SEIFEM 2018 - Antimicrobial prophylaxis in patients with lymphoproliferative diseases: where do we stand?

Alessandro Busca, Chiara Cattaneo, Elena De Carolis, Gianpaolo Nadali, Massimo Offidani, Marco Picardi, Anna Candoni, Eleonora Ceresoli, Marianna Criscuolo, Mario Delia, Roberta Della Pepa, Ilaria Del Principe, Rosa Fanci, Francesca Farina, Nicola Fracchiolla, Claudia Giordano, Michele Malagola, Francesco Marchesi, Monica Piedimonte, Lucia Prezioso, Angela Maria Quinto, Angelica Spolzino, Maria Chiara Tisi, Fabio Trastulli, Enrico Maria Trecarichi, Patrizia Zappasodi, Livio Pagano.

Blood Reviews, submitted

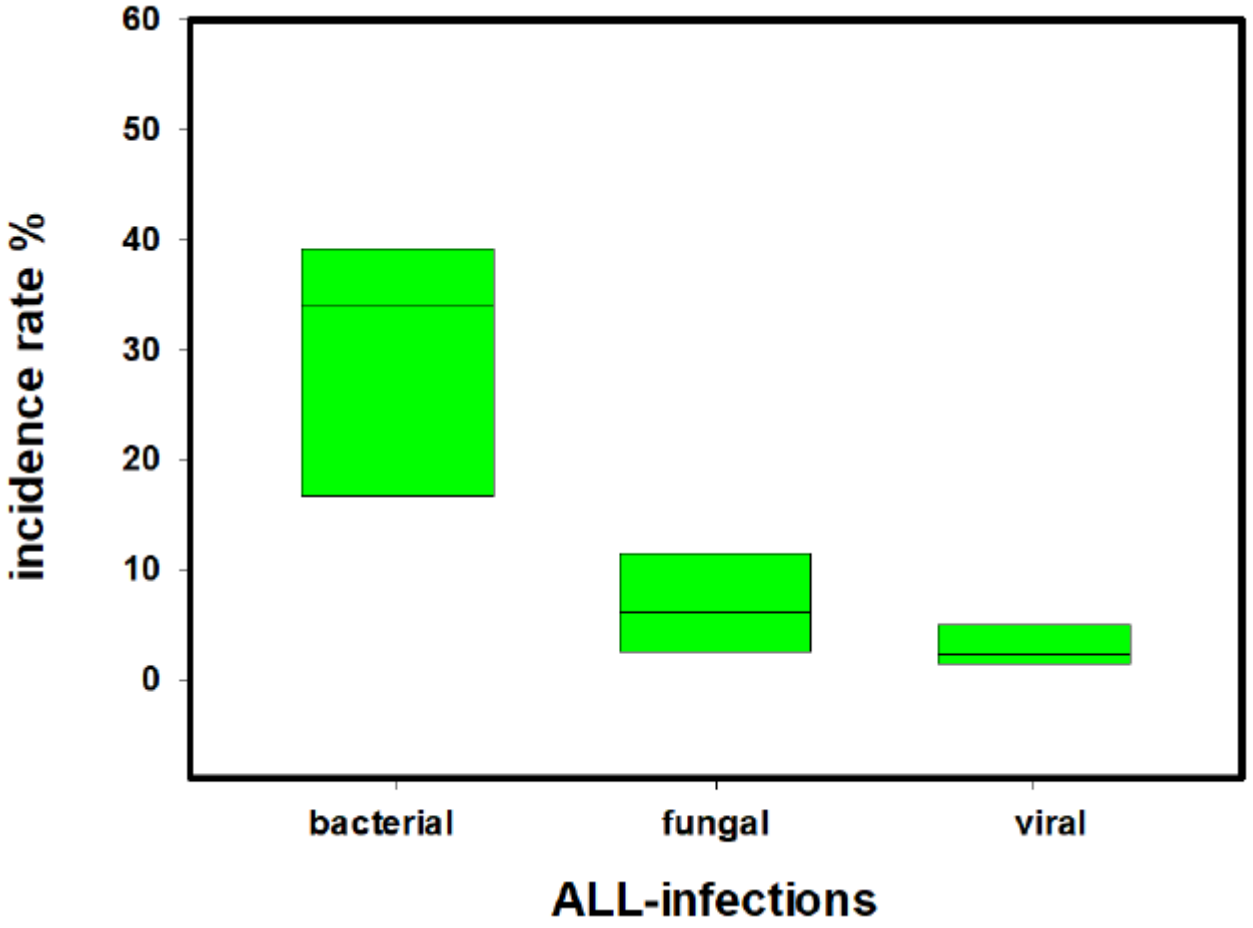
METHODS: We conducted a comprehensive electronic literature search from January 2008 to June 2018, using the PubMed database.

FOUR TOPICS:

1. **ALL**
2. **CLL**
3. **Lymphomas**
4. **Multiple Myeloma**

ALL

Median rates of bacterial, fungal and viral infections in patients with ALL as reported by the studies published in literature over the last 10 years.

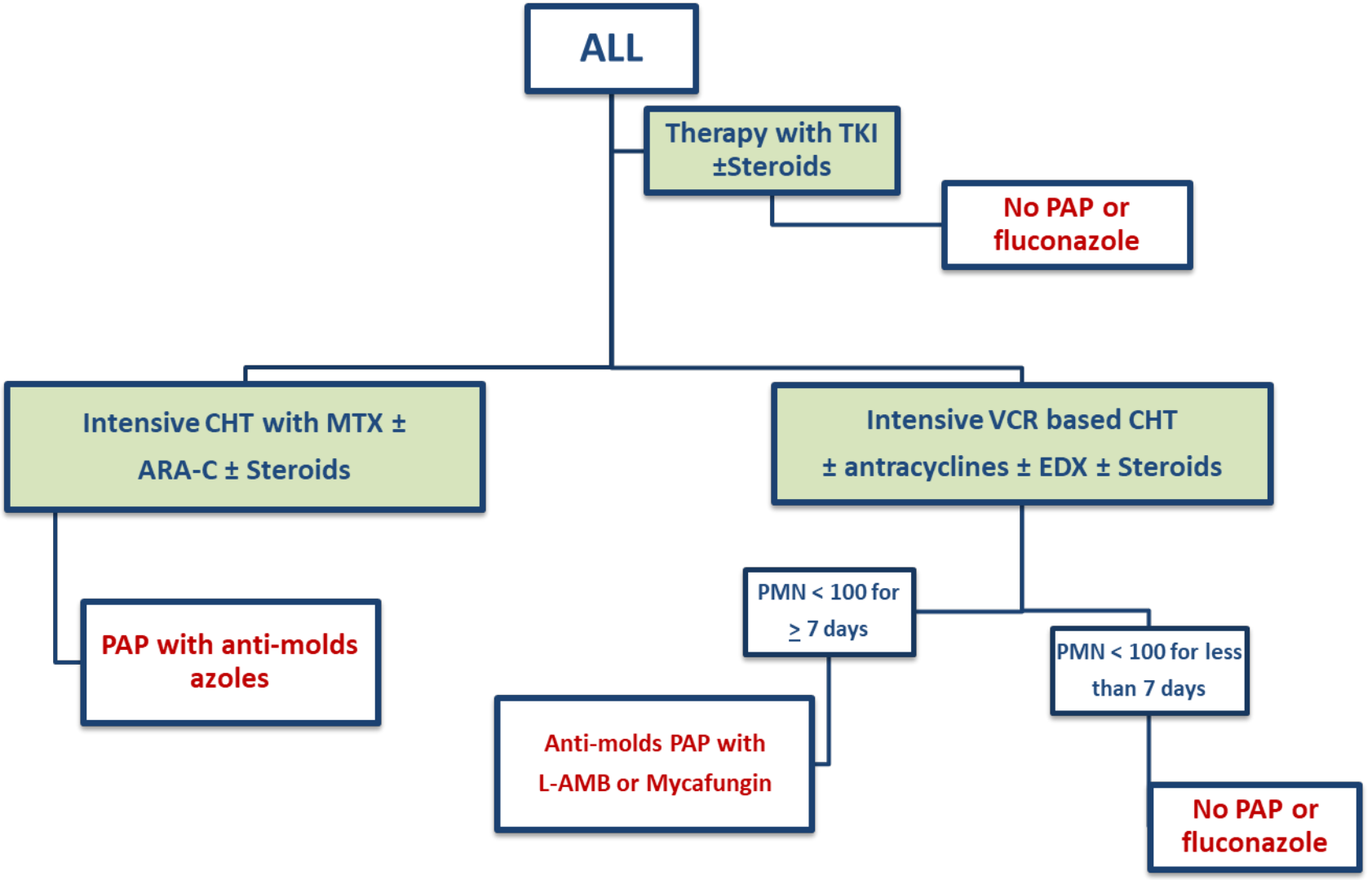


ALL

***Key points for antibacterial prophylaxis*.** Antibacterial prophylaxis with fluoroquinolones (FQ) should be considered during induction/reinduction phase of treatment, with a ≥7 day expected severe neutropenia. Close monitoring of bacterial epidemiology should also be done, in order to detect early emerging antibiotic resistant strains.

Key points for antifungal prophylaxis. the current data support the utility of PAP in ALL, at least in intensive regimen protocols and particularly in older patients. However, the well documented drug interactions between azole and vinca alkaloids commonly used in the treatment of ALL (e.g. vincristine), which may result in increased incidence of neurotoxicity, are a limitation for the use of antifungal drugs employed in other setting (i.e. AML). No clear benefit has been demonstrated for echinocandins and polyenes in ALL, but at present they are the only available drugs for ALL patients on treatment with vinca alkaloids. Strategies for preventing *P. jirovecii* pneumonia in ALL during the whole tretament include trimethoprim/sulfamethoxazole as first line

Proposal for antifungal prophylaxis in ALL patients according to the antileukemic therapy



ALL

Key points for antiviral prophylaxis. Antiviral prophylaxis is not recommended in ALL patients except for HSV prevention with acyclovir in seropositive patients at least during induction treatment. Close monitoring of CMV DNAemia should be considered in heavily immunosuppressed patients. Considering the high percentage of life-threatening lower respiratory tract complication, flu vaccination is strongly recommended for ALL patients during chemotherapy, although the efficacy of seasonal flu vaccination in hematological cancer patients receiving chemotherapy may be low, as well as pre-emptive treatment with oseltamivir during epidemic period in case of upper respiratory symptoms appearance.

CLL

Key points for antibacterial prophylaxis. Specific antibacterial prophylaxis or growth factors support is generally not recommended, although FQ prophylaxis could be considered in FCR and BR regimes. Monitoring of local epidemiology may be considered mandatory to set up the appropriate antibiotic treatment.

Key points for antifungal prophylaxis**.** At present, data available are not sufficient to expect benefit from universal use of antifungal prophylaxis in CLL, but there the need for further studies in patients treated with ibrutinib, to define those patients who are candidate for mold-active prophylaxis strategies. PJP prophylaxis is recommended for all patients receiving Idelalisib and for a period of 2 to 6 months after discontinuation as well as for patients receiving Fludarabine based chemotherapy.

Key points for antiviral prophylaxis. Due to the emergence of CMV infections in patients treated with idelalisib, there is a strong recommendation to carefully monitor patients with a prospective PCR-based diagnostic strategy for CMV reactivation. Based on the current data, an antiviral prophylaxis for HSV and HZV with acyclovir or valaciclovir should be administered in CLL patients treated with purine analogues.

Ibrutinib and Fungal infections in CLL patients

Reference	Disease and No. patients	Overall rate of IFI	aspergillosis	candida	PJP	cryptococcus	other
Ghez, Blood 2018 (185)	CLL pts	33 IFI (rate not applicable)	27	-	1	4	1
Ruchlemer, Blood 2017 (186)	CLL 20 pts	28 IFI (rate not applicable	18	-	1	7	2
Varughese, CID 2018 (82)	CLL 165 pts	6%	-	-	-	-	-
Williams 2018 (89)	CLL 263 pts	3.9 %	-	-	-	-	-

Lymphomas

Key points for antibacterial prophylaxis. Prophylaxys with FQ should be considered in case of intensive and/or deeply immunosuppressive, immuno-chemotherapeutic schemes, and in case of advanced therapeutic lines, mainly, but not only, considering the risk of prolonged neutropenia (<7 days, ANC<1000/mmc). It should be underscored that antibacterial prophylaxis does not have a clearly demonstrated impact on mortality attributable to infection, while the issue of resistant strains selection is an emerging issue .Underlining the importance of neutropenia in the infectious risk management of lymphoma patients, primary prophylaxis with G-CSF is recommended in patients receiving Obinutuzumab if the expected febrile neutropenia rate is ≥20%, and in patients treated front-line with Brentuximab-vedotin plus AVD for stage III-IV HL . A brand new field of investigation is represented by patients who received adaptive immunotherapy with CD 19-targeted chimeric antigen receptor-modified T (CAR-T) cells, in whom prophylaxis with levofloxacin 750mg /die is recommended in the case of ANC < 500/$mm^{3,}$.

Lymphomas

Key points for antifungal prophylaxis. In the case of first-line antineoplastic therapy with R-CHOP or ABVD regimens no antifungal prophylaxis is recommended. In the case of second or further line of treatment, Trimethoprim/Sulfamethoxazole (TMP/SMX) is recommended in patients with HL >60 years until 2-6 months after chemotherapy discontinuation, while Fluconazole is used in patients with NHL. PJP prophylaxis is mandatory in patients treated with brentuximab vedotin as consolidation or salvage therapy following stem cell transplantation . Based on the preliminary results of the CAR-T cells studies, immunoglobulin repletion and antifungal prophylaxis are needed for these high-risk patients.

Lymphomas

Key points for antiviral prophylaxis. Prophylaxis against *Varicella zoster* might be considered in patients receiving conventional chemotherapy . We recommend for seropositive patients in treatment with Idelalisib to perform regular CMV-PCR. Idelalisib should be discontinued and Ganciclovir/Valganciclovir preemptively initiated in patients with positive CMV-PCR and symptoms consistent with CMV infection .

Any patient receiving brentuximab presenting new-onset signs and symptoms of CNS abnormalities should hold treatment for any suspected case of PML and discontinue if a diagnosis of PML is confirmed (neurologist consultation, brain MRI, and lumbar puncture recommended).

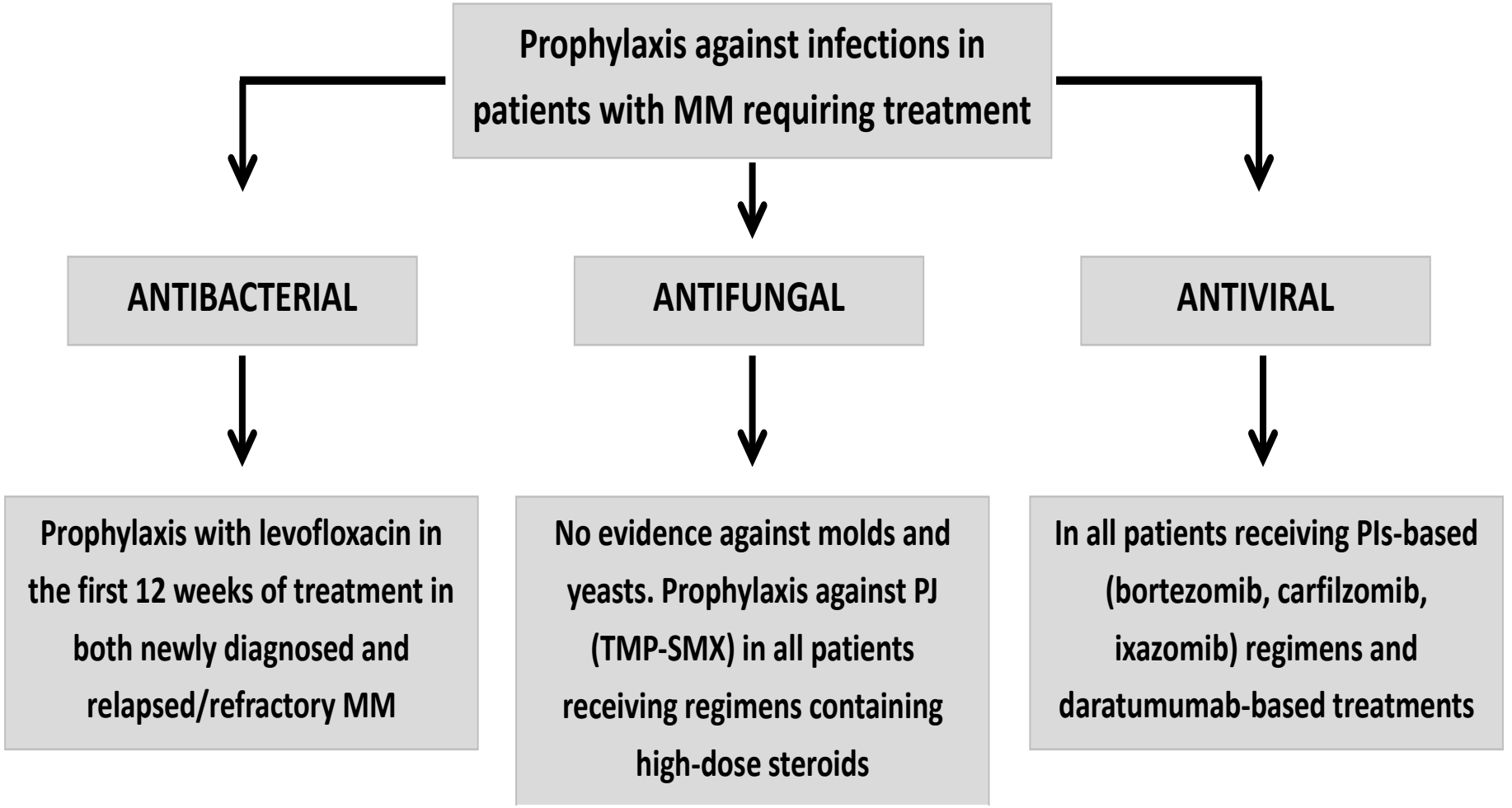
Myeloma

Key points for antibacterial prophylaxis.The risk of infection in patients with MM is high regardless of neutropenia, especially in the first 3-4 months of induction therapy, and infection is still the first cause of death for these patients particularly in older patients. FQ-based prophylaxis during the first 12 weeks of induction, particularly in older patients and in those with high burden of disease, is recommended, although definitive data are still lacking.

Key points for antifungal prophylaxis. The use of TMP-SMZ prophylaxis against *P. jirovecii* is mostly recommended among MM patients who receive high dose corticosteroids treatment. Due to the low rate of invasive fungal infection in patients with MM, routinely antifungal prophylaxis is not recommended. However, in patients who receive high-dose therapy, severe mucositis could require yeast prophylaxis.

Key points for antiviral prophylaxis. Acyclovir or valaciclovir prophylaxis is recommended to reduce viral-related morbidity and should be used during the treatment with proteasome inhibitors and after ASCT. Duration of prophylactic treatment should be considered for 6 to 12 months after the end of the therapy. In the setting of multiple lines of therapy with associated CD4 lymphopenia, monitoring for CMV viremia could be considered.

Figure 3 Proposal of anti-infective prophylaxis in patients receiving treatment for MM



Key points

- In patients with ALL, FQ prophylaxis should be considered during induction/reinduction phase of treatment, although monitoring of bacterial epidemiology should be done, in order to detect early emerging antibiotic resistant strains.
- Antifungal prophylaxis should be considered in patients with ALL, at least in intensive regimen protocols and particularly in older patients.
- Patients receiving idelalisib should receive PJP prophylaxis as well as patients receiving Fludarabine based chemotherapy.
- There is a strong recommendation to carefully monitor patients receiving idelalisib, with a prospective PCR-based diagnostic strategy for CMV reactivation.
- PJP prophylaxis is recommended in patients with HL >60 years until 2-6 months after chemotherapy discontinuation, in particular in patients treated with brentuximab vedotin as consolidation or salvage therapy following stem cell transplantation.
- In patients with MM, FQ-based prophylaxis during the first 12 weeks of induction, particularly in older patients and in those with high burden of disease