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Antimicrobial Prophylaxis in Lymphoma by Chemotherapy Regimen

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Abstract

Treatment of lymphomas involves a wide variety of chemotherapy, immunotherapy, and targeted-agents tailored to disease biology and patient characteristics. Each of these regimens carry their own risk of opportunistic infections in an immunocompromised population. In addition to the treatment associated immunosuppression, lymphoma itself is immunosuppressive. Lymphoma associated immunosuppression is secondary to increased production of abnormal lymphocytes resulting in decreased production of normally functioning lymphocytes. Additionally, lymphoma cells induce both humoral and cellular immunosuppression through effects on numerous cytokines, T-cells, myeloid-derived suppressor cells, and macrophages. Clinical trials, patient co-morbidities, and institutional preferences all play a role in determining the preferred antimicrobial prophylaxis. While there is a paucity of data on systematic reviews and guidelines for standardized chemotherapy regimens in lymphoma patients, the efficacy and recommendations for antimicrobial prophylaxis in specific chemotherapy regimens for lymphoma has not been fully reviewed. According to the National Comprehensive Cancer Network, lymphoma is generally regarded as an 'intermediate risk' cancer with regards to overall infection risk. This results in discordance between research data and clinical practice. This is reiterated in the SIGNIFICANT trial which reported that while guidelines previously advised against fluoroquinolone prophylaxis in lymphoma and solid cancers, a survey of 3,600 physicians revealed that 45% routinely used fluoroquinolone prophylaxis despite these recommendations. This review article analyzes numerous research studies with summarization of findings and antimicrobial prophylaxis recommendations based on specific lymphoma chemotherapy regimens. With regards to each specific chemotherapy regimen assessed, indications for anti-bacterial, anti-viral, anti-fungal, and *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis were determined for each regimen. The degree of immunosuppression and the necessary prophylaxis varies across different regimens and lymphoma subgroups; and thus, an individualized approach is necessary to optimize the supportive care during lymphoma treatment.

Keywords: Cancer immunology, Lymphoma, Non-Hodgkin's lymphoma (NHL), Antimicrobial prophylaxis, Anti-bacterial, Anti-viral, Anti-fungal, Pneumocystis jiroveci pneumonia (PJP), Infection, Chemotherapy

Introduction

Due to the immunosuppression associated with malignancy treatment, infection reigns as one of the largest culprits of cancer-related deaths [1]. Of all cancer-related deaths, studies have found that approximately 60% of these are infection-related or directly caused by infections [1]. Rates of infection-related deaths are higher in hematologic malignancies compared to solid tumors [1]. The mortality rate of fatal infections in patients with malignancy occurs in approximately 260/100,000 persons per year, three times that of the general population [1]. With the large numbers of infection-related deaths in patients with malignancy, focus on infection prevention remains a vital role of cancer management. With

improvements in infection prophylaxis, the mortality rates of fatal infections in cancer patients have decreased in recent decades [1].

Infection prevention in cancer patients is aimed at prevention of conventional and opportunistic infections in four major infectious categories: bacterial infections, viral infections, fungal infections, and PJP. These infections can occur within the context of febrile neutropenia (FN), which presents additional management considerations and increases risk of morbidity and mortality. Neutropenia is defined as an absolute neutrophil count (ANC) ≤ 1500/mm^3, with severe neutropenia being defined as an ANC ≤ 500/mm^3 [2,3]. In FN, fever is defined as a single temperature measurement ≥ 38.3°C (101.0°F) or a temperature of ≥ 38.0°C (100.4°F) for ≥ one hour duration. With FN being one of the most serious adverse events in malignancy with risk of life-threatening complications, prevention of FN is fundamental in cancer management [2,3]. This primary prevention is achieved with prophylactic antimicrobial agents targeting each of these types of infections. Recommendations regarding when prophylactic antimicrobial agents are indicated vary depending on cancer type and treatment regimen used.

Generally, the overall risk of infection in patients with cancer is classified into 'low risk', 'intermediate risk', and 'high risk' depending on the type of cancer and treatment regimen used. These classifications commonly guide when antimicrobial prophylaxis is indicated. Patients classified as 'low risk' typically have anticipated neutropenia ≤ 7 days duration and classically do not require routine antimicrobial prophylaxis [4]. Patients classified as 'intermediate risk' typically have anticipated neutropenia between 7-10 days duration and indications for antimicrobial prophylaxis is controversial [4,5]. Patients classified as 'high risk' typically have anticipated neutropenia ≥ 10 days duration and generally require antimicrobial prophylaxis [4,5]. Examples of scenarios classified as 'high risk' include acute leukemia, moderate to severe graft versus host disease, and patients undergoing allogeneic hematopoietic cell transplantation [4,5]. The ambiguity with regards to antimicrobial indications in patients classified as 'intermediate risk' poses the greatest need for further research to guide recommendations in clinical practice.

Prior to the SIGNIFICANT trial in 2005, research on the role of antimicrobial prophylaxis in hematologic malignancies was primarily studied regarding leukemia, with less research tailored towards lymphoma. While the SIGNIFICANT trial addressed antibiotic prophylaxis in non-Hodgkin's lymphoma (NHL), a majority (90.7%) of the patients studied received cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) [6]. Although CHOP is a commonly used chemotherapy regimen in NHL, many other regimens are used in clinical practice. There are several studies referencing antimicrobial prophylaxis across lymphoma chemotherapy regimens, though a concise review that evaluates the use of all antimicrobial prophylaxis (anti-bacterial, anti-viral, anti-fungal, and PJP prophylaxis) in specific chemotherapy regimens has yet to be conducted. Antimicrobial prophylaxis that is tailored to the specific lymphoma regimen is critical for clinicians to be mindful of to improve the overall management of these patients.

In this review article, eight commonly used chemotherapy regimens in the treatment of lymphoma were addressed with regards to their differing risks of developing bacterial, viral, fungal, and PJP infections. The chemotherapy regimens assessed in this review article include: R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone), BR (bendamustine, rituximab), AVD (doxorubicin, vinblastine, dacarbazine) containing chemotherapy, P-R-CHP (polatuzumab vedotin + rituximab + cyclophosphamide, doxorubicin, prednisone), HD MTX (high-dose methotrexate), Hyper-CVAD/MTX-Ara-C (cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine), RICE (rituximab, ifosfamide, carboplatin, etoposide), and bispecific antibodies. Examples of AVD containing chemotherapies assessed include: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), BV + AVD (brentuximab vedotin + doxorubicin, vinblastine, dacarbazine), and N + AVD (nivolumab + doxorubicin, vinblastine, dacarbazine). With regards to these chemotherapy regimens addressed, the specific drug targets of each chemotherapy agent can be referenced in **Table 1**. Additionally, the reported two-year progression-free survival (PFS) for each chemotherapy regimen can be referenced in **Table 2**.

General prophylaxis indications and duration of antimicrobial therapy can be referenced in **Table 3**. Assuming no definite contraindications, the preferred first-line antimicrobial prophylactic agents are: levofloxacin 500 mg or 750 mg daily for anti-bacterial prophylaxis, acyclovir 400 mg twice daily for anti-viral prophylaxis, fluconazole 400 mg daily for anti-fungal prophylaxis, and trimethoprim-sulfamethoxazole (TMP-SMX) 1 double strength (800 mg/160 mg) tablet three times weekly for PJP prophylaxis.

R-CHOP (Rituximab + Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)

With regards to the management of NHL, R-CHOP is one of the more commonly used chemotherapy regimens. The addition of rituximab, an anti-CD20 monoclonal antibody, has been shown to markedly enhance the efficacy of chemotherapy in NHL treatment and thus, is commonly included as a front-line treatment agent for B-cell NHL [7]. The use of rituximab has been shown to prolong the time to disease progression and extend overall survival in follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, marginal zone lymphoma, and Burkitt lymphoma [7]. Rituximab leads to

Table 1. Drug targets of chemotherapy regimens used in lymphoma.

Chemotherapy Regimen:	Chemotherapy Drug Targets:
R-CHOP	**Rituximab (R):** Antibody against CD20 [7] **Cyclophosphamide (C):** Inhibition of DNA replication, induction of programmed cell death [57] **Doxorubicin (O):** Free radical formation, cell membrane disruption, drug-intercalation into DNA [58] **Prednisone (P):** Programmed cell death in certain lymphoid cell populations [59]
BR	**Bendamustine (B):** Inhibition of DNA repair, induction of cell death [25] **Rituximab (R):** Antibody against CD20 [7]
AVD containing chemotherapy ABVD BV + AVD N + AVD	**Doxorubicin (A):** Free radical formation, cell membrane disruption, and drug-intercalation into DNA [58] **Vinblastine (V):** Depolymerization of microtubules [60] **Dacarbazine (D):** Inhibition of DNA, RNA, and protein synthesis [61] **Bleomycin (B):** Induction of DNA strand breaks leading to inhibition of cell replication [62] **Brentuximab Vedotin (BV):** Antibody against CD30 [36] **Nivolumab (N):** Inhibition of PD-1 [63]
P-R-CHP	**Polatuzumab Vedotin (P):** Antibody against CD79B [43] **Rituximab (R):** Antibody against CD20 [7] **Cyclophosphamide (C):** Inhibition of DNA replication, induction of programmed cell death [57] **Doxorubicin (H):** Free radical formation, cell membrane disruption, drug-intercalation into DNA [58] **Prednisone (P):** Programmed cell death in certain lymphoid cell populations [59]
HD MTX	**Methotrexate (MTX):** Disruption of folate-related enzymes leading to inhibition of cell division [64]
Hyper-CVAD/MTX-Ara-C	**Cyclophosphamide (C):** Inhibition of DNA replication, induction of programmed cell death [57] **Vincristine (V):** Inhibition of microtubule formation [65] **Doxorubicin (A):** Free radical formation, cell membrane disruption, drug-intercalation into DNA [58] **Dexamethasone (D):** Programmed cell death in certain lymphoid cell populations [59] **Methotrexate (MTX):** Disruption of folate-related enzymes leading to inhibition of cell division [64] **Cytarabine (Ara-C):** Integration into DNA disrupting DNA replication [66]
RICE	**Rituximab (R):** Antibody against CD20 [7] **Ifosfamide (I):** Induction of apoptosis, upregulation of reactive oxygen species leading to DNA damage and cessation of protein formation [67] **Carboplatin (C):** Cross linking of DNA strands leading to inhibition of DNA, RNA, and protein synthesis [68] **Etoposide (E):** Inhibition of topoisomerase II leading to inhibition of DNA re-ligation [69]
Bispecific Antibodies	**Bispecific Antibodies:** Antibodies against CD20 and CD3 [52]

R-CHOP: Rituximab + Cyclophosphamide, Doxorubicin, Vincristine, Prednisone); BR: Bendamustine, Rituximab; AVD: Doxorubicin, Vinblastine, Dacarbazine); ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine), BV: Brentuximab Vedotin; N: Nivolumab; PD-1: Programmed Cell Death Protein 1; P-R-CHP: Polatuzumab vedotin + Rituximab + Cyclophosphamide, Doxorubicin, Prednisone; HD MTX: High-Dose Methotrexate); Hyper-CVAD/MTX-Ara-C: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone/Methotrexate, Cytarabine; RICE: Rituximab, Ifosfamide, Carboplatin, Etoposide

Table 2. Two-year progression-free survival (PFS) rates by chemotherapy regimen in lymphoma.

Chemotherapy Regimen:	Two-Year Progression-Free Survival (PFS):
R-CHOP	70.2% [a] [44]
BR	87.0% [b] [70]
AVD containing chemotherapy ABVD BV + AVD N + AVD	 77.2% [c] [36] 82.1% [c] [36] 98.0% [d] [71]
P-R-CHP	76.7% [a] [44]
HD MTX	55.0% [e] [72]
Hyper-CVAD/MTX-Ara-C	82.0% [f] [73]
RICE	54.0% [g] [74]
Bispecific Antibodies	75.9% [h] [75]

[a] Previously untreated intermediate-risk or high-risk DLBCL

[b] Frontline treatment for advanced-stage follicular lymphoma

[c] Previously untreated stage 3 or 4 classic Hodgkin's lymphoma

[d] Frontline treatment for classic Hodgkin's lymphoma

[e] Induction treatment for primary CNS lymphoma

[f] Frontline treatment for mantle cell lymphoma

[g] PFS after second-line treatment with RICE followed by ASCT for relapsed or primary refractory DLBCL

[h] PFS for mosunetuzumab monotherapy in patients with follicular lymphoma

PFS: Progression-Free Survival; R-CHOP: Rituximab + Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; BR: Bendamustine, rituximab; AVD: Doxorubicin, Vinblastine, Dacarbazine; ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine; BV: Brentuximab Vedotin; N: Nivolumab; PD-1: Programmed Cell Death Protein 1; P-R-CHP: Polatuzumab Vedotin + Rituximab + Cyclophosphamide, Doxorubicin, Prednisone; HD MTX: High-Dose Methotrexate; Hyper-CVAD/MTX-Ara-C: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone/ Methotrexate, Cytarabine; RICE: Rituximab, Ifosfamide, Carboplatin, Etoposide; DLBCL: Diffuse Large B-cell Lymphoma; ASCT: Autologous Stem Cell Transplantation

Table 3. Antimicrobial prophylaxis indications and duration based on chemotherapy regimen.

Chemotherapy Regimen:	Prophylaxis Recommendations:	First-Line Prophylaxis Regimens:	Prophylaxis Duration:
R-CHOP	Anti-Bacterial: **High-risk only** [a] Anti-Viral: **YES** Anti-Fungal: **NO** PJP: **High-risk only** [b]	Anti-Bacterial: **Levofloxacin** Anti-Viral: **Acyclovir** Anti-Fungal: **---** PJP: **TMP-SMX**	Anti-Bacterial: **Seven days post-chemotherapy** Anti-Viral: **Throughout all chemotherapy cycles** Anti-Fungal: **---** PJP: **Throughout all chemotherapy cycles**
BR	Anti-Bacterial: **NO** Anti-Viral: **YES** Anti-Fungal: **NO** PJP: **YES**	Anti-Bacterial: **---** Anti-Viral: **Acyclovir** Anti-Fungal: **---** PJP: **TMP-SMX**	Anti-Bacterial: **---** Anti-Viral: **While CD4 count is ≤ 200/µl** [c] Anti-Fungal: **---** PJP: **While CD4 count is ≤ 200/µl** [c]

AVD containing chemotherapy [d]	Anti-Bacterial: **NO** Anti-Viral: **NO** Anti-Fungal: **NO** PJP: **NO**	Anti-Bacterial: **---** Anti-Viral: **---** Anti-Fungal: **---** PJP: **---**	Anti-Bacterial: **---** Anti-Viral: **---** Anti-Fungal: **---** PJP: **---**
P-R-CHP	Anti-Bacterial: **NO** Anti-Viral: **YES** Anti-Fungal: **NO** PJP: **YES**	Anti-Bacterial: **---** Anti-Viral: **Acyclovir** Anti-Fungal: **---** PJP: **TMP-SMX**	Anti-Bacterial: **---** Anti-Viral: **Throughout all chemotherapy cycles** Anti-Fungal: **---** PJP: **Throughout all chemotherapy cycles**
HD MTX	Anti-Bacterial: **NO** Anti-Viral: **YES** Anti-Fungal: **NO** PJP: **YES**	Anti-Bacterial: **---** Anti-Viral: **Acyclovir** Anti-Fungal: **---** PJP: **TMP-SMX**	Anti-Bacterial: **---** Anti-Viral: **Throughout all chemotherapy cycles** Anti-Fungal: **---** PJP: **Throughout all chemotherapy cycles** [e]
Hyper-CVAD/MTX-Ara-C	Anti-Bacterial: **YES** Anti-Viral: **YES** Anti-Fungal: **YES** PJP: **YES**	Anti-Bacterial: **Levofloxacin** Anti-Viral: **Acyclovir** Anti-Fungal: **Fluconazole** PJP: **TMP-SMX**	Anti-Bacterial: **During anticipated neutropenia** Anti-Viral: **Throughout all chemotherapy cycles** Anti-Fungal: **During anticipated neutropenia** PJP: **Throughout all chemotherapy cycles**
RICE	Anti-Bacterial: **YES** Anti-Viral: **YES** Anti-Fungal: **NO** PJP: **NO**	Anti-Bacterial: **Levofloxacin** Anti-Viral: **Acyclovir** Anti-Fungal: **---** PJP: **---**	Anti-Bacterial: **Throughout all chemotherapy cycles** Anti-Viral: **Throughout all chemotherapy cycles** Anti-Fungal: **---** PJP: **---**
Bispecific Antibodies [f]	Anti-Bacterial: **NO** Anti-Viral: **YES** Anti-Fungal: **NO** PJP: **YES**	Anti-Bacterial: **---** Anti-Viral: **Acyclovir** Anti-Fungal: **---** PJP: **TMP-SMX**	Anti-Bacterial: **---** Anti-Viral: **Throughout all chemotherapy cycles** Anti-Fungal: **---** PJP: **Throughout all chemotherapy cycles**

[a] High-risk patients (anti-bacterial) [13]: see Table 4

[b] High-risk patients (PJP): comorbid autoimmune disorder, history of solid organ transplant, R-CHOP 14 treatment regimen [21-24]

[c] Monitor CD4 count bimonthly [28,29,32,33]

[d] Examples of AVD containing chemotherapy: ABVD, BV + AVD, N + AVD

[e] Must hold PJP prophylaxis with TMP-SMX during MTX treatment until serum MTX cleared $\leq$ 0.1 μM [19]

[f] Examples of bispecific antibodies: mosunetuzumab, epcoritamab, glofitamab

R-CHOP: Rituximab + Cyclophosphamide, Doxorubicin, Vincristine, Prednisone); PJP: Pneumocystis Jiroveci Pneumonia; TMP-SMX: Trimethoprim-Sulfamethoxazole; BR: Bendamustine, Rituximab; AVD: Doxorubicin, Vinblastine, Dacarbazine; P-R-CHP: Polatuzumab vedotin + Rituximab + Cyclophosphamide, Doxorubicin, Prednisone); HD MTX: High-Dose Methotrexate; Hyper-CVAD/MTX-Ara-C: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone/Methotrexate, Cytarabine); RICE: Rituximab, Ifosfamide, Carboplatin, Etoposide; ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine; BV: Brentuximab Vedotin); N: Nivolumab

B-cell depletion and consequent hypogammaglobulinemia, factors that reduce vaccine efficacy, increase severity of sinopulmonary infections, and poor control of viral infections exemplified by reactivation of hepatitis B [8].

Anti-bacterial

The recommendations regarding the use of anti-bacterial prophylaxis in R-CHOP is generally that no prophylaxis is indicated in the standard population [9-12]. To establish scenarios when the use of anti-bacterial prophylaxis is indicated, risk stratification to determine patients that would benefit from prophylaxis is necessary. The risk of hospitalization for febrile neutropenia in R-CHOP over a total of six cycle's was 23%, with the primary risk occurring during cycle one and cycle two (6% and 8% respectively). Factors associated with increased risk for hospitalization for febrile neutropenia were early chemotherapy cycles (cycle's one and two), age ≥ 65 years old, baseline serum albumin level ≤ 3.5 g/dL, ANC ≤ 1500/mm^3, planned average relative dose intensity (ARDI) ≥ 80% for cyclophosphamide and doxorubicin, and the presence of comorbid hepatic disease [13]. A summary of these factors associated with increased risk for bacterial infections can be referenced in **Table 4**. Using these increased risk factors can aid in determining which scenarios require the use of anti-bacterial prophylaxis with levofloxacin. Additionally, anti-bacterial prophylaxis is often considered in clinical practice for patients who develop FN during R-CHOP therapy, particularly patients who require hospitalization.

Anti-viral

Multiple studies showed a clinical benefit to using anti-viral therapy with acyclovir in patients treated with R-CHOP and thus, prophylaxis throughout all chemotherapy cycle's is recommended in this patient population [10,11,12,14].

Anti-fungal

Studies have shown a low risk of fungal infection with the use of R-CHOP and thus, the use of anti-fungal prophylaxis is not recommended for this general population [9,15,16].

PJP

Use of rituximab is associated with increased risk for PJP when compared to non-rituximab containing regimens [17,18]. While studies have showed increased rates of PJP with the addition of rituximab, the guidelines regarding recommendations for prophylaxis with TMP-SMX remains unclear. Broadly among all malignancies and chemotherapy regimens, PJP prophylaxis is required if patients have a ≥ 3.5% risk of developing PJP infection [19]. The lack of clarity regarding recommendations for PJP prophylaxis in patients with lymphoma treated with rituximab is due to conflicting studies that show differing rates of PJP in these scenarios. Through literature review, three pertinent studies identified were in favor of the use of PJP prophylaxis with TMP-SMX in this patient population [17,18,20]. In contrast, five pertinent studies were identified that argued against the use of PJP prophylaxis in this patient population [9,11,12,18,19]. Given the ambiguity of reported incidence of PJP in lymphoma patients treated with R-CHOP, the recommendation for PJP prophylaxis with TMP-SMX is only indicated in select populations with additional risk factors for developing PJP. These patients found to have increased risk for developing PJP compared to the general patient population include those with comorbid autoimmune disorders and patients who have

Table 4. High-risk patient factors treated with R-CHOP to guide anti-bacterial prophylaxis indications.

High-Risk Patient Factors [13]:
Early chemotherapy cycles (cycle's one and two)
Age ≥ 65 years old
Baseline serum albumin ≤ 3.5 g/dL
ANC ≤ 1500/mm^3
Planned ARDI ≥ 80% [a]
Presence of comorbid hepatic disease

[a] ARDI of cyclophosphamide and doxorubicin

R-CHOP: Rituximab + Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; ANC: Absolute Neutrophil Count; ARDI: Average Relative Dose Intensity

undergone solid organ transplant [21,22]. Additionally, studies have shown an increased risk of developing PJP in patients treated with R-CHOP 14 (patients receiving R-CHOP every 14 days) when compared to patients treated with R-CHOP 21 (patients receiving R-CHOP every 21 days). Recommendations are that patients treated with R-CHOP 14 receive PJP prophylaxis with TMP-SMX throughout the full chemotherapy course [23,24]. Those without additional risk factors do not require PJP prophylaxis. Ongoing research regarding this is essential in developing better defined recommendations for PJP prophylaxis in this patient population.

BR (Bendamustine, Rituximab)

While bendamustine has similar alkylating agent properties to other commonly used alkylating agents such as cyclophosphamide or cladribine, its antimetabolite effects on DNA repair and induction of cell death differs from these standard alkylating agents [25]. Due to the mechanism of action of bendamustine, its use in the treatment of lymphoma has been shown to result in prolonged CD4+ T-cell lymphopenia lasting up until seven-to-nine months after the final bendamustine treatment. This has been associated with an increased risk of opportunistic infections [26,27].

Anti-bacterial

The risk of bacterial infection in patients treated with BR has been shown to be lower than that of other chemotherapy regimens used in the treatment of lymphoma. Given these findings and recommendations from additional articles, no anti-bacterial prophylaxis is recommended in this patient population [11-13].

Anti-viral

Given the resultant prolonged lymphopenia associated with bendamustine, it is recommended that patients undergoing BR chemotherapy be treated with anti-viral prophylaxis with acyclovir until their CD4 cell count increases ≥ 200/µl. Bimonthly CD4 monitoring is recommended in these patients until the CD4 cell count stabilizes ≥ 200/µl [9,28,29].

Anti-fungal

Overall, there has been shown to be a low risk of fungal infection associated with patients treated with BR. Given this, the general recommendation is that there is no indication for anti-fungal prophylaxis in this patient population [30,31].

PJP

Given the prolonged CD4+ T-cell lymphopenia associated with BR therapy, it is recommended that this patient population undergo bimonthly CD4 monitoring and be treated with PJP prophylaxis with TMP-SMX until their CD4 cell count increases ≥ 200/µl [9,32,33]. Patients frequently will require prophylaxis for 6-12 months after completion of chemotherapy, with discontinuation based on CD4 count recovery.

AVD (Doxorubicin, Vinblastine, Dacarbazine) Containing Chemotherapy

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)

BV + AVD (brentuximab vedotin + doxorubicin, vinblastine, dacarbazine)

N + AVD (nivolumab + doxorubicin, vinblastine, dacarbazine)

With regards to the treatment of Hodgkin's lymphoma, AVD combined with an additional therapeutic agent is commonly used for management. The three major additional agents combined with AVD are bleomycin (ABVD), brentuximab vedotin (BV + AVD), or nivolumab (N + AVD) [34,35]. While neutropenia is a common complication associated with ABVD, occurring in approximately 34% of patients, the incidence of FN is much less frequent. The overall incidence of neutropenic complications in these patients treated with ABVD has been shown to be < 1% [34]. Brentuximab vedotin is an anti-CD30 monoclonal antibody drug conjugate that, when used in conjunction with AVD, has shown superior efficacy compared to ABVD in treatment naive patients with advanced-stage Hodgkin's lymphoma in the ECHELON1 study [36]. ECHELON1 noted superior progression free survival and overall survival for BV + AVD compared to ABVD, but with higher rates of febrile neutropenia, and growth factor prophylaxis was consequently recommended [36]. The recent SWOG study comparing BV + AVD to N + AVD for advanced stage Hodgkin's lymphoma reported improvements in progression free survival with N + AVD with lower rates of both neutropenia and febrile neutropenia [37,38]. At this time, the guidelines for antimicrobial prophylaxis in ABVD, BV + AVD, and N + AVD largely mirror each other [39]. As the use of BV + AVD and N + AVD increases in the future, ongoing research assessing their associated infection risks is needed to further develop antimicrobial prophylaxis guidelines.

Anti-bacterial

Indications for anti-bacterial prophylaxis in patients treated with ABVD differ across different research studies. For example, the SIGNIFCANT trial evaluated the use of anti-bacterial prophylaxis in the setting of ABVD treatment. The results showed a significant reduction in the incidence of infection and hospitalization for neutropenic infection when anti-bacterial prophylaxis was used. Given these findings, the SIGNIFICANT trial recommended using anti-bacterial prophylaxis with levofloxacin in this population for seven days after chemotherapy to cover for anticipated neutropenia [6]. In contrast, multiple other studies, including a thorough review article (Neutropenia and Neutropenic Complications in ABVD Chemotherapy for Hodgkin Lymphoma), reported

no significant improvement in these patients treated with anti-bacterial prophylaxis [34]. Similarly, the risk of bacterial infection remains low in patients treated with BV + AVD and N + AVD [39]. Given these findings, the general recommendation is that anti-bacterial prophylaxis is not indicated in patients with Hodgkin's lymphoma undergoing ABVD, BV + AVD, or N + AVD therapy.

Anti-viral

According to the Guidelines of Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology, the strength of recommendation for using anti-viral prophylaxis in patients with Hodgkin's lymphoma treated with ABVD is a 'C' (range A-D), indicating only a marginal support of recommendation for use [28]. The recommendation for anti-viral prophylaxis is equivalent for BV + AVD and N + AVD when compared to ABVD [39]. Given this, no anti-viral prophylaxis is recommended for this patient population.

Anti-fungal

No anti-fungal prophylaxis is recommended in patients with Hodgkin's lymphoma treated with ABVD, BV + AVD, or N + AVD [39,40].

PJP

At this time, the general recommendation is that PJP prophylaxis is typically not necessary in patients with Hodgkin's lymphoma treated with ABVD [41]. This is reiterated by studies that showed prophylaxis did not significantly decrease the incidence of PJP in this patient population [42]. While this is the current recommendation, the overall incidence and mortality associated with PJP in patients treated with ABVD is increased and thus, further research is necessary to clarify the optimal recommendations [41,42]. With regards to patients treated with BV + AVD, rates of PJP have been shown to be low (0.1-1.0%) and PJP prophylaxis is not recommended [39]. Similarly, patients treated with N + AVD without additional risk factors, such as additional prolonged steroid use, do not require PJP prophylaxis [39].

P-R-CHP (Polatuzumab Vedotin + Rituximab + Cyclophosphamide, Doxorubicin, Prednisone):

Polatuzumab vedotin is an anti-CD79B monoclonal antibody that has been used in conjunction with R-CHP to treat relapsed/refractory lymphoma [43]. Treatment of higher risk DLBCL with P-R-CHP has shown a decreased risk of disease progression, relapse, or death when compared to patients treated with R-CHOP and P-R-CHP can be considered as a front-line agent in these patients [44]. When compared to patients treated with R-CHOP, while the incidence of febrile neutropenia was higher in patients receiving P-R-CHP compared to R-CHOP (14.3% vs 8.0%), there was no significant findings suggesting a higher overall incidence of infection [44].

Anti-bacterial

Generally, no anti-bacterial prophylaxis is necessary in patients treated with P-R-CHP for lymphoma [45].

Anti-viral

According to the FDA prescribing recommendations for P-R-CHP, the use of anti-viral prophylaxis with acyclovir is recommended throughout all chemotherapy cycles [45].

Anti-fungal

While there is less data on the rates of fungal infection with P-R-CHP, the addition of polatuzumab vedotin to R-CHP does not significantly increase the risk of fungal infection in this patient population and thus, no anti-fungal prophylaxis is recommended [15].

PJP

According to the FDA prescribing recommendations for P-R-CHP, the use of PJP prophylaxis with TMP-SMX is recommended throughout all chemotherapy cycles [45].

HD MTX (High-dose Methotrexate)

High-dose methotrexate is a commonly used chemotherapy regimen to treat primary CNS lymphoma due to its ability to cross the blood-brain-barrier at high doses [46].

Anti-bacterial

Recommendations are that no anti-bacterial prophylaxis is indicated in patients with primary CNS lymphoma treated with HD MTX [10].

Anti-viral

The use of anti-viral prophylaxis with acyclovir is recommended throughout the full treatment course in patients treated with HD MTX [10].

Anti-fungal

Generally, there is a low risk of fungal infection in patients treated with HD MTX and thus, no anti-fungal prophylaxis is necessary in this patient population [10,31].

PJP

In patients treated with HD MTX, the general recommendation is to use PJP prophylaxis with TMP-SMX throughout all chemotherapy cycles. As noted in **Table 3**, TMP-SMX must be held during each MTX treatment until the MTX is cleared (serum MTX level ≤ 0.1 μM) due to TMP-SMX's effect on the excretion of MTX [10,12,19].

Hyper-CVAD/MTX-Ara-C (cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine)

Hyper-CVAD/MTX-Ara-C is an alternating chemotherapy regimen which typically uses hyper-CVAD during odd chemotherapy cycles (e.g., cycles one, three, five, seven) and MTX-Ara-C during even chemotherapy cycles (e.g., cycles two, four, six, eight). It is commonly used to treat high grade lymphomas such as Burkitt lymphoma [47].

Anti-bacterial, anti-viral, anti-fungal, and PJP

It has been recommended to use anti-bacterial prophylaxis with levofloxacin during anticipated neutropenia, anti-viral prophylaxis with acyclovir throughout all chemotherapy cycles, anti-fungal prophylaxis with fluconazole during anticipated neutropenia, and PJP prophylaxis with TMP-SMX throughout all chemotherapy cycles in patients treated with hyper-CVAD/MTX-Ara-C [47]. These recommendations have been reiterated in multiple large center guidelines including Stanford University, Michigan University, and UCLA [10-12].

RICE (Rituximab, Ifosfamide, Carboplatin, Etoposide)

In patients with relapsed or primary refractory NHL, salvage or consolidative stem cell transplantation (SCT) is often considered as a treatment alternative. For these relapsed or primary refractory NHL, a second-line chemotherapy regimen that does not cause stem cell toxicity is necessary prior to evaluation for SCT. In these scenarios, the chemotherapy regimen RICE is often used [48]. This chemotherapy regimen has been shown to have an overall higher risk of infection (>20% risk of neutropenic fever) when compared to other chemotherapy regimens (10-20% risk of neutropenic fever) used in the treatment of lymphoma [19,49].

Anti-bacterial

Given the significant neutropenia and high risk for neutropenic fever associated with RICE therapy, the use of anti-bacterial prophylaxis with levofloxacin is recommended throughout the full treatment course [50].

Anti-viral

In patients treated with RICE chemotherapy, it is generally recommended that anti-viral prophylaxis with acyclovir be used throughout the full chemotherapy treatment course [11,12].

Anti-fungal

The overall risk of invasive fungal disease in lymphoma patients treated with RICE is typically defined as 'low risk' (~2% incidence) [31]. Studies have demonstrated the incidence of invasive fungal disease in ICE therapy of 0.0% consistent with a 'low risk' classification [51]. Given this, anti-fungal prophylaxis is not indicated in patients treated with RICE therapy. This is reiterated by Michigan University guidelines [12].

PJP

Generally, the use of PJP prophylaxis in patients treated with RICE is not recommended in this patient population [10-12].

Bispecific Antibodies

Bispecific antibodies have emerged as a promising new treatment option for patients with relapsed or refractory NHL. Some examples of bispecific antibodies used in these patient scenarios are mosunetuzumab, epcoritamab, and glofitamab. These bispecific antibodies target both CD20 on malignant B-cells and CD3 on malignant T-cells [52]. Overall rates of infection in patients treated with bispecific antibodies range between 15-45% with a large proportion of infections classified as grade three severity or higher [53].

Anti-bacterial

Generally, no anti-bacterial prophylaxis is recommended in patients treated with bispecific antibodies [54,55].

Anti-viral

In patients treated with a bispecific antibody, recommendations are to use anti-viral prophylaxis treatment with acyclovir throughout the entire treatment course [54,55].

Anti-fungal

Patients treated with bispecific antibodies for NHL have been found to have a low risk of fungal infections, thus no anti-fungal prophylaxis is recommended in this patient population [16].

PJP

It is recommended across all patients treated with bispecific antibodies that they be treated with PJP prophylaxis with TMP-SMX throughout the full treatment course [54-56].

Conclusions

Certain cancer subtypes, such as acute leukemia, and their associated chemotherapy regimens are clearly defined as 'high risk' with regards to infectious complications, while other cancer subtypes such as solid tumors and their associated chemotherapy regimens are clearly defined as 'low risk'. These classifications make determining the indications for antimicrobial prophylaxis clear in these cancer subtypes. In contrary, the infection risk for patients with lymphoma is often classified as 'intermediate risk', creating a broad

range for clinical interpretations when determining the appropriate indications for antimicrobial prophylaxis [4]. The recommendations for antimicrobial prophylaxis vary across different chemotherapy regimens used in the treatment of lymphoma and have not been succinctly reported in literature review. This data-driven review on antimicrobial prophylaxis in this patient population will help to guide providers in clinical management.

Eight commonly used chemotherapy regimens in the treatment of both NHL and Hodgkin's lymphoma were addressed in this review article (R-CHOP, BR, AVD containing chemotherapy (ABVD, BV + AVD, N + AVD), P-R-CHP, HD MTX, Hyper-CVAD/MTX-Ara-C, RICE, bispecific antibodies). First-line antimicrobial prophylaxis regimens and doses are stated in the 'Introduction' section of this review article. Of note, it is important to remember that these medications are the preferred first-line prophylactic regimens in patients without any contraindications, and thus, if patients have a contraindication to any of these medications, alternative antimicrobials should be sought out. A summary of each chemotherapy regimens antimicrobial prophylaxis recommendations and duration of therapy can be found in **Table 3**.

Given the complexity in determining the appropriate antimicrobial prophylaxis in lymphoma based on the specific chemotherapy regimen, classifying prophylaxis indications based on treatment regimens will assist in guiding clinicians when treating lymphoma. Conversely, understanding indications for prophylaxis is imperative to preventing unnecessary prescribing of antimicrobial prophylaxis. This knowledge will limit medication adverse effects, prevent antibiotic resistance, and reduce avoidable costs.

Conflict of Interest

The authors have no conflict of interests.

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