How I treat ALL in Down's syndrome: pathobiology and management

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Short title: How do I treat DS-ALL

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Abstract

Children with Down Syndrome are at high risk for developing B cell precursor acute lymphoblastic leukemia (DS-ALL) associated with poor outcome due to both a high relapse rate and increased treatment related mortality (TRM) from infections. Biologically, these heterogeneous leukemias are characterized by underrepresentation of the common cytogenetic subgroups of childhood ALL and overrepresentation of CRLF2-IL7R-JAK-STAT activating genetic aberrations. Although relapse is the major determinant of poor outcomes in this population, de-escalation of chemotherapy intensity might be feasible in the 10-15% DS-ALL patients with ETV6-RUNX1 or high hyperdipoidy in whom TRM is the major limiting event. As infection associated TRM occurs during all treatment phases, including the maintenance period, increased surveillance and supportive care is required throughout therapy. Improvement in outcome will require better understanding of the causes of treatment failure and TRM, incorporation of new therapies targeting the unique biological properties of DS-ALL and enhanced supportive care measures to reduce the risk of infection-related TRM. To facilitate these goals, an international collaboration plans to establish a prospective DS-ALL registry and develop specific supportive care recommendations for this at-risk population.
Children with Down Syndrome (DS) are at an increased risk for development of both acute myeloid and lymphoid leukemias (DS-ML and DS-ALL, respectively)\(^1\)\(^2\). While DS-ML is highly curable, the prognosis of DS-ALL is relatively poor compared to the excellent outcomes for ALL in children without DS\(^3\).

The following cases highlight several aspects of the diagnosis and management of Down syndrome ALL:

**Case 1:** A 4 year old boy was diagnosed with common B cell precursor, NCI standard risk, CNS-neg, normal karyotype ALL. He had previously been treated for Acute Myeloid Leukemia (normal karyotype, positive for GATA-1 mutation) at the age of 23 months with 4 courses of intensive chemotherapy without exceptional problems and remained in remission of AML at diagnosis of ALL. He was treated according to the standard risk arm of UKALL 2003\(^4\) and obtained a rapid morphological marrow response at day 15 of a 3 drug induction comprising Vincristine, Pegylated asparaginase and dexamethasone but was high risk by the level of minimal residual disease (MRD> 10\(^{-4}\)) at day 29. He received the most intensive protocol consisting of augmented consolidation and two delayed intensifications (DI) interspersed with escalating dose intra-venous Capizzi MTX without folinic acid rescue. Although he tolerated the intensive consolidation and DI courses, including 12 Pegylated asparaginase doses (1000 U/m\(^2\) sub-cutaneously), without excess toxicity, he had prolonged pancytopenia and moderately severe mucositis after the second Capizzi MTX dose (100 mg/m\(^2\)) and, thereafter, received standard interim maintenance instead.

The first year of maintenance therapy was complicated by leg pains and limp, which improved on withholding vincristine and dexamethasone pulses, and an episode of E.Coli septicemia. In view of the latter, and frequent episodes of prolonged neutropenia despite reduced doses of mercaptopurine and methotrexate, his maintenance was shortened from 3 to 2 years. He remains in complete remission seven years from diagnosis.

**Case 2:** A girl diagnosed with common ALL at the age of 4.5 years, with normal karyotype. She was treated according to a modified version of the BFM-based DCOG ALL-10 protocol for children with Down syndrome, i.e. only 2 Daunorubicin dosages in induction instead of 4 dosages, and a lower dose of MTX. As a child with DS-ALL she also received anti infectious prophylactic therapy with ciprofloxacine and itraconazole during intensive chemotherapy phases in addition to the customary cotrimoxazole.

The first induction cycle was complicated by mucositis and an oral herpes simplex infection, for which she was admitted and treated with acyclovir IV. Six weeks post-diagnosis she was admitted with bilateral pneumonia which required mechanical ventilations for 8 days. She did not receive chemotherapy for approximately 4 weeks, after which protocol 1B was continued. Cyclophosphamid at the end of protocol 1B was not given.
Despite these delays in therapy PCR-MRD evaluation was negative and the patient stratified in the standard risk arm of the protocol, consisting of oral 6-MP and MTX. She frequently needed dose-adaptations for low leucocyte counts, and continued to receive ciprofloxacin prophylaxis during at least one year during maintenance, as she suffered from frequent viral upper airway infections and we wanted to prevent bacterial superinfection. No other severe complications arose. She is in remission, approximately 1.5 years after stopping chemotherapy.

Case 3: An 8 year old girl with DS was found to have a WBC of 234,000/cmm. The blasts marked as early pre-B-cell ALL; cytogenetic abnormalities included t(X;14)(p22.3;q32), likely corresponding to an IGH-CRLF2 gene rearrangement leading to overexpression of CRLF2. CRLF2 overexpression was confirmed by flow cytometry, and a JAK2 mutation was identified by sequence analysis. She was treated according to AALL0232, a COG high-risk ALL protocol utilizing a 4-drug induction. A bone marrow evaluation at end-induction showed morphologic remission but a high level (2.3%) of minimal residual disease by flow cytometry. She received extended induction chemotherapy, followed by an augmented BFM consolidation, a modified interim maintenance with escalating doses of methotrexate beginning at 0.5 gm/m2, delayed intensification and maintenance chemotherapy. Her course was complicated by several episodes of febrile neutropenia, each with negative blood cultures.

While receiving maintenance chemotherapy, she was found to have circulating blasts signifying recurrence of her ALL. She received reinduction chemotherapy according to the UK ALLR3 chemotherapy regimen; despite antimicrobial prophylaxis she developed sepsis due to Stenotrophomonas bacteremia and expired.

While the occurrence of both AML and ALL in the same DS patient is quite rare and reflect the increased risk of both types of leukemias in DS, the rest of the course of the first child reflects many of the typical issues encountered in children with DS-ALL. The leukemia is typical B cell precursor but usually with normal karyotype lacking any of the usual genetic aberrations of childhood ALL. It often responds poorly to therapy and thus is classified as high risk. This child generally tolerated intensive therapy quite well, however he suffered excess toxicity during maintenance that necessitated therapy modification. The girl in the second case depicts the rarer child with standard risk ALL, based on excellent MRD response. She suffered life endangering toxicity during the initial intensive phase of therapy. The third case illustrates the association of DS-ALL with specific cytogenetic abnormalities, and highlights the challenges in managing TRM in relapsed DS-ALL despite aggressive supportive care.
Notwithstanding the poorer prognosis of DS-ALL compared with ALL in children without DS (NDS-ALL), it is important to stress that like the first two patients, the majority of children with DS-ALL are cured. Together these three cases depict the challenges in treatment of ALL in children with DS. It is a delicate balancing act between the need for intensive chemotherapy and the markedly increased toxicity of such therapy. Questions about the risks and benefits of intensive chemotherapy, despite the anticipated toxicity, and the role of reductions in therapy are constantly raised.

Here we will provide some guidelines to assist clinicians in dealing with these questions by reviewing recent data on the biology of this disease and the clinical course of children with DS-ALL treated with contemporary protocols.

**Epidemiology and Genetics** (table 1)

The risk of ALL in children with DS is about 20 fold higher compared to children without DS and children with DS comprise 2-3% of all children enrolled on prospective treatment protocols of ALL. The epidemiology of DS-ALL is very different from DS-ML. While transient myeloid neoplasms are present at birth in about 5% of all DS infants, and full blown DS-ML usually develops before the age of 4 yrs, infant ALL is extremely rare in DS. In fact, the peak age of ALL is slightly higher than in children without DS and age of diagnosis extends into adolescents and young adulthood.

Another striking feature of DS-ALL is the almost complete absence of T-ALL. In the recent study conducted by the Ponte Di Legno working group on childhood ALL (herein PdL study), only 5 patients among 708 DS-ALL patients had T-ALL compared with the 10-15% expected rate. Thus the increased risk of ALL in DS is limited to the B cell precursor phenotype. Interestingly, acquired polysomy of chromosome 21 is also found mainly in B cell precursor ALL in children without DS (NDS-ALL), for example in the hyperdiploid phenotype.

The myeloid leukemia of DS is a unique syndrome characterized by an acquired mutation in the GATA1 transcription factor which is encoded by a gene on chromosome X in virtually all cases. In contrast, DS-ALL is not a single biologic entity. This heterogeneity is confirmed by both gene expression and cytogenetic analyses. The common cytogenetic subgroups of childhood NDS-ALL are less common in DS. Approximately 15% of DS-ALLs are positive for the \textit{ETV6-RUNX1}
translocation or are high hyperdiploid compared with about 40% of NDS-ALLs. Similarly the unfavorable translocations *BCR-ABL* and *MLL-AF4* are also less common in DS-ALL. Consequently, similar to the first two cases presented, 40% of DS-ALLs have a normal karyotype compared with only 7% of NDS-ALLs. As detailed below, these genetic differences between DS and NDS ALLs have implications for therapy outcome.

Recently abnormal expression of the cytokine receptor CRLF2 has been identified in about 60% of DS-ALLs. CRLF2, together with the alpha chain of the receptor to interleukin 7 (IL7R), forms a receptor for the cytokine thymic stromal lymphopoietin (TSLP). The TSLP receptor is normally present on dendritic cells, CD4+ T lymphocytes and basophils and mediates allergic and inflammatory responses to TSLP which is secreted by epithelial cells in the bronchial tree or the gut and by keratinocytes (reviewed in). Thus, as illustrated in the third case, in 60% of DS-ALLs this pathway is "hijacked" by the leukemic cells, enabling them to respond to TSLP with increased survival and proliferation.

Interestingly in at least half of these CRLF2 positive DS-ALLs, there are additional activating mutations either in the CRLF2 or IL7R proteins or in the signaling components downstream that include the enzymes JAK2 and JAK1. These mutations lead to constitutive activation of this pathway. The CRLF2 abnormalities are probably not associated with worse prognosis in DS-ALL except when associated with deletions in the *IKZF1* gene. However they provide a pathway relevant to a substantial proportion of DS-ALLs that may be targeted by inhibitors of the JAK-STAT or mTOR pathways.

Thus, while no unique genetic aberrations have been identified in DS-ALL to date, the distribution of the cytogenetic subgroups is markedly different from NDS-ALL. Host factors are also altered, as all the normal blood and body cells of DS patients contain a trisomy of chromosome 21. These differences in the biology of the disease and the host impact the clinical course.

**Clinical course.**

*Relapse risk*

In sharp contrast to the excellent prognosis of the myeloid leukemias of DS, the prognosis of children with DS-ALL is significantly worse than children without DS. The 10 year survival of 653 DS-ALL patients enrolled in 16 international...
prospective therapeutic studies between 1995-2005 analyzed in the PdL study was 70% compared with 88% in children without DS. This poor outcome is related to increased relapse risk coupled with increased therapy related mortality (TRM).

That intrinsic resistance of DS-ALL to therapy is the major cause of treatment failure was also suggested by two smaller studies. Whitlock et al, analyzing the outcome of DS-ALL in CCG treatment protocols, reported the surprising observation that the poorer outcome of DS-ALL was limited to the NCI Standard Risk (SR) group, suggesting that the NCI criteria do not accurately predict outcome in DS-ALL due to the unique biology of DS-ALL. Indeed, intensified chemotherapy may be associated with improved prognosis of these patients as DS patients stratified to NCI high risk (HR) treatment groups fared similarly to non DS patients. These observations were confirmed by Maloney et al who demonstrated that DS-ALL patients fared worse because of the paucity of favorable risk chromosomal aberrations, namely ETV6-RUNX1 and hyperdiploidy.

One confounding factor that could affect the high incidence of relapse in DS-ALL is poor adherence of physicians to protocol guidelines. A recent study from the NOPHO collaborative group indicated that physicians were less willing to increase MTX/6MP maintenance doses for DS patients with WBC counts above the target level. Consequently the median doses of these medications were 25% lower for children with DS compared with NDS patients. Other studies reported that about 40% of DS patients underwent dose reductions during specific protocol courses, especially during high dose MTX blocks. Thus it is possible that reduction of therapy caused by the concerns of increased toxicity contributed to relapses in some DS-ALL patients. However, the notion that the biological properties of the leukemias also play a major role in determining resistance to therapy is supported by cellular in-vitro cytotoxicity assays demonstrating relative resistance of DS-ALL blasts to a variety of chemotherapeutic agents.

Taken together these observations suggest that some children with DS-ALL may benefit from intensified chemotherapy and that physicians need to be careful in reducing treatment intensity.
Treatment Related Mortality

A recommendation for intensified treatment in some children with DS-ALL is offset by the well-recognized increased chemotherapy associated toxicity in children with DS-ALL. Fatal infections, most commonly bacterial and viral, are the major causes of toxicity-related mortality (TRM) in children with DS-ALL. The causes of infectious toxicities are multifactorial. Increased tendency for cellular apoptosis coupled with altered intracellular metabolism of certain drugs, such as methotrexate, lead to breakdown in cellular barriers and increased mucositis. Immunodeficiency, narrowed and hyperactive respiratory tract and, often, congenital cardiac defects increase the risk for respiratory and other infections.

The toxicity associated with the administration of methotrexate (MTX) is the best studied specific toxicity of a chemotherapeutic drug in DS. It is mainly related to a pharmacodynamic effect. Gene dosage effect of extra copies of the reduced folate carrier SLC19A1, located on chromosome 21, appears to cause increased intracellular accumulation of MTX in trisomy 21 cells. This gene dosage effect may also explain the increased sensitivity of hyperdiploid ALL blasts, which uniformly carry 3 or 4 copies of chromosome 21. However in DS, the presence of trisomy 21 in constitutional cells also increases susceptibility to the systemic toxicity of MTX. Therefore in protocols using high dose MTX (HD-MTX) it is generally recommended to reduce higher dosages of MTX in children with DS. For example, the BFM-AIEOP protocol recommends reduction from 5000 mg/m² to 500mg/m² of MTX in the first block of HD-MTX with gradual increase in subsequent courses as tolerated.

Despite these concerns about the toxicity of MTX in DS-ALL, the recent international PdL study has shown that TRM in DS-ALL is not linked to MTX blocks or to any other treatment element. Similarly, escalating-dose MTX was associated with increased toxicity but not increased TRM in DS-ALL patients in the CCG-1991 study, and DS-ALL patients who received the intensified MTX therapy had better survival than those who did not. Neither is TRM limited to the intensive phases of the treatment protocol as 40% of TRMs occur during maintenance.

The immunodeficiency of DS is complex and incompletely understood (reviewed in). Several immune regulatory and developmental genes such as those encoding the interferon alpha and gamma receptors, AIRE, the suppressors of the NFAT pathway (RCAN and DYRK1A), RUNX1, mir125b, and more are located on chromosome 21.
Recent analysis of fetal and perinatal hematopoiesis in DS revealed severe defects in early B cell development\textsuperscript{37-38}. This B cell deficiency is only partially corrected later in childhood; B lymphocytes especially naïve B cells remain below the 10\textsuperscript{th} percentile\textsuperscript{39-41}. Defects in B cell function are reflected in mild dysgammaglobulinemia, decreased salivary IgA levels and reduced antibody responses to immunization\textsuperscript{42-48}.

Mild to moderate T cell dysfunction was also reported in children with DS. The NFAT-Calcineurin pathway is a major regulator of T cell development and function and is inhibited in DS due to the increased dosage of RCAN and DYRK1A\textsuperscript{49-50}. This is the same pathway that is targeted by the immunosuppressants cyclosporine and tacrolimus. It is also tempting to speculate that the rarity of T-ALL in DS is also possibly due to the block in the NFAT pathway. The major T cell defect has been recently shown to be in decreased thymic output of new T cells, as reflected by reduced T cell receptor excision circles (TREC)\textsuperscript{51}. These immunodeficiencies are reflected in increased susceptibility to severe respiratory infections and bacteremias in non-leukemic children with DS\textsuperscript{35}.

**Current treatment approaches**

In an attempt to reduce the excess treatment associated morbidity and mortality, a majority of cooperative groups presently modify the treatment for DS-ALL patients as revealed in a survey of 20 national study groups (personal communication, AV). To date, treatment is stratified by MRD response by all groups surveyed. All groups limit exposure to high doses of intravenous methotrexate by adopting a dose capping (500 mg/m\textsuperscript{2} – 1000 mg/m\textsuperscript{2} with folinic acid rescue) or a cautious dose escalation strategy (starting dose 500-2000 mg/m\textsuperscript{2}). None of the groups give cranial radiotherapy to patients with DS-ALL. NOPHO (Nordic), UKALL and COG limit the use of anthracyclines in induction to patients with a slow morphological marrow response (> 25% blasts) at day 15 of a 3 drug regimen (steroid, vincristine and pegylated asparaginase). DCOG (Dutch) and FRALLE (French) groups avoid exposure to induction anthracyclines in all DS patients whereas AIOEP-BFM (Italian-German consortium) give 2 – 4 doses depending on karyotype and early MRD response, similar to patients with NDS-ALL. Whereas dexamethasone is given in induction to all DS patients in the UK, the COG gives it only to patients <10 years old and AIEOP-BFM (Italian-German consortium) to patients with T-cell phenotype and a good response to prednisolone pre-phase. There are no planned alterations in maintenance therapy except in the UK and in DS-ALL patients in COG protocols.
where the duration of maintenance has been shortened from 3 to 2 years for boys with DS-ALL, and with reduction in monthly vincristine/steroid pulses in COG protocols.

Interestingly, despite these variabilities in treatments, no significant differences in outcome were detected between the major therapeutic protocols of DS-ALL.

Additional supportive care measures are recommended for DS-ALL patients by all groups ranging from antibiotic and antifungal prophylaxis during periods of neutropenia to intravenous immunoglobulin infusions to maintain IgG level above a defined threshold. However, there is no evidence of the efficacy of these measures in this setting and, for that reason, no consensus on the matter.

**Facing the challenge – how best to treat** (table 2)

**Children with newly diagnosed ALL**

- We strongly recommend that, like every other child with ALL, DS children should be treated on prospective treatment protocols. More than 70% of children with DS-ALL treated with such protocols will be cured.

- As DS-ALL is a high risk disease, we recommend avoidance of any dose reduction that is not specified in the protocol. Children with high risk criteria, e.g. high MRD should be treated according to high risk protocols.

- As poor adherence to dosing in maintenance has been shown to be associated with increased relapse in DS-ALL, We recommend that fear of infection should not deter clinicians from timely protocol specific dose escalations in patients with stable counts.

- The child with DS-ALL with TEL-AML1 or hyperdiploidy has excellent prognosis similar to NDS-ALL with most deaths due to toxicity. For these children and probably for those with negative MRD at the end of induction, we recommend to consider treatment reduction in the face of moderate to severe toxicity.

- It should be emphasized that the risk of infectious related TRM is increased even during maintenance. Hence children with DS-ALL should be reviewed more frequently during both intensive and maintenance periods.
should be initiated at the earliest suspicion for infection even in the absence of neutropenia.

- Sensible approaches for preventing respiratory viral infections by limiting exposure and vaccinating family members against influenza are warranted.

- The role of prophylactic antibiotics is unclear, and the protocols we represent (COG, UK, Dutch and AIEOP-BFM) as well as our infectious disease specialists differ in their opinions. Some experts recommend ciprofloxacin prophylaxis during intensive treatment periods, or ampicillin for children with frequent respiratory viral infections.

- There is similar debate regarding antifungal prophylaxis, especially as there is no evidence for increased fungal infections in these patients.

- Hypogammaglobulinemia should be aggressively investigated and treated; common recommendations for acquired hypogammaglobulinemia are to measure IgG monthly and treat with IVIG 0.5 g/kg every 3-4 weeks if levels drop below 4 g/l.

**Approach for relapse / role of novel and emerging technologies**

Treatment of Relapse. Despite children with relapsed DS-ALL having more favorable prognostic factors than relapsed NDS-ALL\(^52\), the prognosis of relapse of DS-ALL is grim. A recent study analyzing the outcome of 49 DS-ALL patients treated on the BFM relapse protocol\(^52\) demonstrated only 17% long term survival, with TRM being the major factor determining the worse prognosis compared with NDS-ALL. There is a general reluctance to use SCT, as this therapy is considered to be too toxic. Interestingly, however, of 18 patients transplanted in the PdL cohort, 6 were cured, 2 died from infections, one from GVHD and 9 from relapse\(^7\). Similarly in another smaller cohort\(^53\), relapse and not TRM was the major reason for failure after SCT. Hence SCT can be considered for DS-ALL patients in good general health, with good response to relapse induction chemotherapy. As CNS toxicity of total body irradiation (TBI) is a concern in DS, a radiation free approach should be considered as a preparatory regimen.
Novel therapies:

1) Antigen-directed immune therapies (e.g. Blinatumomab – bispecific anti CD19 antibody or engineered autologous T cells) are exciting new technologies for therapy of B cell precursor ALL\textsuperscript{54-57}. Although we currently do not know if their T cells react similarly to NDS children, participation of eligible children with DS and either refractory or relapsed ALL in immunotherapy trials is recommended. DS-ALL patients may particularly benefit from such therapy due to a reduction in myelosuppression and concurrent TRM.

2) JAK and mTOR inhibitors: Uniquely, 60% of DS-ALLs express the cytokine receptor CRLF2 that signals through JAK-STAT and mTOR pathways. Preclinical trials demonstrate activity of either JAK or mTOR inhibitors\textsuperscript{58}. As these drugs are completing phase I trials in children we recommend that eligible children with DS and relapsed or refractory CRLF2 positive ALL be enrolled in future clinical trials with these drugs. Our unfortunate case 3 represent a child that could have benefited from such therapy.

As Ruxolitinib (a dual JAK1/JAK2 inhibitor) is approved for adults with myeloproliferative neoplasms, we recommend considering treatment of adults patient with DS-ALL (provided that it is CRLF2 positive). These patients are rare, often have refractory disease and cannot tolerate either the aggressive pediatric ALL regimens nor SCT.

3) Liposomal formulations of standard cytotoxic agents used in the treatment of ALL such as daunomycin and vincristine offer the promise of improved therapeutic index leading to both improved outcomes and a reduction in toxicities in all children with ALL. Similarly, high-dose cytarabine which is usually tolerated by DS children treated for AML may have a role in DS-ALL; however, to date, no data are available regarding the potential benefits of these agents in DS-ALL.

Improvement in outcomes for DS-ALL will only be realised from a better understanding of the causes of treatment failure and TRM. The available evidence indicates that DS-ALL patients have distinct host and leukemic blast biology which necessitates the development of specific treatment approaches. Given the relatively small numbers of patients available for study within national groups, international collaboration is essential to develop and test innovative treatment strategies. One
such collaboration has been established within the international BFM group with representatives from European, North and South American, Taiwanese and Japanese study groups. In addition to providing a forum for discussion of existing treatment approaches and outcomes, the collaborative aims to establish an international prospective registry to collect demographic, biological and clinical outcome data on a large group of DS-ALL patients and to agree on uniform immune monitoring and supportive care recommendations. The longer term aspiration is to develop an international DS-ALL protocol that addresses treatment questions informed by analysis of the registry data.

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Authorship Contributions

SI, AV, MZ, JW wrote the paper.

Conflict of Interest Disclosure

The authors declare no conflict of interest.
References


Tables

**Table 1:** Clinical and Biological Features of DS-ALL

**Biological Features**

- Heterogeneity - no DS ALL typical genetic abnormality as in DS myeloid leukemias
- Decreased prevalence of favorable chromosomal aberrations of childhood ALL (*ETV6-RUNX1*, high hyperdiploid)
- Decreased prevalence of unfavorable chromosomal aberrations of childhood ALL (*BCR-ABL*, *AF4-MLL*)
- Aberrant expression of CRLF2 in 60% of DS-ALLs
- Large proportion of cytogenetically normal ALL
- Almost exclusively B cell precursor immunophenotype

**Clinical Features**

- No Infant leukemia
- High risk of relapse
- High infectious associated therapy related mortality throughout treatment period
Table 2: Therapeutic challenges and possible solutions

Reducing relapse:
- Caution at reducing chemotherapy dosages in the absence of toxicity
- Incorporating clinical trials with novel agents targeting unique biological features (e.g. JAK and mTOR inhibitors for CRLF2 expressing DS-ALL)

Reducing Therapy Related Mortality
- Consider chemotherapy dose reduction in patients with ETV6-RUNX1 or High hyperdiploidy DS-ALL or MRD negativity at the end of induction, and excessive toxicity
- Careful surveillance throughout therapy including maintenance period
- Intense monitoring/supervision during periods of prolonged neutropenia
- Aggressive treatment of suspected infections even in absence of neutropenia or fever
- Influenza immunization of family members and reduced exposure to respiratory infections
- Intravenous immunoglobulin therapy for children with low/normal or hypogamaglobulinemia.
- Antimicrobial prophylaxis for children with recurrent respiratory infections
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