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Short Report

Bronchoalveolar lavage to evaluate new pulmonary infiltrates in allogeneic hematopoietic stem cell transplant recipients: impact on antimicrobial optimization

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SUMMARY

Background: Pulmonary complications cause significant morbidity and mortality after allogeneic hematopoietic stem cell transplant (AHSCT). Bronchoscopy with targeted bronchoalveolar lavage (BAL) is often used in AHSCT patients with suspected lower respiratory tract infection (LRTI) to help guide management.
Aim: To evaluate how positive BAL results change antimicrobial management of AHSCT recipients with suspected LRTI.
Methods: We performed a retrospective review of BAL results from January 2014 to July 2016 for 54 AHSCT recipients. A positive BAL was determined by culture, multiplex polymerase chain reaction (PCR), *Aspergillus* galactomannan antigen (AGA), and cytology.
Findings: BAL was positive for infectious etiologies in 63%, and antimicrobials were adjusted in 48/54 (89%) of patients. Antibacterial escalation was predicted by a positive BAL bacterial culture (OR 7.61, P=0.017). Antibiotic de-escalation was more likely with an elevated AGA (OR 3.86, P=0.035). Antiviral initiation was more likely with positive BAL multiplex PCR (OR 17.33, P=0.010). Antifungals were more likely to be escalated or

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changed with an elevated AGA (OR 4.33, P=0.020). The patients with a negative BAL were more likely to be started on steroids (OR 0.19, P= 0.043).

Conclusions: BAL was helpful to determine the etiology of pulmonary complications and optimize antimicrobials. The addition of AGA and multiplex PCR to standard BAL significantly impacted de-escalating antibiotics and adjusting antifungals to provide adequate coverage. The association with an elevated AGA with antibacterial de-escalation highlights a new role for BAL in antimicrobial optimization.

Introduction

Bronchoscopy with bronchoalveolar lavage (BAL) is an important diagnostic tool to evaluate AHSCT recipients with new pulmonary infiltrates or without clinical response to empiric therapy [1,2]. Its utility is dependent on culture and molecular diagnostic results and the capability of changing medical management [3]. In studies prior to the availability of polymerase chain reaction (PCR), antibiotics were withdrawn in up to 50% of AHSCT recipients [4,5]. This study aims to determine how *Aspergillus* galactomannan antigen (AGA) and multiplex PCR added to traditional BAL testing affects antimicrobial treatment in AHSCT recipients with new pulmonary infiltrates.

Methods

The first BAL completed after AHSCT in patients over age 18 between January 2014 and July 2016 at the authors' institution were included. The decision to perform a BAL was at the discretion of the attending physician caring for the patient. BAL fluid was submitted for gram stain, bacterial, mycobacterial and fungal cultures, multiplex PCR, AGA, and cytopathology. This study was approved by Virginia Commonwealth University's Institutional Review Board.

A positive BAL was defined by a positive culture, multiplex PCR, elevated AGA (optic density (OD) >0.49), and/or cytology (which includes detection of *Pneumocystis jirovecii*). A positive bacterial culture required species isolation, excluding coagulase-negative *Staphylococcus* and mixed respiratory flora. A positive fungal culture required the presence of fungal colonies, except non-cryptococcus yeast. The multiplex PCR used was the commercial kit BioFire FilmArray® that can detect adenovirus, coronavirus, human metapneumovirus, human rhinovirus/enterovirus, influenzae A, influenzae B, parainfluenza (subtypes 1−4), respiratory syncytial virus (RSV), *Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae*. Diffuse alveolar hemorrhage (DAH) was diagnosed per guidelines [6]. A change in management was defined by escalation or de-escalation of antibiotics, antifungals, or antivirals, adaptation of antifungals, or initiation of prednisone within 7 days after BAL since this is the time interval to obtain AGA results at the authors' institution. De-escalation was defined as cessation of one or multiple agents, conversion to oral therapy, or transition to a more narrow spectrum. Escalation was defined as adding a new antimicrobial agent or transitioning to a broader spectrum. Fungal adaptation was a transition to an alternative agent within the same class of antifungals. Antimicrobial use within 7 days of BAL was considered prior therapy.

AHSCT was performed on the Bone Marrow Transplant Unit at the authors' institution. The conditioning regimen, immunosuppressive, and supportive therapies followed internationally accepted protocols. Levofloxacin and fluconazole were used as anti-infective prophylaxis and prophylaxis for cytomegalovirus (CMV) and *Pneumocystis jirovecii* pneumonia were used according to guidelines [7].

A descriptive analysis performed using medians and interquartile ranges (IQR) for continuous variables due to non-normal distributions and frequencies and percentages for categorical variables. We used a Fisher's exact test to compare categorical variables and ANOVA for continuous variables. A P-value of less than 0.05 was considered statistically significant. All analysis was performed using JMP Pro 12 [SAS Institute, Cary, NC, USA].

Results

BAL was performed in 120 AHSCT recipients during the study period. 66 procedures were excluded for patient age<18 (n=1), subsequent procedures on the same patient (n=34), and BAL performed before transplant (n=31). 54 patients who had a BAL after AHSCT were included.

Patient demographics, antimicrobials at bronchoscopy, and BAL results are described in Table I. Most antimicrobial therapy was started within two days (n=11) or over 7 days (n=18) before BAL. Eleven patients were not receiving antimicrobials. BAL was positive for infectious etiologies in 63%, mostly with elevated AGA (17/54), followed by multiplex PCR (13/54), positive bacterial (8/54), fungal (4/54) and AFB culture (1/54). None of the patients with a positive bacterial culture were on levofloxacin prophylaxis. Of the patients with a positive fungal result, 14/17 were on antifungal prophylaxis. Only 2/17 patients with a positive BAL AGA also had a positive serum AGA. All of the positive multiplex PCR were for viruses. Nine patients had multiple infectious etiologies, all with a positive multiplex PCR. Twenty-eight patients had concomitant non-pulmonary infections. No patients were found to have *Pneumocystis jirovecicii*, *Legionella*, or *Cryptococcus* by cytology or antigen testing.

Antimicrobials were adjusted in 48/54 (89%) of patients (Table II). Overall antibiotic escalation occurred in 19/54, and was associated with a positive BAL bacterial culture (OR 7.61, P=0.017) (Table II). Antibiotic de-escalation was more likely with an elevated AGA (OR 3.86, P=0.035) (Table II). Antiviral initiation was more likely with positive BAL multiplex PCR (OR 17.33, P=0.010) (Table II). Antifungals were more likely to be escalated or changed with an elevated AGA (OR 4.33, P=0.020) (Table II). The patients with a negative BAL were more likely to be started on steroids (OR 0.19, P= 0.043).

Table I
Patient characteristics summarized by frequencies and percentages or medians and interquartile range (n=54)

Characteristic	
Transplant	
Preceding autologous SCT	4 (7%)
AHSCT	
Related	16 (30%)
Unrelated	38 (70%)
Hematologic Disease	
AML	14 (26%)
MDS/Myelofibrosis	13 (24%)
ALL	8 (15%)
CML	6 (11%)
Non-Hodgkin Lymphoma	6 (11%)
CLL	1 (2%)
Other	6 (11%)
Months since AHSCT	3.5 (1–9.25)
Prior GVHD requiring treatment	24 (44%)
Current GVHD Treatment	37 (69%)
Immunosuppression at BAL	
Tacrolimus	26 (49%)
Prednisone	21 (39%)
Cyclosporine	9 (7%)
Sirolimus	4 (7%)
Neutrophil <1000 (cells/μL)	18 (33%)
Age at Bronchoscopy (years)	56.2 (41.1–62.9)
O2 requirement (L/min)	32 (59%)
Mechanical Ventilation	4 (8%)
Antimicrobial prophylaxis at time of bronchoscopy	
Cytomegalovirus prophylaxis	51 (94%)
Pneumocystis jirovecii prophylaxis	27 (50%)
Bactrim	4 (8%)
Atovaquone	5 (9%)
Pentamidine	18 (34%)
Fungal prophylaxis	43 (80%)
Voriconazole	21 (39%)
Fluconazole	12 (22%)
Micafungin	7 (13%)
Posaconazole	3 (6%)
Levofloxacin prophylaxis	16 (30%)
Antimicrobials at bronchoscopy	43 (80%)
No antimicrobials	11 (20%)
Antibacterials	40 (74%)
Vancomycin	22 (41%)
Meropenem	15 (28%)
Cefepime	14 (26%)
Levofloxacin	7 (13%)
Other	8 (15%)
Antifungal	26 (48%)
Micafungin	10 (18%)
Voriconazole	10 (18%)
Posaconazole	4 (7%)
Amphotericin B	2 (4%)
Antiviral	8 (15%)
Ribavirin	3 (5%)
Foscarnet	2 (4%)
Tamiflu	1 (2%)
Ganciclovir	1 (2%)
Cidofovir	1 (2%)
Duration of antimicrobials prior to BAL	
0 days	11 (20%)
1–2 days	11 (20%)
3–4 days	8 (15%)
5–7 days	7 (13%)
>7 days	18 (33%)
Nasopharyngeal PCR Testing (n=46)	
Positive	12 (26%)
Influenzae	2 (4%)
Parainfluenza	3 (7%)
Rhinovirus/enterovirus	2 (4%)
RSV	4 (9%)
RSV + rhinovirus/enterovirus	1 (2%)
Negative	22 (48%)
Serum AGA >0.49	2 (4%)
Overall BAL results[a]	
Positive	34 (63%)
Bacterial Culture	8 (15%)
Fungal Culture	4 (8%)
Fungal hyphae on cytology	6 (11%)
AGA >0.49	17 (31%)
Viral multiplex PCR	13 (24%)
AFB Culture	1 (2%)
CMV on cytology	2 (4%)
DAH	2 (4%)
Negative	20 (37%)
Culture Results	
Bacterial culture	8 (15%)
Pseudomonas aeruginosa	2 (4%)
Haemophilus influenzae	1 (2%)
Stenotrophomonas maltophilia	1 (2%)
MRSA	1 (2%)
VRE	1 (2%)
Nocardia nova complex	1 (2%)
Streptococcus agalactiae	1 (2%)
Fungal culture	4 (8%)
Aspergillus fumigatus	2 (4%)
Rhizomucor spp.	1 (2%)
One fungal colony	1 (2%)
AFB culture	
Mycobacterium avium complex	1 (2%)
Viral multiplex PCR	
Positive	13 (24%)
Influenzae	2 (4%)
Parainfluenza	4 (8%)
Rhinovirus/enterovirus	4 (8%)

(*continued on next page*)

Table I (*continued*)

Characteristic	
RSV	4 (8%)
Multiple Pulmonary Infections	9 (17%)
Bacterial + viral	2 (4%)
Viral + AGA	7 (13%)

SCT = stem cell transplant, AHSCT = Allogeneic hematopoietic stem cell transplant, AML =acute myeloid leukemia, MDS =myelodysplastic syndrome, ALL = acute lymphoid leukemia, CML = chronic myeloid leukemia, CLL = chronic myeloid leukemia; GVHD = graft versus host disease, BAL = bronchoalveolar lavage, O2 = oxygen, AGA = *Aspergillus* galactomannan antigen, PCR = polymerase chain reaction, DAH = diffuse alveolar hemorrhage, AFB = acid-fast bacilli, RSV = respiratory syncytial virus, CMV = cytomegalovirus.

[a] Patients had multiple results on BAL.

Discussion

BAL was helpful to determine the etiology of pulmonary complications and optimize antimicrobials. This included escalating antibiotics to target organisms that were isolated. We believe it changes practice as BAL is not only valuable when results are positive, but when an aggregate negative BAL work up offers assurance for providers to address noninfectious etiologies. This is critical in intensive care settings when anti-inflammatory therapy, such as high dose steroids, tumor necrosis factor inhibitors, or T-cell depleting agents are considered for pulmonary graft versus host disease, with suspected superimposed infection. Only 5 patients required initiation of targeted therapy for a microorganism isolated on bacterial culture that was not previously covered, including virulent organisms such as *Nocardia nova complex, Pseudomonas aeruginosa, Haemophilis influenzae, and Stentrophomonas maltophilia*. Antibiotics were also escalated due to severity of illness despite negative culture data (n=8) and to cover an alternative infection (n=6), such as endocarditis. Likely the use of antimicrobial prophylaxis effectively limited bacterial infections due to susceptible organisms, but may have added to the selection of more resistant bacteria such as *Stenotrophomonas* and *Nocardia spp*.

BAL was critical to recognize and treat invasive fungal infections, prompting antifungal escalation in 33% and initiation of targeted treatment for isolated *Rhizomucor spp*. Only two of the patients with an elevated BAL AGA also had an elevated serum AGA. BAL assisted in the diagnosis of these infections. This finding is important in that delays in treatment carry the potential for increased mortality [8]. This is recognized in the 2019 American Thoracic Society guidelines, which suggest moving to BAL AGA and requesting BAL Aspergillus PCR when serum AGA is negative. At a cutoff of 0.5, the serum AGA sensitivity is approximately 74—88% and at 1.0, it is 79—88%. At a cutoff of 1.5, sensitivity reduces to 59% and specificity increases to 95%. For BAL AGA with a cutoff of 1.0, the sensitivity and specificity increases to 90% and 94% respectively [9]. In addition, *Aspergillus spp*. accounts for only 70% of invasive fungal infections in AHSCT, and the remaining 30% includes deadly pathogens including zygomycetes (6—8%), fusarium (6—7% in USA), dematiaceous, and other rare molds that may

Table II

Change in management associated with specific bronchoalveolar lavage results. Antimicrobials were adjusted in 48/54 (89%) of patients. Positive etiologies for bacteria, *Aspergillus spp* and virus determined by culture results, multiplex viral polymerase chain reaction and *Aspergillus* galactomannan antigen testing >0.49. (n=54).

Positive BAL result (N)	Outcome	N[a]	OR (95% CI)	*P* Value
Overall (35/54 positive)	Escalation/Addition Antibiotics	19/54	2.10 (0.62, 7.12)	0.257
	De-escalation Antibiotics	20/54	2.37 (0.70, 8.00)	0.245
	Escalation/Addition Antifungals	18/54	2.80 (0.77, 10.18)	0.142
	Adaptation Antifungals	5/54	2.53 (0.26, 24.41)	0.641
	De-escalation Antifungals	5/54	0.35 (0.05, 2.33)	0.347
	Steroid initiation	7/54	**0.19 (0.03, 1.08)**	**0.043**
Bacterial (8/54)	Escalation/Addition Antibiotics	6/8	**7.61 (1.36, 42.71)**	**0.017**
	De-Escalation Antibiotics	1/8	0.20 (0.02, 1.79)	0.234
	Escalation/Adaptation Antifungal	1/8	0.17 (0.02, 1.50)	0.122
	De-escalation Antifungal	1/8	1.5 (0.14, 15.46)	0.567
	Escalation/Addition Antiviral	0/8	0	1.000
Aspergillus/AGA (17/54)	Escalation/Addition Antibiotics	5/17	0.68 (0.20, 2.36)	0.760
	De-Escalation Antibiotics	10/17	**3.86 (1.15, 12.90)**	**0.035**
	Escalation/Adaptation Antifungal	11/17	**4.33 (1.28, 14.67)**	**0.020**
	De-escalation Antifungal	0/17	0	0.168
	Escalation/Addition Antiviral	3/17	3.54 (0.53, 23.53)	0.315
Viral (13/54)	Escalation/Addition Antibiotics	7/13	2.82 (0.78, 10.15)	0.181
	De-Escalation Antibiotics	5/13	1.08 (0.30, 3.92)	1.000
	Escalation/Adaptation Antifungal	6/13	1.34 (0.38, 4.71)	0.750
	De-escalation Antifungal	1/13	0.77 (0.08, 7.58)	1.000
	Escalation/Addition Antiviral	4/13	**17.33 (1.72, 174.29)**	**0.010**

BAL = bronchoalveolar lavage, AGA = *Aspergillus* galactomannan antigen.

The bolded areas represent statistically significant p values <0.05.

[a] Number of patients with each outcome out of those with the same etiology on BAL. These were the numbers used to develop odds ratios.

require culture or tissue biopsy diagnosis. Endemic mycoses only account for 1% of invasive fungal infections in AHSCT and may be amenable to serologic or antigen testing without invasive procedures [8].

A positive multiplex PCR was associated with antiviral initiation (ribavirin for parainfluenza or peramivir for influenzae), (Table II). However, the results were similar on nasopharyngeal and BAL multiplex PCR, as noted in prior studies [10]. It is unclear if this multiplex PCR test is adequate for diagnosing LRTI and more studies will need to be done to evaluate this. BAL remained necessary to detect coinfections, as 9/13 patients with a positive multiplex PCR also had a positive bacterial culture (n=2) or elevated AGA (n=7) (Table I). Reports of viral and bacterial coinfection, particularly with adenovirus or rhinovirus have been associated with higher morbidity/mortality but the understanding of this is limited [11,12]. It would be interesting to further investigate with larger studies the effect of viral illnesses on bacterial or fungal coinfections and how they affect treatment outcomes to determine if these more aggressive prophylaxis and diagnostic testing would benefit these patients.

BAL also had a major role in antimicrobial de-escalation. Antibiotics were either stopped or converted to oral in 20 patients with a negative BAL bacterial culture. An elevated AGA was predictive of antibiotic de-escalation (Table II), which highlights a new role for BAL in antibiotic optimization [13].

A negative BAL was associated with initiation of steroids for treatment of other conditions including graft versus host disease, pneumonitis, DAH, and complications of engraftment (Table II). Even though the BAL did not aid in these diagnosis (except DAH), it mitigated the risk of starting steroids by lowering suspicion for pulmonary infections.

Study limitations include potential selection bias (only patients who had a BAL were included) and the fact our results are from a single hospital. BAL was performed at the discretion of the attending physician, and therefore the patient group only includes those deemed eligible for the procedure, which was likely urged by clinical status. A control group comparison (with or without available sputum cultures, nasal multiplex respiratory pathogen panel, serum AGA and fungal urine antigen testing) would be likely biased to include those who were deemed less sick as well as those considered too high risk to be eligible for bronchoscopy, due to high oxygen requirement or bleeding risk. It would be unethical to randomly assign patients to bronchoalveolar lavage due to known risks and benefits. Additional studies across multiple hospitals would be valuable to confirm our results. A multivariate regression analysis could not be performed due to low sample size.

In summary, our study found that BAL is a beneficial diagnostic tool to evaluate new pulmonary infiltrates in AHSCT recipients. BAL permitted targeted antimicrobial treatment and positively affected antimicrobial de-escalation and guided management of non-infectious diagnostic considerations. These data will inform local antimicrobial stewardship efforts. Additional studies are needed to confirm our findings and to identify how BAL can be used to improve antimicrobial prescribing.

Conflicts of interest

The authors declare that they have no conflict of interest or financial disclosures.

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