Thinking About Secondary Immunodeficiency

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Disclosures

- Speaker's bureau
  - Genentech, AstraZeneca, Regeneron, CSL Behring
- Grants
  - CSL Behring

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Outline

- Primary versus secondary immunodeficiency (SID)
- Causes of SID
- Considerations in management of SID

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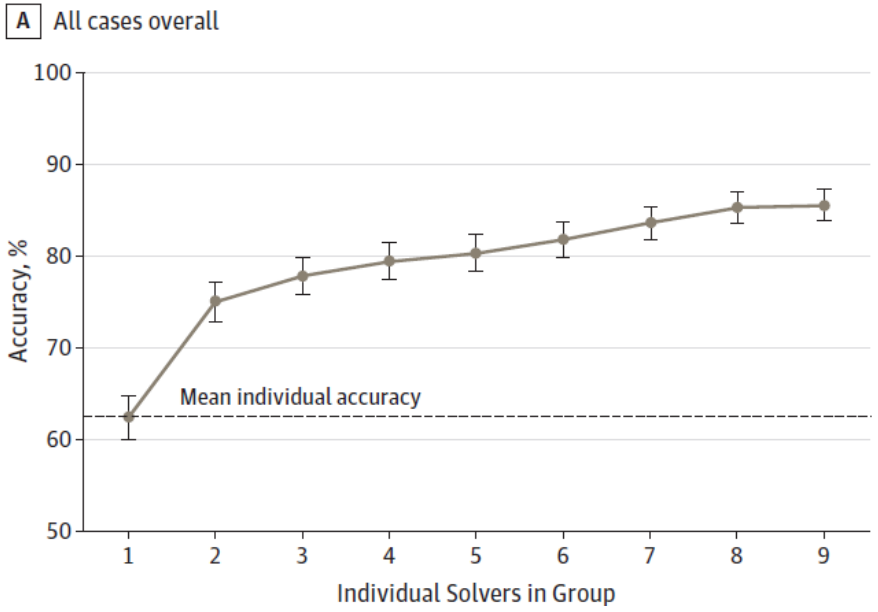
Multi-disciplinary Approach

JAMA Network | Open

Original Investigation | Health Informatics

Comparative Accuracy of Diagnosis by Collective Intelligence of Multiple Physicians vs Individual Physicians

Michael L. Barnett, MD, MS; Dhruv Boddupalli, MD, MBA; Shantanu Nundy, MD, MBA; David W. Bates, MD, MSc



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Barnett. JAMA Network Open 2019; 2(3): e190096.

PIDD versus SID

PIDD

SID

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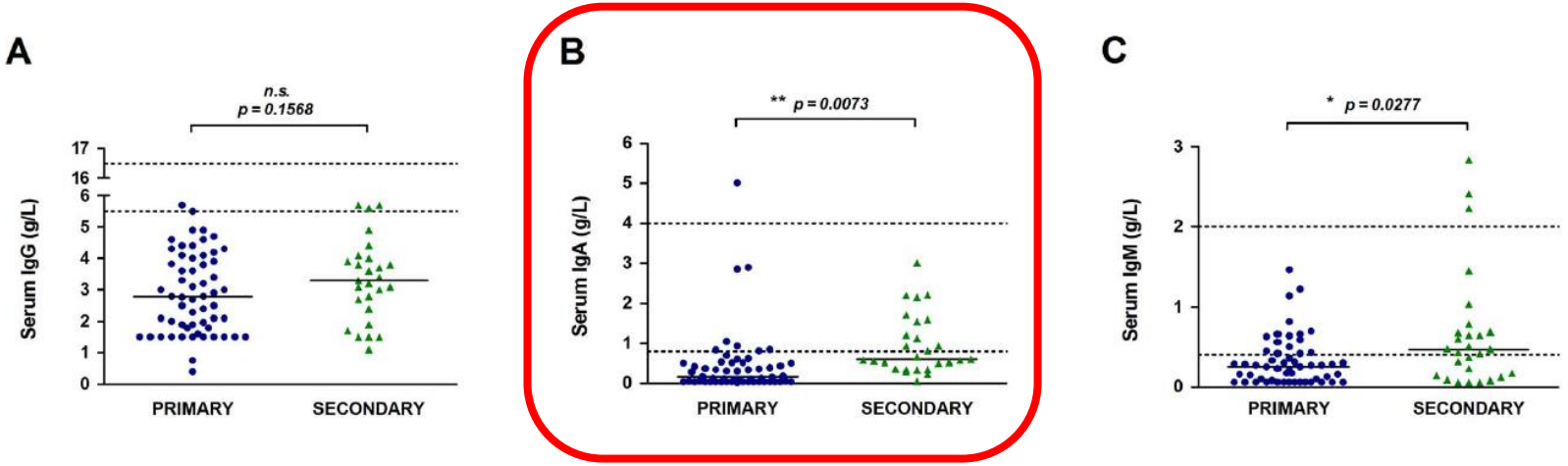
PIDD versus SID

Case 1	
IgM (50-300 mg/dL)	25
IgG (700-1600 mg/dL)	271
IgA (40-350 mg/dL)	< 18

Case 2	
IgM (50-300 mg/dL)	40
IgG (700-1600 mg/dL)	348
IgA (40-350 mg/dL)	72



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Duraisengham. PLoS One 2014; 9(6): e100324.

Diagnosis of PIDD

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Conley. Clin Immunol 1999; 93: 190.

Causes of SID

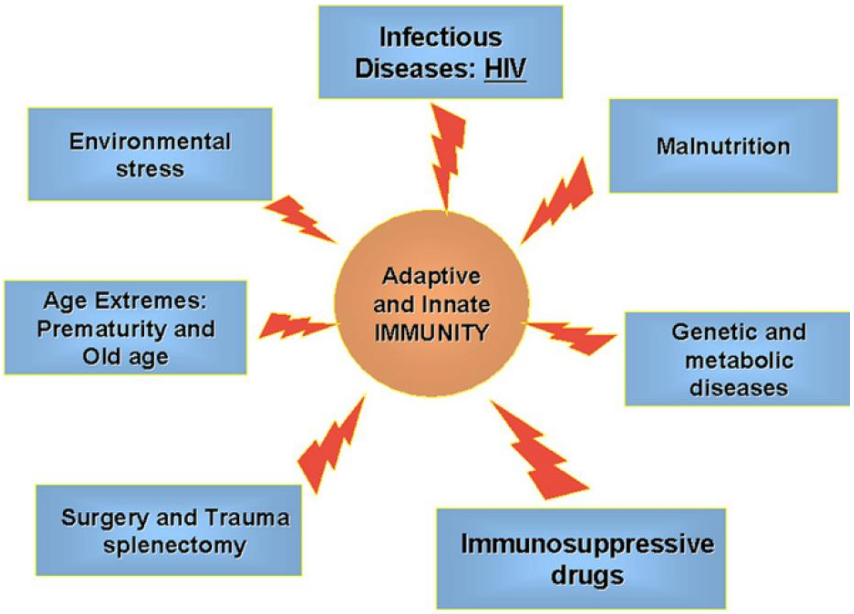

FIG 1. Secondary immunodeficiencies affecting the immune system.

- Renal disease
- GI malabsorption
- Malignancy
  - Multiple myeloma
  - Chronic lymphocytic leukemia
- Medications
  - Systemic steroids
  - Anticonvulsants
  - Rituximab
  - Ibrutinib

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Chinen. JACI 2008; 121: S388.

Case

- 54 y/o AA gentleman with DM presents to the emergency department with fevers, cough, and yellow sputum production. The patient had a similar presentation 4 months previously that required a 4 day ICU admission and treatment with IV antibiotics.
- PMH: DM
- PSH: Sinus surgery at age 28
- Meds: metformin, gabapentin
- SH: No tobacco use
- FH: No hx of malignancy
- PE: HR = 115, thin, dec breath sounds b/l

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Evaluation

- CBC wbc = 13.4, hct = 38.1, plts = 221
- Chem normal with cr = 1.1
- EKG: Normal
- CXR: RUL and RLL opacity, ? Bronchiectasis
- IgG = 3049 (700-1600 mg/dL), IgM = 12 (40-230 mg/dL) IgA = 9 (70-400 mg/DL)
- SPEP: Reveals monoclonal gammopathy = 3.2 g/dL
- UPEP: 5% albumin and monoclonal band = 92% of excreted protein, immunofixation reveals free lambda light chains
- Bone marrow biopsy: Hypercellular marrow. Plasma cells markedly increased in number and present in sheets. Plasma cell constitute > 30% of all nucleated cells. Mildly increased reticulin. Giemsa stain normal.

Case

- 58 y/o Caucasian woman with CLL diagnosed in 2013 presents with frequent episodes of sinusitis and bronchitis. Also reports profound fatigue. Episodes of sinusitis and bronchitis are marked with productive cough, documented fevers, swollen lymph nodes, and myalgias. Episodes are treated with antibiotics with eventual improvement, but then recurrence of symptoms. In the last one year, the patient has received 6+ courses of antibiotics. Several have been extended beyond the typical duration.

Case

- PMH: mdd, AR s/p AIT as a child
- PSH: None
- Meds: Bactrim DS (M, W, F), ibrutinib, allopurinol, bupropion, flonase
- SH: No tobacco use.
- FH: Brother with history of CML
- PE: thin, anxious woman

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Evaluation

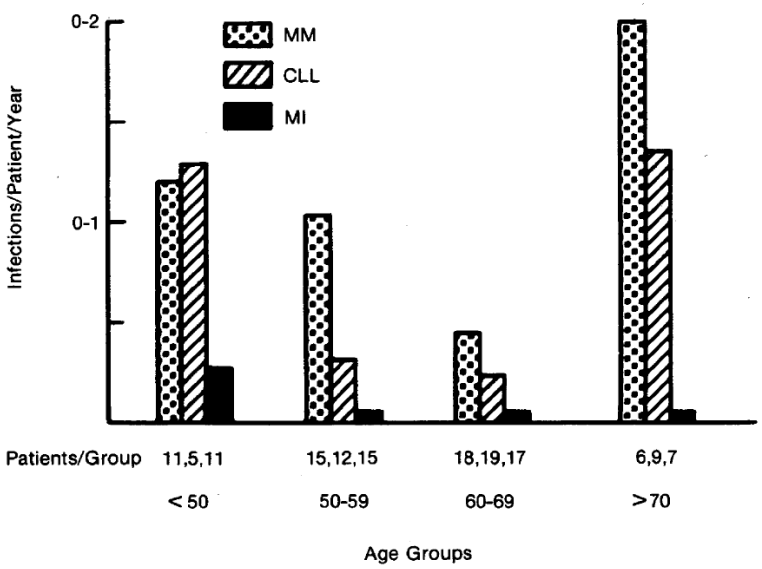
- SPT: negative for common aeroallergens
- CT chest: nonspecific nodules < 3 mm, no bronchiectasis
- IgG = 632 mg/dL, IgM = 55 mg/dL, IgA = 165 mg/dL
- Diphtheria IgG = 0.63, s/p vaccination = 0.60
- Tetanus IgG = 0.97, s/p vaccination = 3.2
- S. pneumo IgG > 1.4 for 6/23 serotypes, s/p vaccination > 1.4 for 5/23 serotypes

Risk of Infection

Summary of Findings*

Category	MM	CLL	MI
Total No. of patients	50	45	50
% of patients with ≥1 infection	78	84	18
Period in years under observation (average ± SD)	1.58 ± 1.4	3.17 ± 2.4	2.17 ± 3.2
Average annual infection rate	0.026	0.009	0.002
Total No. of infections	102	71	9
% of infections while receiving therapy	36	37	. . .
Total mortality	36	30	11
% of deaths primarily due to infections	50	63	9
Site of infection			
Pulmonary	49(9)†	36(6)	4(1)
Urinary tract	22	13	4
Ectodermal	11(1)	14	1
Septicemia	10(5)	4(4)	0
Meningitis	7(4)	1(1)	0
Miscellaneous	3	3	0
Pathogens			
Total identified	73	54	8
Pneumococcus	26(3)‡	9(2)	8
Staphylococcus	10(3)	14(6)	1
Escherichia coli	13(2)	11(3)	2
Pseudomonas	6(1)	6(5)	1
Proteus mirabilis	4(1)	7(2)	3
Haemophilus influenzae	5(2)	2	0
Klebsiella enterobacter	4(1)	2(1)	0
Streptococcus	2	2	0
Meningococcus	0	1	0
Mycobacterium tuberculosis	2	1	0
Herpes zoster	1	4	0
Monilia albicans	0	2(1)	0

* MM indicates multiple myeloma; CLL, chronic lymphocytic leukemia; MI, myocardial infarction.
† Numbers in parentheses are those in which infection was the major factor causing death.
‡ Numbers in parentheses are those in which infections were fatal.



Twomey. Arch Int Med 1973; 132: 562.

Mortality Associated with Infection

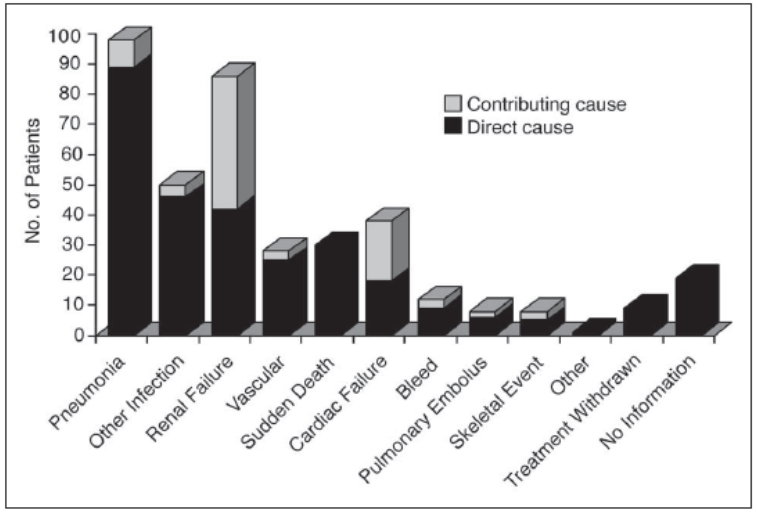


Fig 1. Causes of early deaths. The number of deaths within 60 days of trial entry by direct cause of death and the additional number of patients in whom clinical modality contributed to the cause of death are shown.

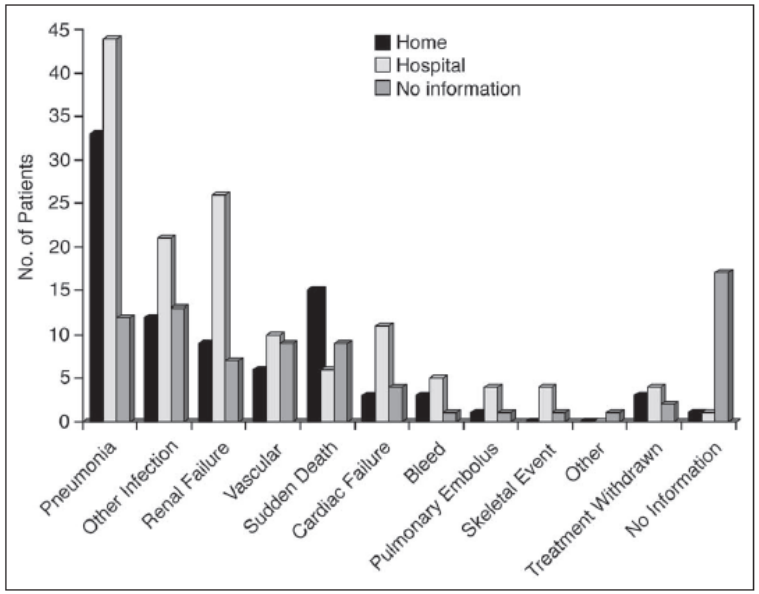


Fig 2. Origin of the final illness. Patients are grouped by the direct cause of death. For each cause, numbers of patients are shown for those in whom the final illness developed at home, in hospital, or for whom information was not available.

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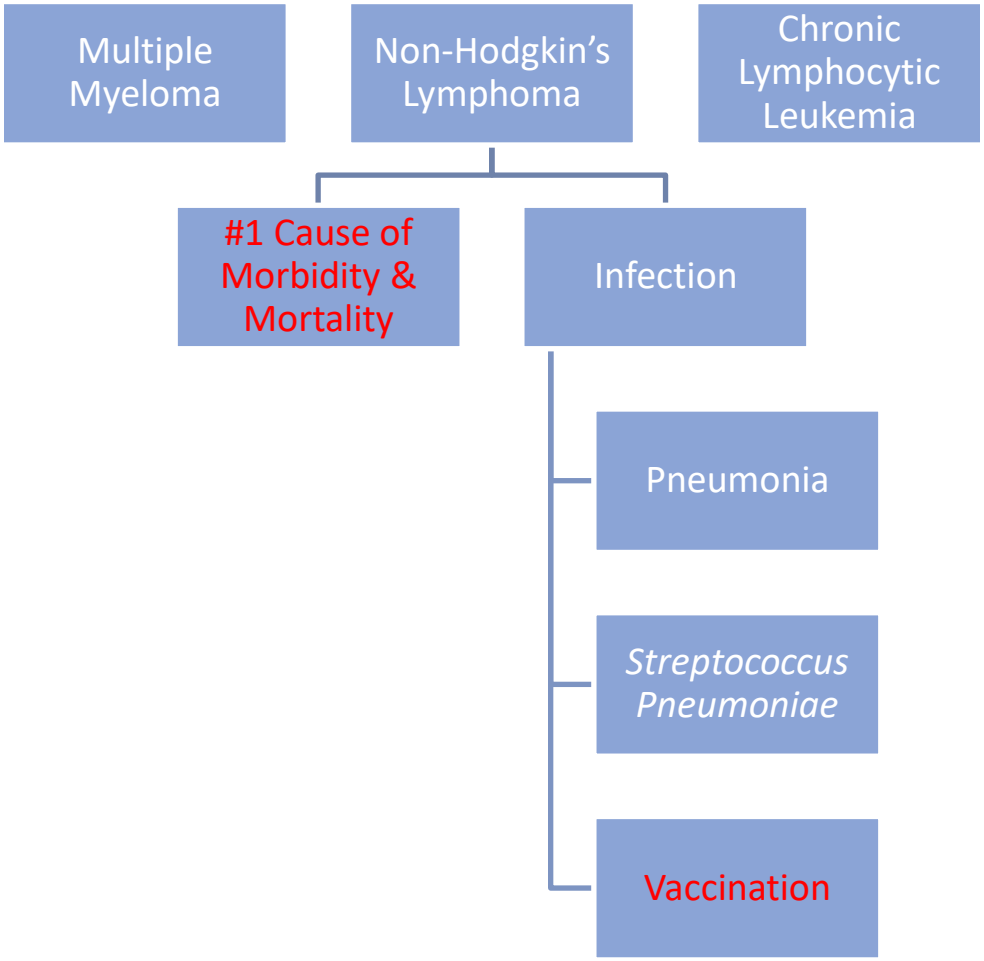
Augustson. J of Clin Onc 2005; 23(36): 9119.

Standard of Care



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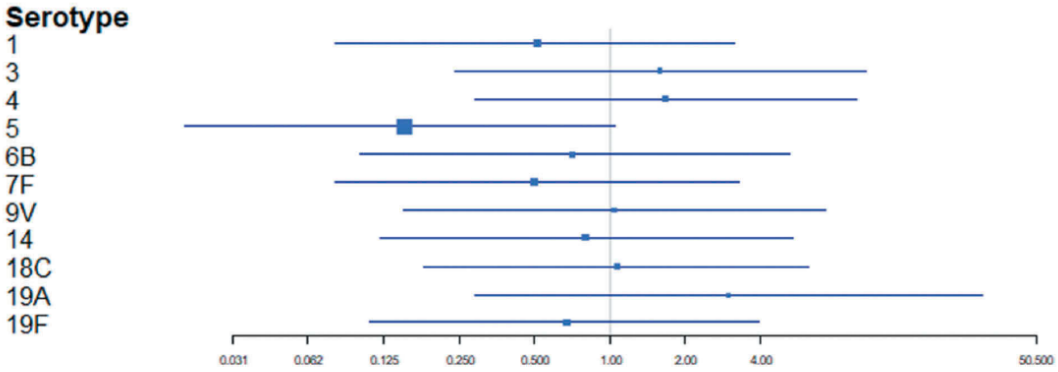
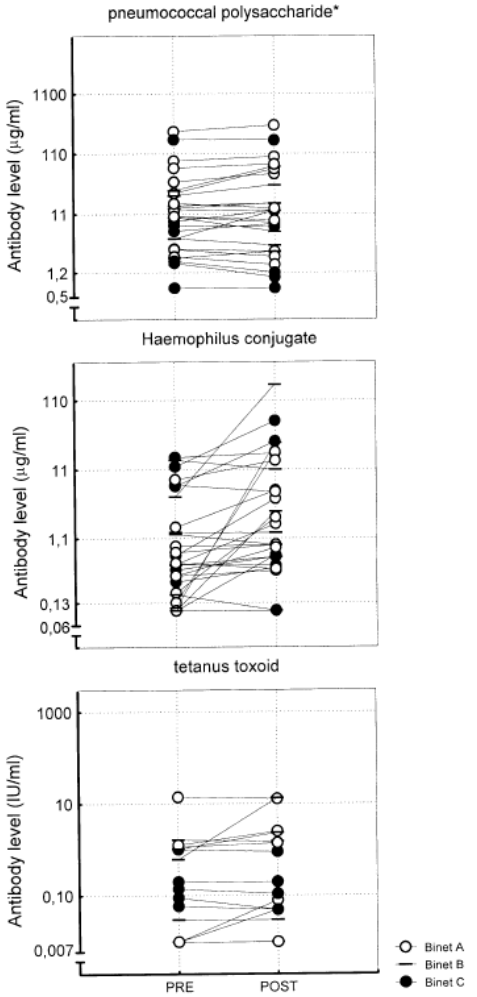
Therapies Aimed at Infections - Vaccination

Table 1 Response to Pneumovax II (total IgG). A protective titre is defined as ≥ 1/640, the geometric mean titre of the normal adult UK population

	Pre-vaccination (*n* = 48)		Post-vaccination (*n* = 43)	
Protective antibody titre	3	6%	17	39%
Suboptimal antibody titre	45	94%	26	61%
Titre below 10th percentile	31	70%	13	30%
Fourfold increase in titre			24	56%
Geometric mean titre	1/53		1/287	



1. Odds ratio of response by IgG serotype with 95% CI



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Nucci. Clin Infec Dis 2009; 49: 1211.
Mustafa. Hum Vac and Immuno 2018.

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Therapies Aimed at Infections – Prophylactic Antibiotics

- Minimal prospective data evaluating efficacy
- Commonly used practice globally
- Guideline-based practice for infection prophylaxis in CLL
- Most commonly used choices are macrolides and sulfa

Table 5. Antimicrobial Agents that Should Be Used with Caution in Patients with Multiple Myeloma

Antimicrobial agent	Comment(s)
CYP2C19 and CYP3A4 inducers (nafcilin and rifampin)	May increase metabolism of bortezomib; monitor therapy
CYP2C19 and CYP3A4 inhibitors (fluconazole, erythromycin, doxycycline, metronidazole, norfloxacin, isoniazid, and tetracycline)	May decrease metabolism of bortezomib; consider therapy modification
Drugs that prolong QT interval (macrolides [erythromycin, clarithromycin, telithromycin, azithromycin], intravenous pentamidine, quinolones [levofloxacin, moxifloxacin], and azoles [fluconazole, itraconazole, voriconazole, posaconazole])	Monitor QT interval and use with caution in patients with cardiac amyloidosis or light chain deposition disease
Nephrotoxic drugs (aminoglycosides, glycopeptides, amphotericin B, foscarnet, and immunomodulators[a])	Use alternative therapies in patients with impaired renal function
Drugs that suppress bone marrow function (linezolid, pirymethamine, and TMP-SMX)	Avoid when possible in patients with poor marrow reserve particularly after receipt of myelosuppressive therapies (including myeloablative conditioning regimens for HCT)

NOTE. HCT, hematopoietic stem cell transplantation; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Immunomodulators include cylcosporin A and tacrolimus.

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Edgar. J of Clin Immunol 2018; 38: 204.

Ig Replacement

Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation (Review)

Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O

Main results

Forty trials were included: thirty included HSCT patients and ten included patients LPD. When polyvalent immunoglobulins or hyperimmune cytomegalovirus (CMV)-IVIG was compared to control for HSCT, there was no difference in all-cause mortality. Polyvalent immunoglobulins significantly reduced the risk for interstitial pneumonitis but increased the risk for veno-occlusive disease and adverse events. In LPD, no benefit in terms of mortality IVIG could be demonstrated but there was a decrease in clinically and microbiologically documented infections.

Authors' conclusions

In patients undergoing HSCT, routine prophylaxis with IVIG is not supported. Its use may be considered in LPD patients with hypogammaglobulinemia and recurrent infections, for reduction of clinically documented infections.

Indication. Recurrent or severe infection with encapsulated bacteria despite prophylactic oral antibiotic therapy in patients with a serum IgG < 5 g/l (excluding a paraprotein).

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Raanani. Cochrane Data Syst Rev 2008. Oct 8(4): CD006501.
Oscier. Brit J of Haem 2012; 159: 541.

Humoral Dysfunction

Table 3 Spontaneous specific IgG antibody titres (results represented as median (range))

Patient group	*Pneumococcal polysaccharides (U/ml)*	*E coli LPS (U/ml)*	*Tetanus (IU/ml)*	*Diphtheria (U/ml)*
Controls (n=62)	63 (0–241)	11 (0–100)	0·40 (0–1·3)	8 (1–122)
Myeloma				
all (n=102)	12 (0–241)	5 (0–93)	0·05 (0–1·3)	2 (0–72)
serious infections (n=49)	12	5	0·06	3
no serious infections (n=53)	11	5	0·04	2

Table 4 Immunisation responses (IgG specific antibodies) in 41 immunised patients

	No serious infections (n=17)		*One or more serious infections* (n=24)*	
Antigen	*Good*	*Poor***	*Good*	*Poor***
Pneumovax II (n=40)	9	8	9	14
Tetanus (n=40)	10	7	12	11
Diphtheria (n=40)	6	11	8	15

* Includes retrospectively defined infections (with good documentary evidence).
** Includes poor and intermediate immunisation responses.
One patient missed immunisation with Pneumovax and another with diphtheria/tetanus.

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Hargreaves. J Clin Path 1995; 48:260

Evaluation of Vaccine Responses

Vaccine	T-cell Independent or Dependent	Protective Response
Haemophilus influenza	Dependent	2-fold increase to > 1.0 µg/ml
Diphtheria	Dependent	2-fold increase to > 0.1 IU/ml
Tetanus	Dependent	2-fold increase to > 0.15 IU/ml
Rabies	Dependent	2-fold increase to 0.5 IU/ml
Meningococcal conjugate	Dependent	2-fold increase to 2.0 µg/ml
Meningococcal polysaccharide	Independent	2-fold increase to 2.0 µg/ml (2 of 4 serotypes)
Pneumococcal polysaccharide (PPV23)	Independent	▪ If baseline < 1.3 µg/ml, increase 2-fold to > 1.3 µg/ml OR increase 4-fold ▪ If baseline > 1.3µg/ml, increase 2-fold ▪ Responses need to be demonstrated by 70% of serotypes
Pneumococcal conjugate (PCV13)	Dependent	▪ If baseline < 1.3 µg/ml, increase 2-fold to > 1.3 µg/ml OR increase 4-fold ▪ If baseline > 1.3µg/ml, increase 2-fold ▪ Responses need to be demonstrated by 70% of serotypes

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Orange. JACI 2012. 130: S1.

Prospective Case Series - CLL

Inclusion Criteria

- Diagnosis of CLL
- Medically stable
- Able to consent and comply with study procedures
- Expected life expectancy > 1 year

Exclusion Criteria

- Previously diagnosed immunodeficiency
- Additional immunosuppressive states
- Previous or ongoing therapy with Ig replacement

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Patient Characteristics - CLL

Demographics	
Participants (n)	19
Male	14 (73.7%)
Female	5 (26.3%)
Age	68 (53-86)
Time since diagnosis	4.7 years (0.25-23 years)

Current Therapy	
None	16 (84.2%)
Ibrutinib	2 (10.5%)
Ublituximab & Umbralisib	1 (5.3%)

Previous Therapies	
No therapy	13
2011 – Fludarabine/rituximab 2013 – Rituximab 2014 – Bendamustine 2014 - Cyclophosphamide	1
2011 – Fludarabine/rituximab	1
2012 – Fludarabine/rituximab 2013 – Fludarabine	1
2014 – Bendamustine/rituximab	1
2015 - Rituximab	1
2016 – Bendamustine/rituximab	1

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Immune Evaluation - CLL

	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)
Median	684	45	102
Range	93-1039	< 12 - 228	26-262

Specific Antibody	Pre-Vaccination IgG	Post-Vaccination IgG	Responders
Diphtheria	0.11 IU/ml	0.14 IU/ml	5/19 (26.3%)
Tetanus	1.21 IU/ML	1.35 IU/ml	7/19 (36.8%)
Streptococcus pneumoniae > 1.3 mcg/ml	8/23 serotypes	7.5/23 serotypes	4/19 (21.1%)

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Case

- 62 y/o Caucasian male with PMH of lymphoma comes in saying he is “sick all the time for the past one year.” Was recently hospitalized for 2 days for bronchitis with hypoxia. Treated with antibiotics and improved. Also reports frequent sinus infections and profound fatigue, which is unusual for him. He also reports intermittent diarrhea. Occurs for a week or two every month for the past 2 years.

Case

- PMH: large cell lymphoma d/xed in 2014
- PSH: None
- Meds: R-CHOP x6 from Nov 2014-March 2016
- SH: Remote history of tobacco use.
- FH: No immunodeficiency.
- PE: Unremarkable

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Evaluation

- CBC normal
- Chemistry panel normal
- IgG = 259 (290 in Jan 2014 while on R-CHOP)
- IgM < 8, IgA = 28, IgE < 2
- Diphtheria IgG = 0.16, s/p vaccination = 0.25
- Tetanus IgG = 0.84, s/p vaccination = 0.80
- S. pneumo IgG > 1.4 for 4/23 serotypes, s/p vaccination > 1.4 for 5/23 serotypes

Prospective Case Series – NHL s/p Rituximab

Inclusion Criteria

- B cell non-Hodgkin's lymphoma
- Treatment with rituximab within 2 years of enrollment
- Medically stable
- Able to consent and comply with study procedures
- Expected life expectancy > 1 year

Exclusion Criteria

- Previously diagnosed immunodeficiency
- Additional immunosuppressive states
- Previous or ongoing therapy with Ig replacement

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Patient Characteristics - NHL

Patient Characteristics	
Participants (n)	16
Male	8 (50%)
Female	8 (50%)
Age ± SD	67.9 ± 9.9
Time since Diagnosis	39.3 months (10-194 months)
Cycles of Rituximab	9.1 (3-30)
Time since Last Cycle	10.9 months (1-24 months)

Malignancy	#
Follicular Lymphoma	7
Diffuse Large B Cell Lymphoma	5
Lymphoplasmacytic Lymphoma	2
Mantle Cell Lymphoma	1
Marginal Cell Lymphoma	1

Therapy	#
Rituximab + Bendamustine	9
R-CHOP*	6
Rituximab monotherapy	1

*CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone

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Immune Evaluation - NHL

	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)
Average ± SD	612 ± 212	113 ± 245	174 ± 238
Median	585	36	121
Range	328-1161	12-991	24-1037

Specific antibody	Pre-Vaccination IgG	Post-Vaccination IgG	Responders
Diphtheria	0.16 ± 0.16 IU/mL	0.42 ± 0.77 IU/mL	4/15 (26.6%)
Tetanus	1.61 ± 1.65 IU/mL	2.16 ± 2.01 IU/mL	1/15 (6.7%)
Streptococcus pneumoniae > 1.3 mcg/mL	5.3 ± 5.8 of 23 serotypes	6.3 ± 6/1 of 23 serotypes	2/15 (13.3%)

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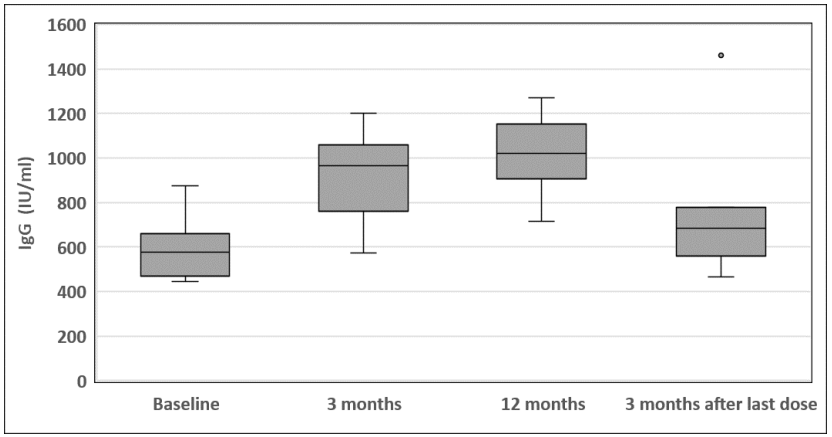
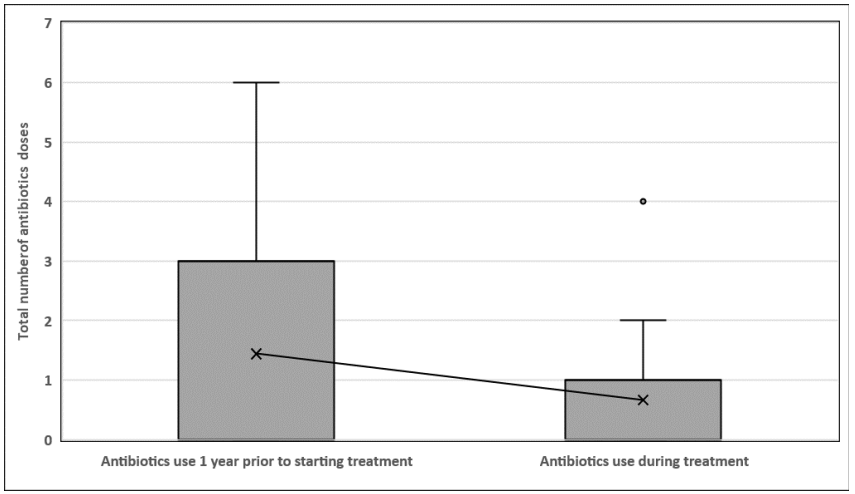
Ig Replacement





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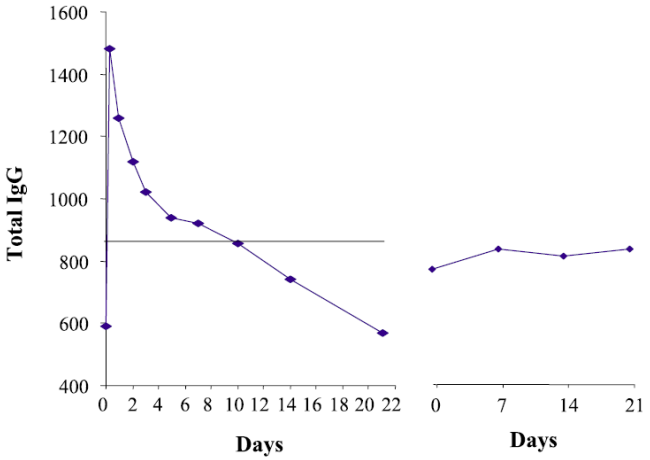
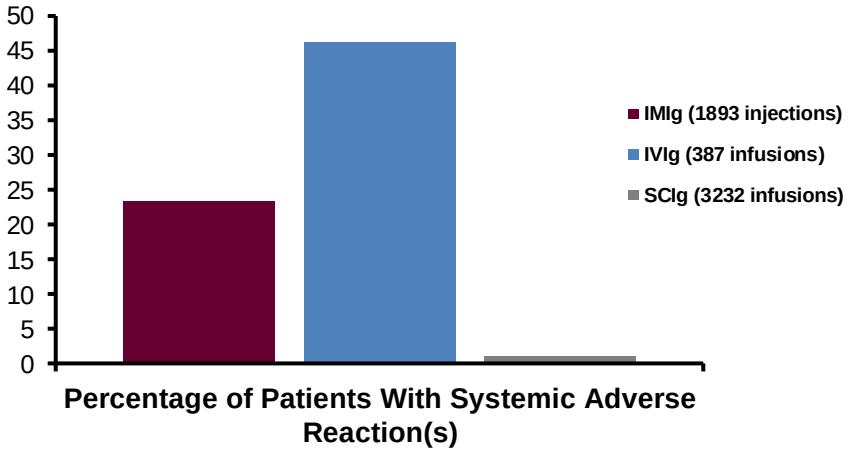
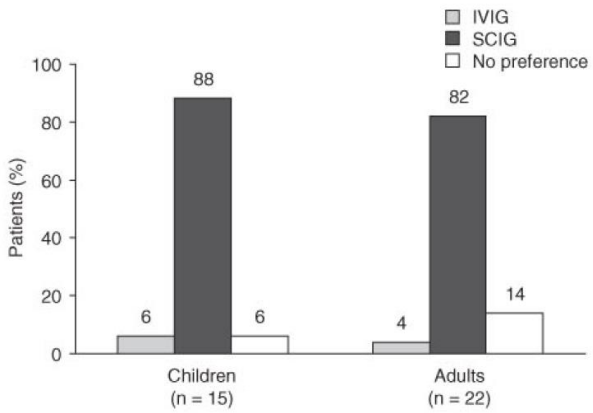
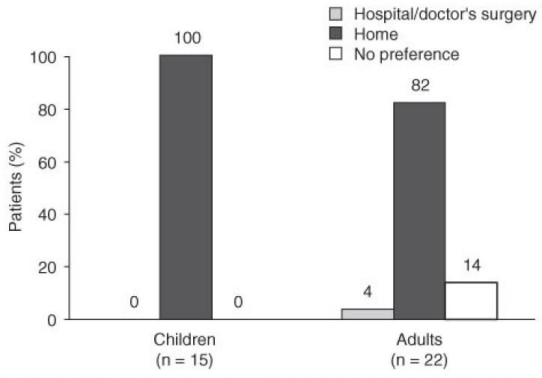
SC Versus IV Ig Replacement









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Gardulf. Lancet 1991. 338(8760): 162.
Gardulf. Biodrugs 2007; 21(2): 105.

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SC Versus IV Ig Replacement

TABLE II. Considerations in the choice of the SC vs IV routes for IgG replacement therapy in primary immunodeficiency diseases

Parameter	SC	IV
Infusion site	SC sites are easily identified and initiated	IV access usually requires trained personnel, may be difficult
Location	Usually given at home	Usually given in the office, hospital, or infusion center
Personnel	Self, partner, or parent	Usually requires a nurse or physician
Characteristics of patients	Reliable, seeks independence	Dependent, wants to be cared for
Costs	Product and infusion supplies, pump	Product, IV supplies, facility fee, nursing charges
AEs	Local site reactions are common but not usually clinically significant; systemic AEs are rare; premedications are not needed	Some patients have systemic AEs may limit rate, may require pre- or postinfusion medication
Dose per treatment	Limited by volume tolerated per site and number of sites	Large dose may be given through a single IV
Infusion frequency	Usually weekly or more often	Once every 3-4 wk
Pharmacokinetics	Steady state achieved by weekly therapy	Peak may be ≥3 times "trough"
"Wear-off effects"	Usually eliminated by steady-state IgG level	Many patients "feel IVIG effects wearing off before next dose is due"

SC, Subcutaneous.

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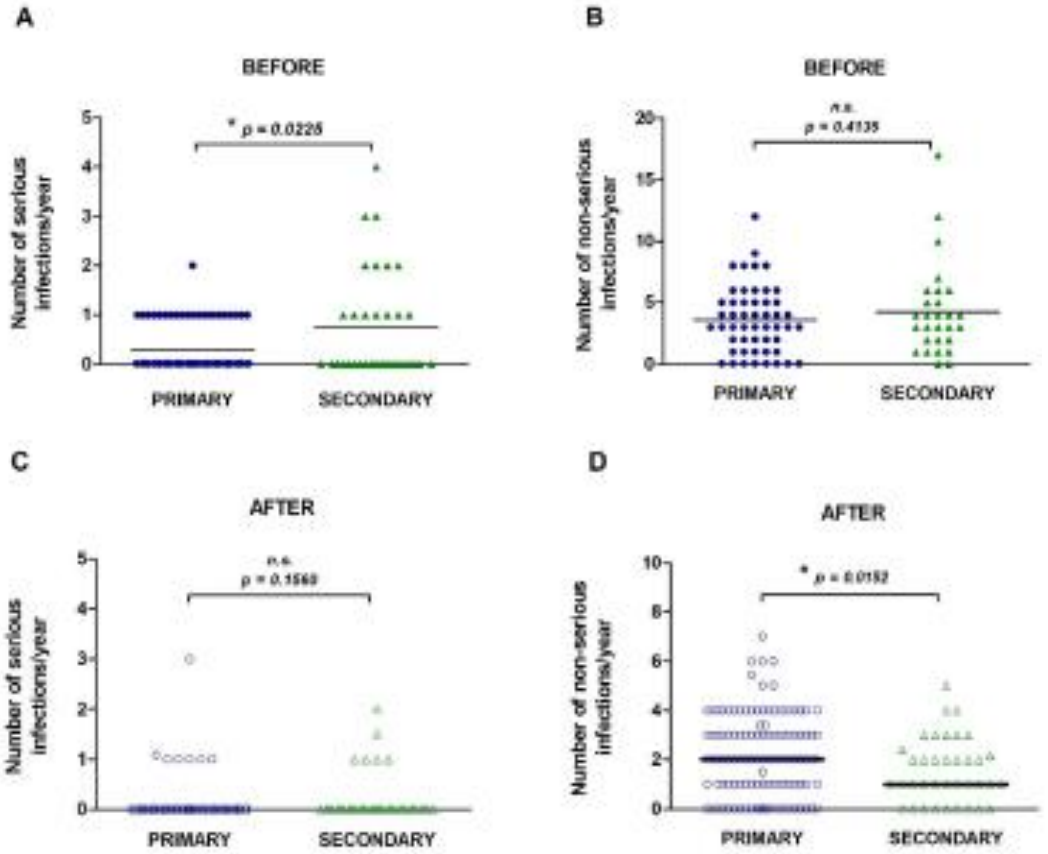
Berger. JACI IP 2013; 1: 558.

Ig in PIDD Versus SID



Duraisengham. PLoS One 2014; 9(6): e100324.

Summary

- SID more common than PIDD
- Malignancy and medications are common causes of SID
- Management strategies for SID
  - Treatment of underlying condition
  - Vaccination
  - Prophylactic antibiotics
  - Ig replacement
- Individualize decision regarding IV versus subq Ig replacement

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Recurrent or Unusual Infections

Trainees	• IgG
Primary Care & Specialists	• IgG, IgM, IgA
Clinical Immunologists	• IgG, IgM, IgA • Vaccine Responses • Lymphocyte subsets • Complement Studies
Hypergam	• SPEP
Hypogam	• Refer
Normal	• Low suspicion: nothing • High suspicion: refer

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Thank You

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