungals it is more distributed, with collective decision making the norm.

Hierarchy and ritual are well recognized cognitive barriers that are difficult to overcome in antibiotic stewardship [14, 29]. However, these were muted by several factors. A lack of self-efficacy (ie, the belief that one can perform a behavior [30]) due to a lack of knowledge/skills actually became an enabler to AFS because hematology and pharmacy willingly deferred to ID for advice. This on-demand access to ID expertise offset mixed perceptions towards guidelines, reducing inappropriate prescribing driven by fear of negative outcomes and/or diagnostic uncertainty expressed by several hematologists. The perennial tension of patient- versus population-level priorities (where the immediacy of treating a sick patient is balanced against the ecological impact of broad-spectrum antimicrobials) was raised by ID and hematology, but was not seen as a barrier to AFS.

The main limitation of this study is that it was conducted at a single center and focused on the hematology unit. Context-specific local and national factors, such as a high lung transplant caseload and a national formulary that covers the costs of antifungal medications for Australian residents, limit generalizability. However, the dominant themes around fungal diagnostics, ad hoc clinical audit, outpatient coverage, and care transitions are likely to resonate. A strength of this study is the participatory approach from a large and diverse professional group with senior and junior voices, using a one-to-one interview strategy that minimized the social influence effects of focus groups or Delphi-like surveys.

CONCLUSIONS

Incorporating the needs and perspectives of stakeholders is important for successful AFS, noting that this step builds upon this step builds upon collective decision making, positive team dynamics, and an appetite for improvement. Antimicrobial stewardship interventions that integrate the behavioral sciences, including context and needs analysis, codesign with stakeholders, and iterative implementation cycles [31], are also relevant to AFS and best activated early as we have done. The next challenge will be implementing theory-informed interventions that address the priorities raised by stakeholders within this complex fluid environment.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Table 1. Subthemes mapped to barriers and enablers in the COM-B domain.

Supplementary Appendix 1. Interview Questions.

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