Seasonal Influenza

Immunity and Correlates/ Surrogates of Immunity in Humans

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Overview on Influenza A Immunity

Homotypic immunity after infection with an influenza virus is potent and lasts for years. The immunity is associated with persistence of serum antihemagglutinin antibody.

Resistance of Volunteers with Prior Influenza A/Hong Kong Virus Infection to Challenge with Homologous Virus

(Couch, et al., Dev Biol Stand, 28:295, 1975)

Duration since Initial Infection (Yrs)	Response to A/Hong Kong Challenge[a]				
	No. Vol.	No. with Viral Isol.	No. with Ab Rise	No. Ill	No. with Fever
4	8	0	0	0	0
3	7	0	2	0	0
2	7	0	0	0	0
1	13	0	0	0	0
Control[b]	17	14	13	13	7

[a]Challenge dose was 1000 $TCID_{50}$

[b]Selected to be free of neutralizing antibody to challenge virus

Persistence of A/H3N2 Neutralizing Antibody in Serum After an Influenza Virus Infection

(Couch, Dev Biol Stand, 28:295, 1975)

Years since Infection	Serum GMT[1]	
	Post Inf	Prechallenge
4	6.5	6.1
3	5.4	4.0
2	6.4	4.9
1	5.4	4.5
0	-	≤1

[1]Log 2; no. = 7-17

Frequency of Preexisting Serum HAI Antibody (≥1:10) to Type A Influenza Virus Among Persons in 1976 and 1977

(From: Parkman et al., JID, 136:5722, 1977 and Couch et al., Unpublished Data)

Year	Virus	17-25 Years	52-88 Years
1976	A/Swine (H1N1)	3.8%	92.2%
	A/Victoria (H3N2)	65.0%	58.0%
1978	A/USSR (H1N1)*	25.0%	79.0%

Note: H3N2 viruses had caused influenza annually since 1969

H1N1 viruses had not caused influenza since 1956

*Some A/USSR had occurred the prior winter

Distribution of Isolates of Influenza Virus from Febrile Patients During Successive Epidemics according to Age (Houston, Texas)

(Couch, Developments in Biologicals, Karger, 115:25-30, 2003)

		No. (%) Of Isolates by Age	
Year	Epidemic Virus	<1-34	35-≥ 65
1977-78	A/Texas (H3N2)	523 (77)	154 (23)
1978-79	A/Brazil (H1N1)	237 (99)	3 (1)

Heterotypic immunity after infection with an influenza virus is reduced in potency with increasing time since infection and is primarily attributable to antigenic variation. The reducing immunity correlates with reducing serum antihemagglutinin antibody to the infecting virus.

Recurrence of Influenza in Relation to Antigenic Change and Time since a Documented Type A (H3N2) Infection. A/Victoria/75 Epidemic

(Gill and Murphy, Med J Aust, 88:761, 1977)

Proven Prior Infection	N	Years since Infection	% A/Vic Ab >8	Infected & Ill
None	94	0	15	27.0%
A/Hong Kong	84	6-7	31	17.9%
A/England	60	4	52	8.3%
A/Port Chalmers	69	2	86	4.3%

Clinical Variables Known to Affect Patterns of Seasonal Influenza Infection and Disease

- Age
  - Children: Increased infections
  - Very young children: Increased illness severity risk
  - Elderly: Increased complications risk
- Health status
  - Healthy: Low complication risk
  - Unhealthy: High complication risk
- Prior Antigen exposure
  - Recent: High level of immunity
  - Remote: Low level of immunity (Antigenic variation)

Correlates/Surrogates/Mediators of Immunity to Influenza

Some Truisms of Human Influenza

- Immunity to reinfection develops following an infection
- Immunity to reinfection with an antigenically similar virus (H, N) is potent and lasts for years
- Immunity to reinfection with an antigenically different virus (H, N) is reduced with time and degree of antigenic variation

Thus, the natural history of influenza defines the dominant basis for immunity to influenza in humans as immune mechanisms directed toward the HA and NA glycoproteins.

There is an inverse correlation between pre-exposure serum anti-HA antibody and occurrence of influenza virus infection on exposure

Febrile Illness among Military Recruits in Relation to Pre-epidemic HAI Antibody

(JID, 116:425, 1966)

Pre-epidemic Titer	No.	% Ill
<8	44	43
8	41	29
16	72	28
32	75	9
64	16	0

Relation of Prechallenge Serum Neutralizing Antibody to Infection with an A/H3N2 Virus after Intranasal Challenge

Pre Ab	HK*	Eng*	PC*	Scot*	Vic*
<2-2	80	60	70	73	100
4-8	62	0	25	9	50
16-32	44	0	33	14	0
64-128	21	0	0	0	0
256-512	6		0	0	0
≥1024	0			0	

*% Infection

N – HK = 121, Eng = 17, PC = 21, Scot = 82, Vic = 25

From the Writings of Thomas Francis

"(Serum) antibody titer of individuals who take sick fall within the lower ranges…..Higher titers in unaffected subjects were indicative of resistance." "It is not possible to predict on the basis of antibody titer whether a given subject will develop the disease."

From the Harvey Lectures 1941-42

Mediators Shown to Convey and/or Correlate with Immunity to Influenza Infection and/or Disease

Immune Mediator	Specificity	Rodents	Humans
Serum antibody to:			
HA	Variant	x	x
NA	Variant	x	x
M2	Type	x	
Secretion antibody:			
HA	Variant	x	x
NA	Variant	x	x
Cell mediated			
Cytotoxic lymphs	Type	x	x
NP, M1, ?others			
Cytokines	Type	x	

Some Contributions of Mouse Models to Understanding Influenza Immunity

- Passive administration of IgG anti-HA antibody can prevent infection
- Passive administration of anti-NA and anti-M2 antibody does not prevent infection but reduces the intensity
- Antibody to internal proteins (NP, MI) do not mediate immunity
- Anti-HA antibody can "cure" an established infection; antibody to the NA and M2 cannot
- IgA knockout mouse infections are the same as those in normal mice
- When contiguous, preferential antigen uptake (and antibody responses) on restimulation is for the HA (not NA, probably not M2)

Some Contributions of Mouse Models to Understanding Influenza Immunity

(Continued)

- CD8 cells are the major T cell in the lung and lower airways during influenza
- CD8 CTLs can mediate recovery from pneumonia
- CT8 CTLs alone can reduce the level of infection in the nasal mucosa
- For action, direct CD8-target cell contact via TCR is required
- Normal recovery can occur in the absence of CD4 or CD8 cells but not when both are absent

The potential role for M2 antibody and CTLs is not for prevention of influenza but in hastening recovery and preventing complications

Antibody to the M2 Protein of Influenza Virus

- Present in low amounts in adults
- Requires repeated infection (antigenic stimulus) for significant levels in mice
- Capable of reducing the intensity of infection and hastening clearance of virus in mice
- Could contribute to hastening recovery and preventing complications of influenza but has not been proven of value in human infection

Serum Antibody Responses to the Ectodomain of Matrix 2 Protein Among Infected Mice and Humans

(Feng et al., Virology 3:102, 2006)

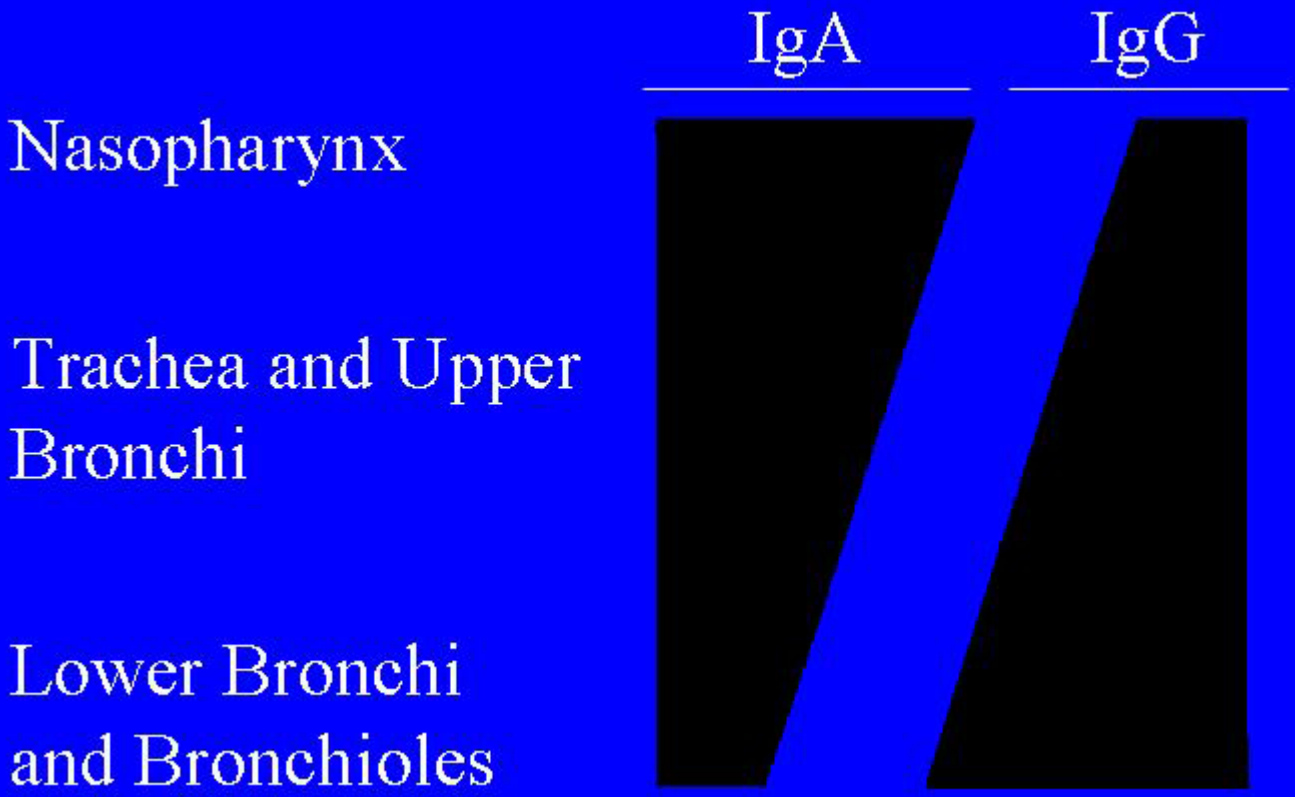
Mice			Humans		
Infection	M2e[1]	NP[1]		M2e[1]	NP[1]
1st	1.9	43	Acute	0.14	20-100
2nd	3.0	51	Conv.	0.56	20-100
3rd	49.0	60	4X↑	49%	21%

[1]microgram/mililiter

Influenza Virus Specific Cytotoxic Lymphocytes in Humans

- Inducible CTLs are present in all healthy persons but are reduced in many elderly
- Reported to hasten clearance of virus in nasal secretions of infected volunteers (McMichael et al.)
- Correlate with protection to clinical influenza in elderly persons (McElhaney et al.)
- That CMI (CTLs) can contribute to immunity in humans seems certain but the relative significance of that contribution in relation to other mediators of immunity in the different age groups and infection, vaccination circumstances have not yet been defined

Relative Proportions IgA and IgG Antibody in Different Parts of the Respiratory Tract



Relation of Antibody to Occurrence of Infection

Antibody Type and Location	% Infected According to Antibody Titer		
	Low or Absent	Intermediate	High
Serum Neut	79	37	15
NS Neut	55	54	18
Serum AN Ab	88	36	43
NS AN Ab	Absent – 56	Present - 0	

*Eleven to 15 volunteers in each group

HA and NA Antibody Conclusion

For maximal/optimal protection against influenza, serum anti-HA (neutralizing) antibody is essential. Anti-NA antibody in serum and anti-HA and anti-NA antibody in nasopharyngeal secretions are highly desirable.

Heterotypic and Heterosubtypic Immunity

- Both immune responses reported decades ago in humans
- In mice:
  - Correlates with crossreactivity in vitro
  - Secretory IgA > IgG
  - Increased by adjuvants – CT
  - Heterosubtypic reported for H1, H2, H3, H5
  - (Also mediated by CMI)

Summary

- Homotypic and heterotypic immunity to influenza that follows infection can be potent and last for years. The degree of immunity correlates with the magnitude of the serum anti-hemagglutinin (HA) antibody to the infecting virus.
- Antibodies to the HA and NA in serum and secretions are proven as powerful mediators of immunity in humans. CTLs appear capable of contributing to immunity but a role for an M2 immune response in human influenza has not been described.