Smallpox Treatment 2002: Topics for Speculation

Peter L. Havens, MS, MD

Medical College of Wisconsin

Children's Hospital of Wisconsin

Milwaukee

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"Because the widespread dissemination of smallpox virus by aerosol poses a serious threat in hospitals, patients should be isolated in the home or other nonhospital facility whenever possible.

Home care for most patients is a reasonable approach, given the fact that little can be done for a patient other than to offer supportive therapy."

Henderson et al. Smallpox as a biological weapon: Medical and public health management. JAMA 1999;281:2127

Supportive Therapy for Influenza A: 11/20/01

Supportive care has come a long way in 30 yrs

In designing the Smallpox Response Plan

Balance:

Patient/Physician expectations for care

Public Health imperatives

Smallpox: Speculations on Possible Treatments, 2002 - Summary

- **Flat / Hemorrhagic: Treat as for shock**
- **Semiconfluent/confluent: Treat as for a burn**
- **All types: Bacterial superinfection likely**
- **Always consider**
  - **Dehydration, renal failure**
  - **Malnutrition**

Koplan JP and Foster SO. Smallpox: Clinical Types, Causes of Death, and Treatment. JID 1979;140:440-1

Smallpox Disease: Variola Major

"The severity of the disease depends on the reaction of the host to the virus…"

Dixon CW. Smallpox. Churchill, 1962.

Poxviruses in cell culture

- **Inhibits cell synthesis of**
  - **DNA, RNA, protein**
- **↑ cell membrane permeability**
- **Leads to cell death**

Moss, Bernard. Poxviridae: the viruses and their replication. In Fields Virology, 3rd edition, 1996

Variola Pathophysiology: Why do people die from smallpox?

- Primarily infects skin and mucous membranes
- Causes focal cell death at those sites
- Organism death from inflammatory response and its complications

Immune response to smallpox

Specific

- Cell mediated immunity (CD4, CD8)
- Humoral immunity

Non specific

- Interferon γ
- Complement
- IL-1
- TNF-a, TNF-b
- Serine proteases
- Natural killer cells

Fenner, Frank. Poxviruses. Fields Virology (3rd ed). 1996

Specific Immunity is Protective: Long-lasting Protection by Smallpox Vaccination in Infancy

Age at Illness Onset (yrs)	Case Fatality Rate (%)	
	Not Vaccinated in infancy	Vaccinated in Infancy
0-4	45	0
5-14	11	0
15-29	14	1
30-49	54	4
>50	50	6

N=1163. Data from Hanna, Liverpool, 1902-3.
In: Cohen J. Science 2001;294:985

←Specific immunity is good

Nonspecific immunity is a mixed blessing→

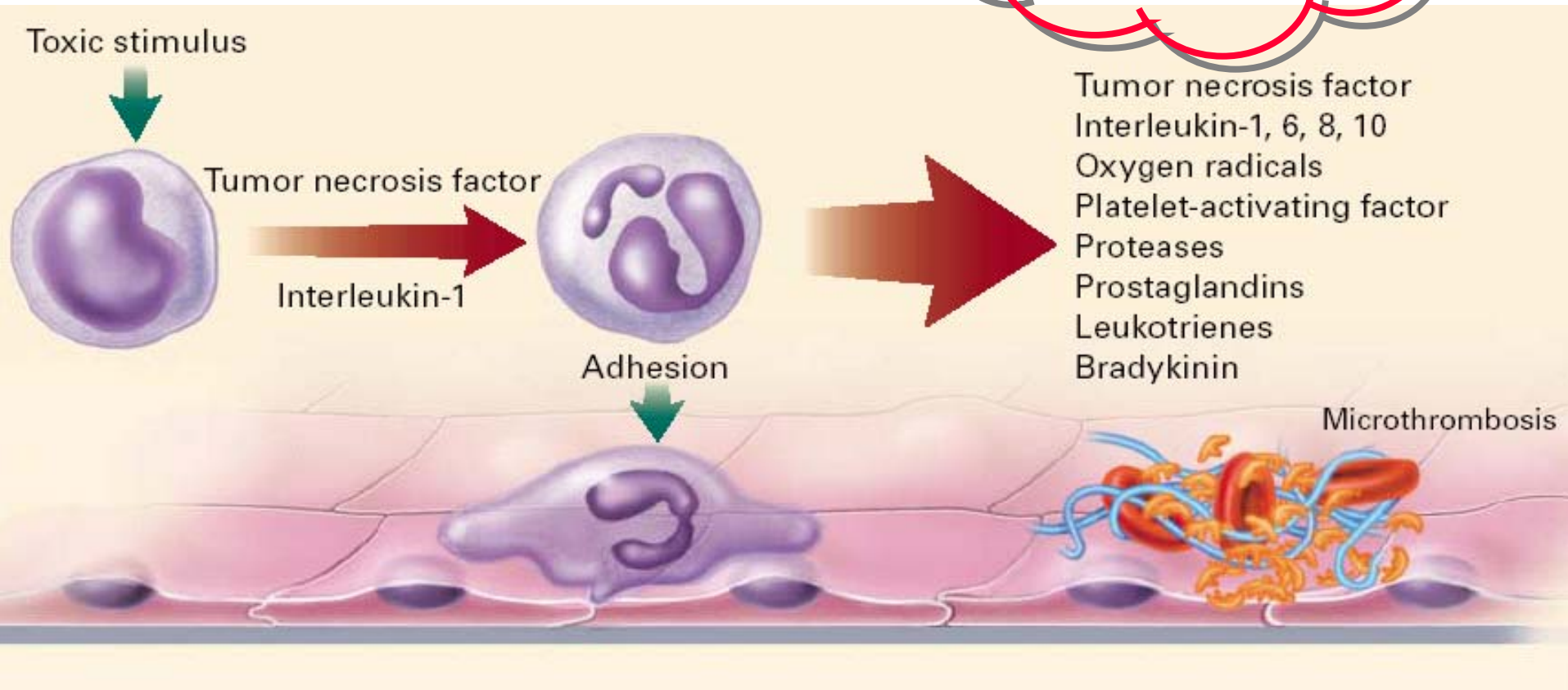
Non-Specific Immune response to Smallpox

- **Interferon γ**
- **Complement**
- **IL-1**
- **TNF-α, TNF-β**
- **Serine proteases**
- **Natural killer cells**

Fenner, Frank. Poxviruses. Fields Virology (3rd ed). 1996

Early Biochemical Events in Sepsis

"Cloud" of inflammatory mediators



Wheeler and Bernard. NEJM 1999;340:207

SIRS, Sepsis, Shock, MODS: ACCP/SCCM Consensus Definitions

- Infection
  - Inflammatory response to microorganisms, or
  - Invasion of normally sterile tissues
- **Systemic Inflammatory Response Syndrome (SIRS)**
  - Systemic response to a variety of processes
- Sepsis
  - Infection plus
  - ≥2 SIRS criteria
- Severe Sepsis
  - Sepsis
  - Organ dysfunction
- Septic shock
  - Sepsis
  - Hypotension despite fluid resuscitation
- **Multiple Organ Dysfunction Syndrome (MODS)**
  - Altered organ function in an acutely ill patient
  - **Homeostasis cannot be maintained without intervention**

Bone RC et al. *Chest.* 1992;101:1644-55.

MODS=Death from inflammatory disease

Effects of the Immune Response to Smallpox: Good News and Bad News

- **Control virus replication**
- **Limit spread**
- **Limit depth and extent of vesicles**
- **Limit duration and severity of illness**

- **Fever**
- **Body aches**
- **Capillary leak**
- **Vasodilatation**
- **Coagulation / DIC**
- **SIRS, Sepsis, Shock, MODS, Death ("without intervention")**

Rabbitpox Model Suggests that Death From Smallpox is from Inflammation and its Complications

- **Rabbitpox**
  - **Hypotension, shock, renal failure, hyperkalemia**

  = SIRS→shock→MODS→Death
- **Smallpox**
  - **"No information is available on blood-pressure or blood-potassium in severe cases of smallpox" (Fenner, 1988, p. 131)**

Smallpox: Clinical Presentations and Possible Treatment Considerations

WHO Classification of Smallpox, and Case-Fatality Rates by Case Type

Type	Case Fatality Rate %
Hemorrhagic	100%
Flat	>90%
Ordinary-confluent	50-75%
Ordinary-semiconfluent	25-50%
Ordinary-discrete	<10%
Vaccine-modified	<10%

Koplan JP and Foster SO. Smallpox: Clinical Types, Causes of Death, and Treatment. JID 1979;140:440-1

Clinical Types of Smallpox, and Case Fatality Rate by Type: 3544 Unvaccinated Hospital Inpatients, Madras

Type	Percent of Total Cases	N in 10,000	Case Fatality Rate %	Deaths in 10,000
Hemorrhagic early	0.7	70	100	70
Hemorrhagic late	1.7	170	96.8	166
Flat	6.7	670	96.5	647
Ordinary confluent	22.8	2280	62.0	1413
Ordinary Semiconfluent	23.9	2390	37.0	874
Ordinary Discrete	42.1	4210	9.3	391
Modified	1.7	170	0	0
Total	100%	10,000	35.5%	3561

46%

64%

Data from Rao, 1972, quoted in Fenner Table 1.2

Dixon's Classification of Smallpox vs Treatment-focused Case Type

Type	Dixon Name	Treatment Focused Case Type	Case Fatality Rate%
1	Fulminating (purpura variolosa)	Inflammatory Shock	100
2	Malignant confluent	Burn / Stevens Johnson Syndrome	70
3	Malignant semiconfluent	Mixed, with Late Bacterial Superinfection Possible	25
4	Benign confluent		20
5	Benign semiconfluent		10
6	Discrete	Minimal Care	2
7	Mild		0
8	Abortive		0
9	Variola sine eruptione		0

Dixon CW. Smallpox. Churchill, 1962

Dixon Type 6: Discrete Smallpox = Minimal Care

- Sudden severe fever
- Fever ↓ within 3 days, at rash onset
- Discrete vesicles
- Secondary fever with pustulation
- Hoarseness and difficulty swallowing rare
- Hemorrhage in areas of trauma, or subconjunctival (vitamin C deficiency?)
- Tertiary fever = secondary infection
- Complications rare. No systemic symptoms after first few days

Most common type

Dixon CW. Smallpox. Churchill, 1962

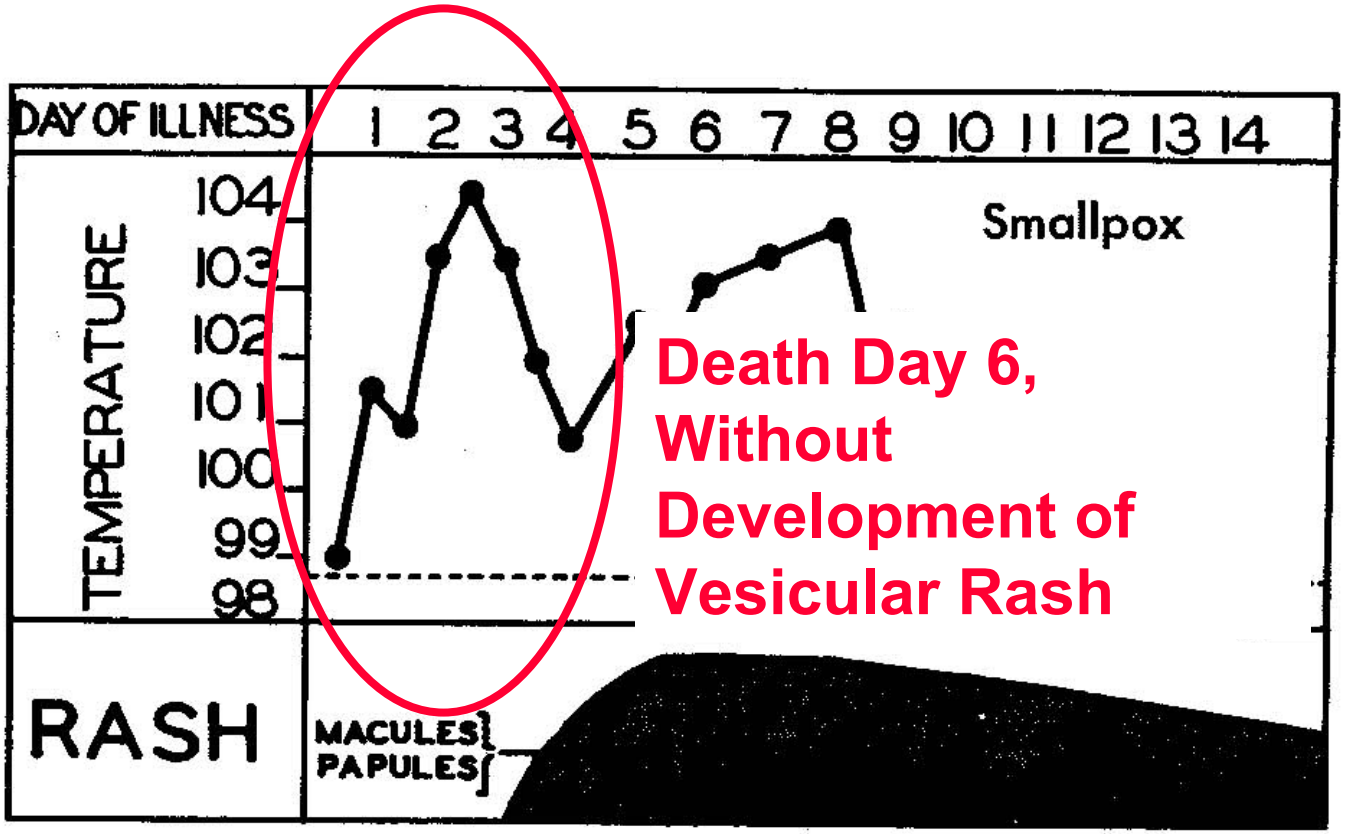
Dixon Type 1: Fulminating = WHO Early Hemorrhagic Smallpox = Inflammatory Shock

Rare

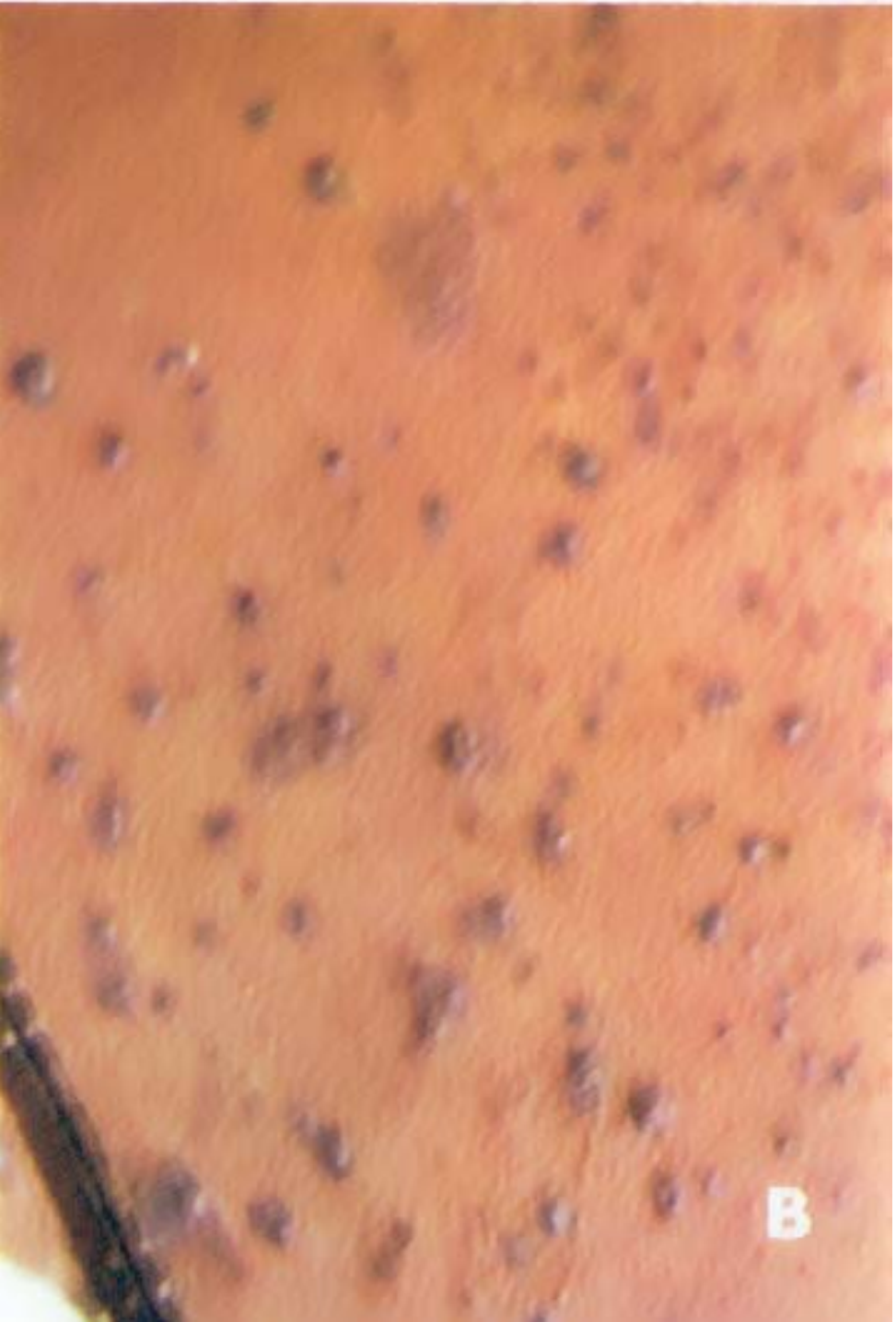
- Hyper-acute course
- Shock, like meningococcemia
- "Intense prostration" with severe headache and backache. Alert, apprehensive.
- Blotchy, blanching erythema arms, trunk,
- Petechiae and hemorrhage mouth and skin.
- May develop superficial vesicles
- Few hemorrhages in respiratory + GI mucosa, myocardium
- ARDS possible
- CBC may suggest leukemia, include myeloblasts

Dixon CW. Smallpox. Churchill, 1962

Early Hemorrhagic Smallpox: Toxemia of the Prodrome continues until Death



"Variolous toxemia is precisely analagous to that of scarlet fever"
Ricketts, Diagnosis of Smallpox. 1908.
Krugman, 1976 (graph)



Hemorrhagic Smallpox: Petechiae and Purpuric Papules: The Rash Does Not Suggest Smallpox

Fenner, Henderson et al. Smallpox and its eradication. 1988. WHO. Plate 1.23B

Hemorrhagic Smallpox in Egypt, 1944

- 17% of cases in this hospital series
- Maculopapular rash: never vesicular
- Measles=most common diagnosis
  - "Angry-looking macules surrounded by a crimson flare"
- Lobster rash (rash ast-acoide)
  - Diffuse bright red erysipelatoid swelling of skin…tense, hot, painful
  - "Hypertoxic scarlet fever"
- White slough covering palate and tongue

Illingworth RS. Smallpox in the middle east.Lancet 1944;2:681

Hemorrhagic Smallpox in Egypt, 1944

- Hematemesis, melena, hematuria
- Persistent fever
- Hemorrhage of palate and conjunctivae
- 12/17 died on day 5 to 12 of illness
  - 3 had pneumonia
  - Most had no vesicles
- Peripheral gangrene "from strangulation of the blood supply by the intense oedema"

Illingworth RS. Smallpox in the middle east.Lancet 1944;2:681

Hemorrhagic Smallpox in Egypt, 1944

- **Leukocytosis (to 38,000) with bands and early lymphocytes**
- **Thrombocytopenia**
- **Prolonged bleeding time**
- **No anemia (hemoconcentration?)**
- **= Systemic Inflammatory response syndrome, capillary leak, and DIC**

Illingworth RS. Smallpox in the middle east.Lancet 1944;2:681

Hemorrhagic Smallpox: Anticipated Treatment Considerations

- Treat as for inflammatory shock
  - Isotonic fluid resuscitation
  - Pressors when needed
  - Tracheal intubation / mechanical ventilation as required for support
    - or for airway obstruction from laryngeal hemorrhage
  - Warm room to prevent vasoconstriction and distal tissue necrosis

Hemorrhagic Smallpox: Anticipated Treatment Considerations-2

- Fever and possible secondary bacteremia
  - Clindamycin (as for Strep/staph TSS)
  - Cefotaxime (as for meningococcemia)
  - and/or penicillin or ampicillin/sulbactam pending bacterial cultures of blood
- Bleeding: DIC and GI mucosal lesions
  - Measure PT, PTT, Platelets
  - Fresh Frozen plasma as indicated
  - Platelet infusions if needed
  - Antacids

Hemorrhagic Smallpox: Anticipated Treatment Considerations-3

- Intense tissue edema
  - Isotonic crystalloid to expand intravascular volume
  - Albumin if severe hypoproteinemia
- Nutritional support: enteral or parenteral alimentation starting early in illness
- Narcotics/anxiolytics for pain/anxiety

Hemorrhagic Smallpox: Other Possible Treatments

Bleeding is a side effect → No!

- **Activated protein C improves survival in patients with severe sepsis**
  - **Bernard GR, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. NEJM 2001;344:699-709**
- **Intravenous Immune globulin (2 grams/kg as a single dose) improves survival in streptococcal toxic shock**
  - **McGeer KR, et al. Intravenous Immunoglobulin appears to be effective for streptococcal toxic shock syndrome. Clin Infect Dis. 1999;28:800-7.**

Dixon Type 2: Malignant Confluent = WHO Flat Smallpox = Burn/SJS

Rare

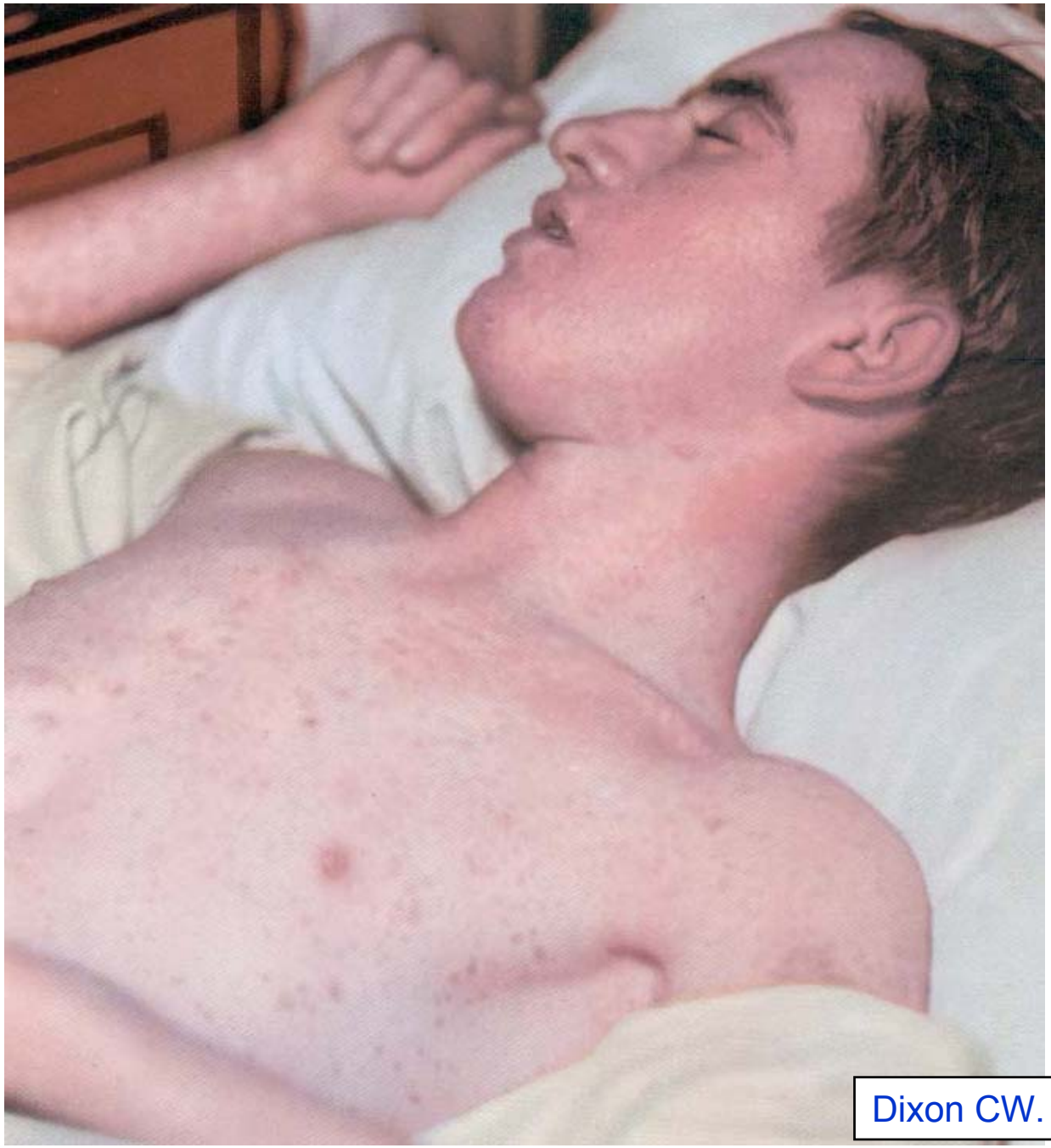
- Sudden onset, T = 38.3-38.9
- Malaise, headache, general muscle aches, backache (often severe), chest pain
- Abdominal pain, vomiting
  - Mucosal/submucosal hemorrhage
  - May have melena
  - Acute abdomen may lead to laparotomy
- Anxiety…"peculiar mental alertness"

Dixon CW. Smallpox. Churchill, 1962

Malignant Confluent / Flat- Day 2 and 3

- **Tachycardia**
- **Irregular petechial and macular rash of chest, neck, back, upper arms**
- **Dusky erythema of face**
  - **Marked intracuticular oedema**
  - **Scalded appearance of skin, like a severe sunburn**
- **Vesicles 4-5 mm, superficial, flattened**

Dixon CW. Smallpox. Churchill, 1962



Type 2: Malignant Confluent Smallpox

Sunburn Facial Rash with Fine Flat Vesicles, predominates on face, little on chest

Dixon CW. Smallpox. Churchill, 1962, fig 17

Malignant Confluent Smallpox = Flat: Intense Skin Edema

Fenner, Henderson et al. Smallpox and its eradication. 1988. WHO. Page 33.

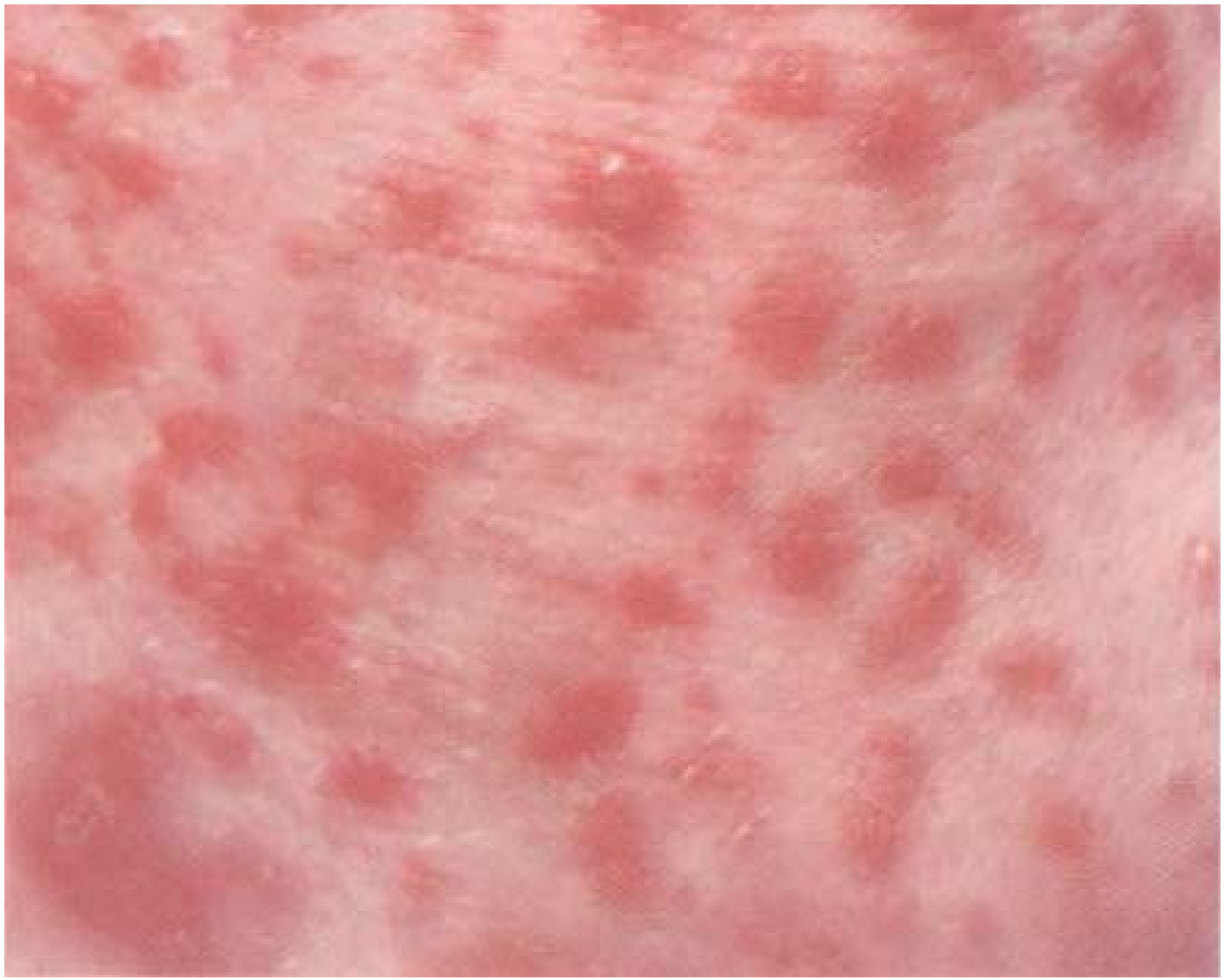
Malignant Confluent Smallpox (= Flat): Intense Skin Edema with Loss of Skin Contours

Fenner, Henderson et al. Smallpox and its eradication. 1988. WHO. Page 33.

Malignant Confluent: Hard Palate Vesicles, Day 6

Dixon CW. Smallpox. Churchill, 1962, fig 26

Type 2, Early Morbilliform Eruption, Day 4



Dixon CW. Smallpox. Churchill, 1962, fig 21

Malignant Confluent, Day 10: “Poor Vesiculation”

Dixon CW. Smallpox. Churchill, 1962, fig 23

Malignant Confluent / Flat: Day 8-14

- Day 8-11: Skin vesicles soft, flat, velvety, some with huge confluent bullae. (like Stevens Johnson Syndrome)
- Day 12-13: Massive exfoliation, like a severe burn
- Keratitis $\rightarrow$ blindness
- Hemoptysis, uterine hemorrhage
- Absence of platelets
- Neutropenia, lymphocytosis

Dixon CW. Smallpox. Churchill, 1962

Malignant Confluent / Flat: Third Week

- Cannot eat or drink, from severe throat pain with swallowing
- Huge areas of skin peeling off with even slight pressure
  - "Widespread stripping of epithelium"
  - "Mortification" from tissue destruction
  - Foetor of smallpox
- Bacterial sepsis
- Death (70%) from severe tissue destruction

Dixon CW. Smallpox. Churchill, 1962

Malignant Confluent: “Mortification”

Dixon CW. Smallpox. Churchill, 1962, fig 40

Malignant Confluent = Flat: Summary of Clinical Presentation

- Clinical presentation like severe Stevens-Johnson syndrome or a severe burn
- Treatment follows same principles
- Treatment-focused case type=Burn/Stevens Johnson syndrome

Malignant Confluent / Flat: Possible Treatment Considerations

- Tissue edema
  - Expand intravascular volume with isotonic crystalloid
  - Replace protein loss as indicated with albumin
  - Monitor electrolytes and renal function
  - Central venous access to monitor central venous pressure and oxygen delivery, and guide treatment

Malignant Confluent / Flat: Possible Treatment Considerations - 2

- Mouth and GI lesions
  - Enteral alimentation if possible, via nasogastric or nasojejunal tube
  - Intravenous hyperalimentation if needed
- Tracheal lesions may require intubation for airway obstruction
- GI Bleeding, DIC
  - Platelets, Fresh Frozen Plasma
  - Antacids

Malignant Confluent / Flat: Possible Treatment Considerations - 3

- "Burn" wounds
  - Fluids as noted
    - "Sunburn" with vesicles $\Rightarrow$ first and second degree burns
    - "Mortification" $\Rightarrow$ third degree burns
    - Volume expansion may limit depth and extent of tissue destruction
  - Debridement of devitalized tissue to prevent infection
  - Topical antibacterial treatment

Malignant Confluent / Flat: Possible Treatment Considerations - 4

- **Secondary infection**
  - **Blood cultures, lesion cultures**
  - **Treat as needed: anticipate Staphylococcus and Group A streptococcus**
  - **Pseudomonas aeruginosa possible, as in a burn wound**

Dixon Type 3: Malignant Semi-confluent = WHO Ordinary Confluent =Mixed Treatment Type

- Starts like Type 2, but rash less widespread
- Remission of fever and symptoms at the beginning of eruptive phase
- Day 8-10: Vesiculation but no pustulation
- Day 10-11: Diffuse lobster-red rash base
- Day 12-15: Death (25%) from "toxemia or hemorrhage" (Bacterial superinfection and DIC)

Dixon CW. Smallpox. Churchill, 1962

Smallpox: Speculations on Possible Treatments

1. Treat as for inflammatory shock
2. Treat as for a burn
3. Bacterial superinfection likely
4. Minimal care type most common

- Always consider
  - Dehydration, renal failure
  - Nutritional support
  - Airway involvement

After Koplan JP and Foster SO. Smallpox: Clinical Types, Causes of Death, and Treatment. JID 1979;140:440-1

Smallpox: Speculation on Specific Treatment Possibilities

(Everything up to this has been supportive care)

Cidofovir is Active Against DNA Viruses

- **Nucleotide analogue, inhibits viral DNA polymerase by competitive inhibition of dCTP**
- **Phosphorylated to active diphosphate form by host cellular enzymes**
- **Cidofovir diphosphate-choline adduct**
  - **T½ = 87 hours**
  - **intracellular reservoir**
  - **weekly administration**
- **FDA approved for treatment of CMV retinitis in persons with AIDS**

Lea AP, Bryson HM. Cidofovir. Drugs 1996;52:225-30

Cidofovir Dosing and Toxicity

- **Usual Dose = 5 mg/kg, intravenously, once weekly**
- **Cleared in kidneys**
- **Toxicities:**
  - **Nephrotoxicity, with proteinuria and ↑ creatinine**
  - **Neutropenia**

Lea AP, Bryson HM. Cidofovir. Drugs 1996;52:225-30

Cidofovir: Preventing Nephrotoxicity

- **Probenecid 2 grams 3 hours before, then 1 gram at 2 and 8 hours after the time of cidofovir administration**
  - **Decreases renal tubular secretion**
  - **Can cause nausea, vomiting, headache, fever, flushing**
- **Normal saline 1-2 liter infusion prior to dosing of cidofovir**

Lea AP, Bryson HM. Cidofovir. Drugs 1996;52:225-30

Cidofovir Toxicity when Administered with Prehydration and Probenecid

Toxicity	Percent
Neutropenia	10 – 15%
Proteinuria, Fanconi, ↑creatinine	5 – 22%
Iritis/uveitis (AIDS patients with CMV retinitis)	10 – 50%
Nausea/vomiting	9%
Fever, myositis	6-16%
Skin rash/pruritis	4%
Discontinued for side effect	20 – 25%

Lea AP, Bryson HM. Cidofovir. Drugs 1996;52:225-30
Plosker, Noble. Cidofovir. Drugs 1999;58:325-45

Cidofovir Protects Mice Against Lethal Cowpox Infection after Intranasal or Aerosol Challenge

- **5 mg/kg cidofovir 100% protective if given day 0 (at the same time as the virus)**
- **100 mg/kg cidofovir needed for protection if given day 1-3 after virus administration**

Bray M. Martinez M. Smee DF. Kefauver D. Thompson E. Huggins JW. Cidofovir protects mice against lethal aerosol or intranasal cowpox virus challenge. Journal of Infectious Diseases.2000 181:10-9.

Timing of Cidofovir for Treatment after Aerosol Cowpox Challenge: Immunocompetent Mouse Model

Day of Administration of Cidofovir 100 mg/kg	Survival after Aerosol Cowpox Challenge
Control	0/10
Day 0	20/20
Day 2 after cowpox	9/10
Day 4 after cowpox	20/20
Day 6 after cowpox	5/10

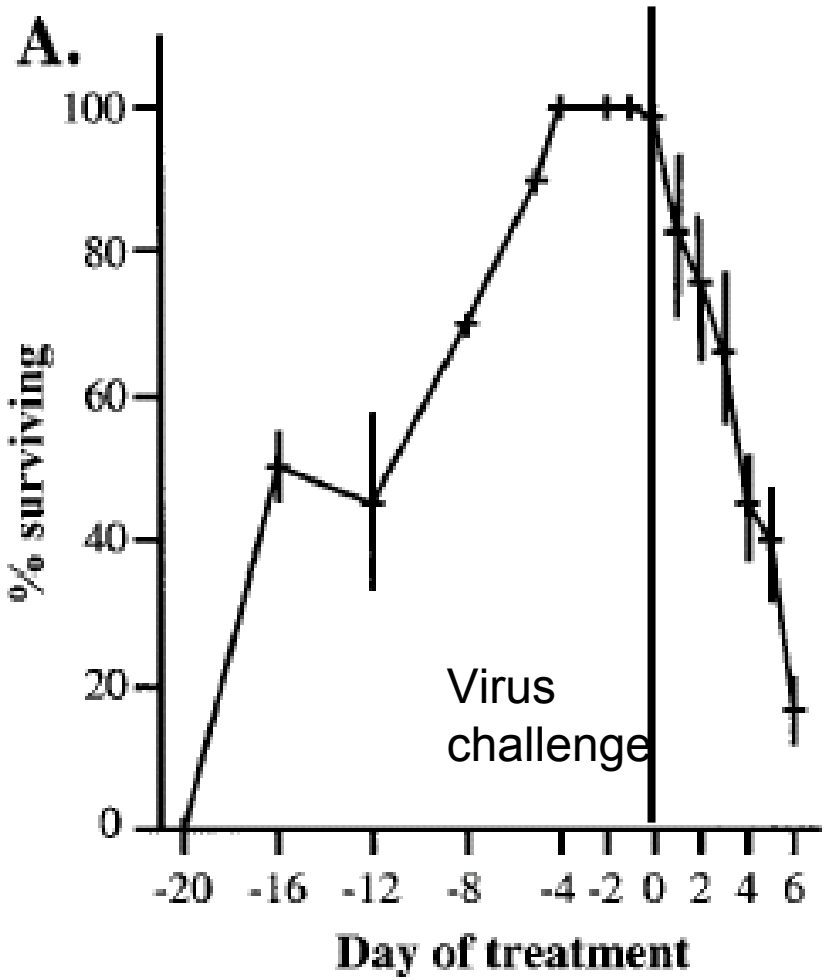
Day 14: clinical smallpox

Bray M. JID.2000 181:10-19.

Prevention and/or Treatment: Timing of Cidofovir 100 mg/kg in Intranasal Cowpox Challenge: Immunocompetent Mouse Model

Cidofovir as prevention:

- Toxicity
- Possible benefit if given before exposure
- ?Prevent vaccine benefit?



Cidofovir as treatment:

- Toxicity
- Possible benefit if given early after infection
- Clinical smallpox = day 14 after virus exposure

Bray M. JID.2000 181:10-19.

Other Therapies for Variola Infection

- **Cidofovir therapeutic index>10**
- **10 other compounds therapeutic index>200**
- **3 compounds therapeutic index>1500**
- **Development ongoing:**
  - **How will clinical benefit be proven? (Historical controls won't work)**

LeDuc JW, Jahrling PB. Strengthening national preparedness for smallpox: an update. EID 2001;7:155-157

Smallpox Treatment Speculation: Summary

Smallpox: Speculations on Possible Treatments, 2002 - Summary

1. Treat as for inflammatory shock
2. Treat as for a burn
3. Bacterial superinfection likely

- Always consider
  - Dehydration, renal failure
  - Nutritional support
  - Airway involvement
- Antivirals helpful? Consider cidofovir.

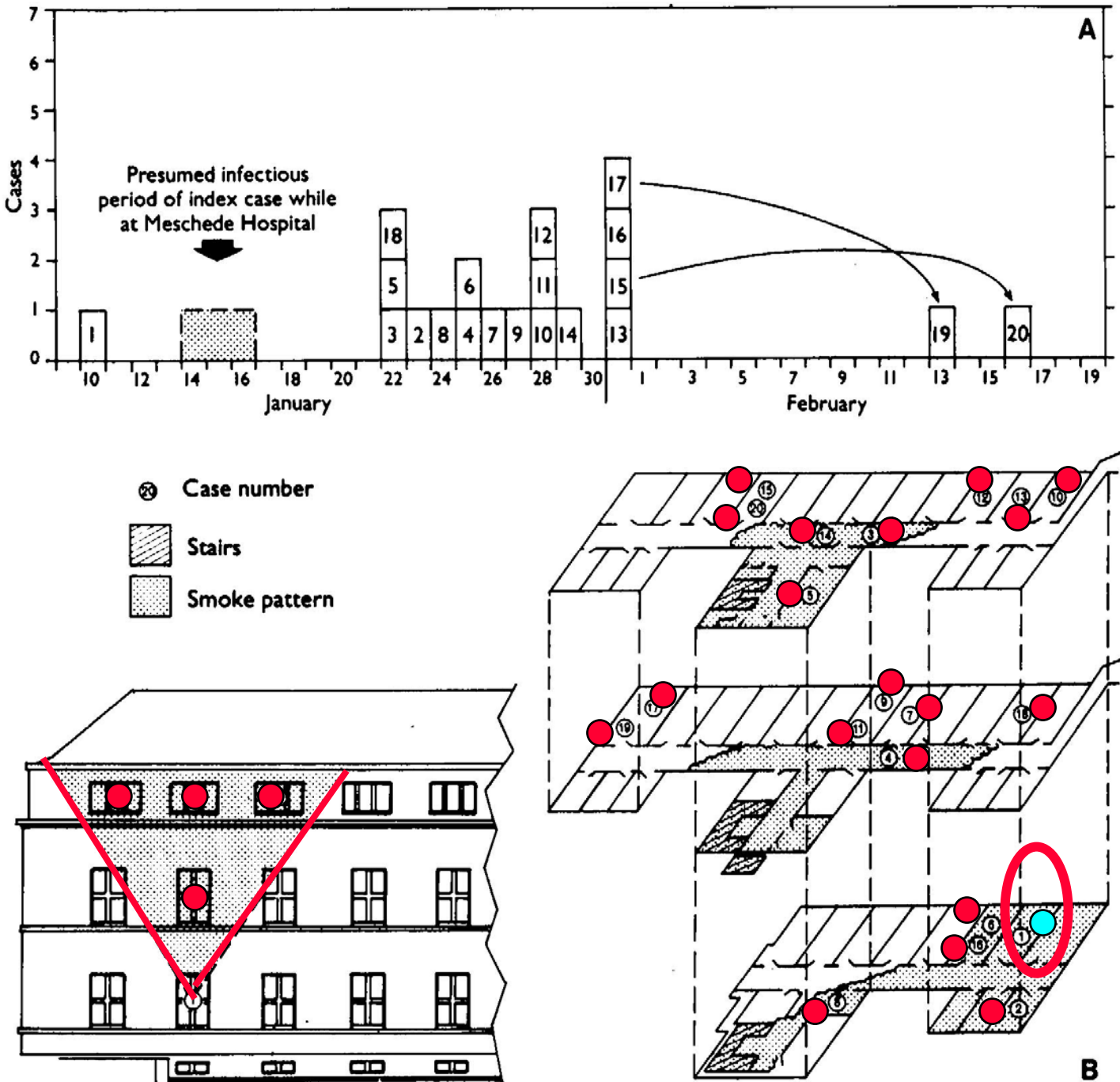
After Koplan JP and Foster SO. Smallpox: Clinical Types, Causes of Death, and Treatment. JID 1979;140:440-1

Hospital Treatment in a Smallpox "Event"

- Patients with fever and prostration will come to the hospital
- They may not look like they have smallpox
- Intensive treatment requirements will rapidly overwhelm existing services and isolation capabilities
- Inhospital spread is certain, and more frequent than spread out of hospitals
- Plans need to include hospital-level treatment (perhaps not in a hospital)

Supplemental Slides

Airborne Spread of Smallpox in the Meschede Hospital



Index case: isolated as Typhoid fever

Fenner. 1988.Fig. 4.9

The Plan Has to Consider Both

Public Health Priorities

Clinical Concerns

Chinzei Hachiro Tametomo

The Archer Prevents the Smallpox Demon from Coming

In a smallpox event, Treatment may help (supportive > specific)

Implementation: at Motel 6?

Fenner. 1988.Fig. 5.3

Non-Hospitalized Patients Were Less Likely to Die: Bangladesh, 1972-3

Location of Care	Case-Fatality Rate %
Hospital	51%
Non-Hospital	21%

Koplan, Azizullah, Foster. Trop Geog Med.1978;30:355

Urban Hospital and Rural Village Smallpox in Bangladesh

- **Only severe cases were admitted to hospital.**
- **Patients with more severe disease were less able to travel to their home villages.**
- **“Devoted family care was better than the nursing provided in grossly overcrowded hospitals”. (Fenner)**

Koplan, Azizullah, Foster. Trop Geog Med.1978;30:355