•2024•
CENLA POTPOURRI
ALEXANDRIA LOUISIANA

INVASIVE GROUP A STREPTOCOCCUS INFECTION IN CHILDREN

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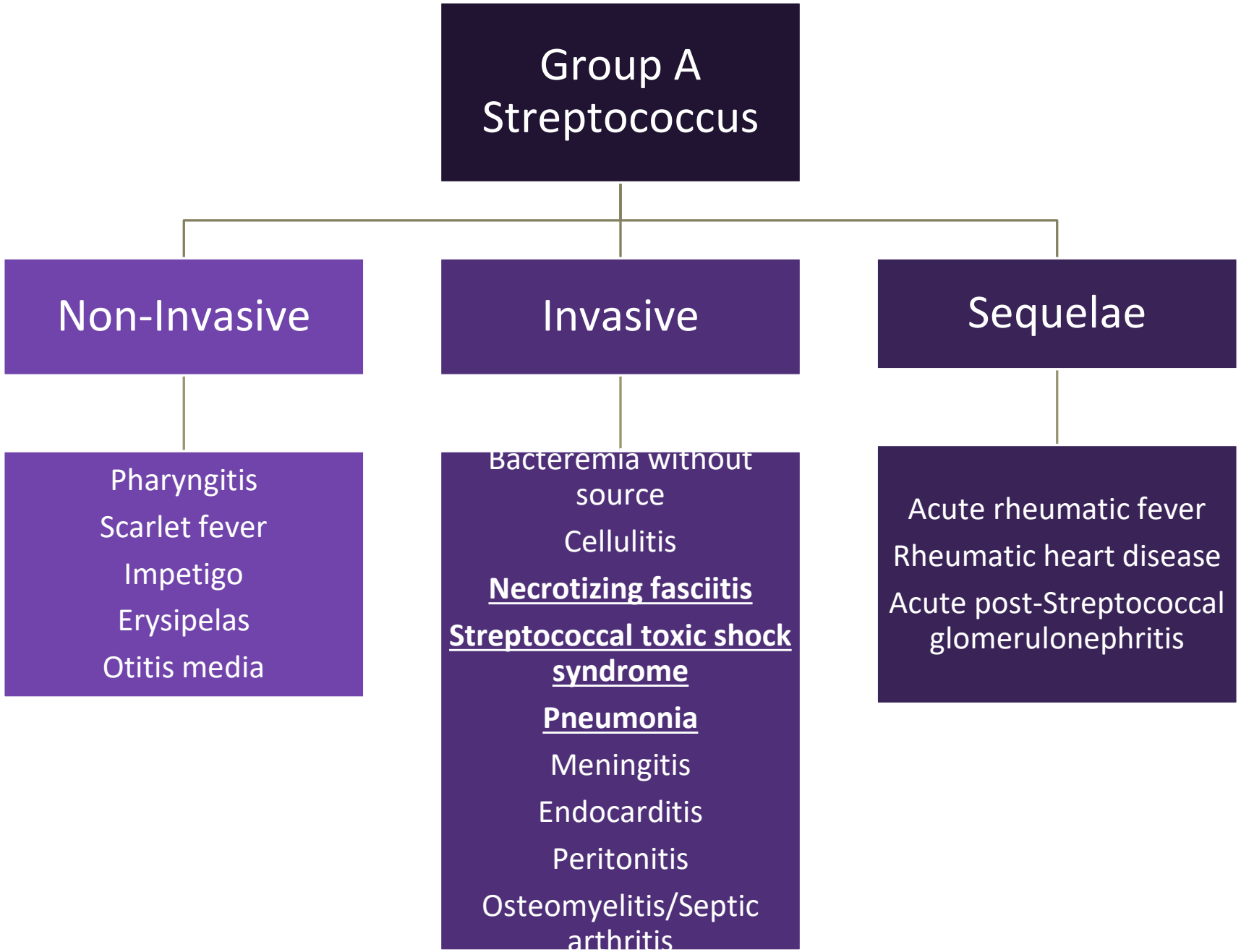
Objectives

- At the conclusion of this activity, learners will be able to:
  - Identify the major manifestations of group A Streptococcal infection in children
  - Plan an appropriate treatment regimen for invasive group A Streptococcal infections
  - Describe the virulence factors of group A Streptococcal infections which lead to critical illness

Join the Q&A and answer MOC part 2 questions at slido.com. Log in with the code #CENLApotpourri


Group A Streptococcus
Non-Invasive
Invasive
Sequelae
Pharyngitis
Scarlet fever
Impetigo
Erysipelas
Otitis media
Bacteremia without source
Cellulitis
Necrotizing fasciitis
Streptococcal toxic shock syndrome
Pneumonia
Meningitis
Endocarditis
Peritonitis
Osteomyelitis/Septic arthritis
Acute rheumatic fever
Rheumatic heart disease
Acute post-Streptococcal glomerulonephritis

Health · Second Opinion

Why deadly invasive strep A infections are

Wellness

CDC warns of a rise in severe strep A infections among children

Common antibiotics are still in shortage as strep cases rise

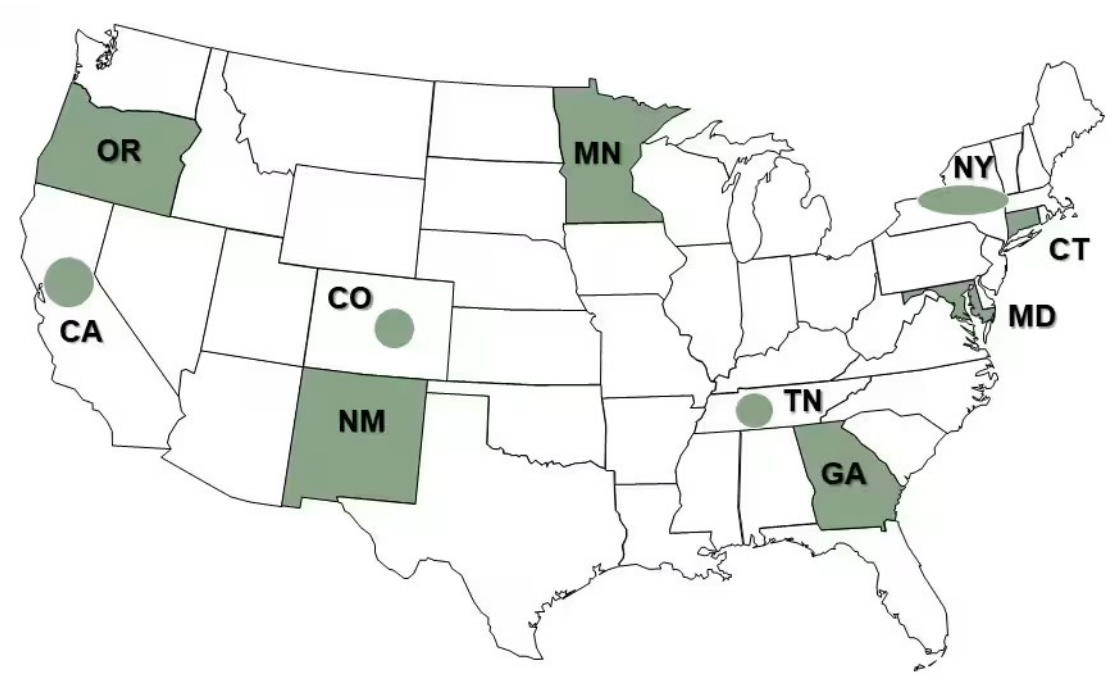
By Amanda Musa, CNN

6 minute read · Published 6:47 AM EST, Wed November 8, 2023

STREPTOCOCCAL SURVEILLANCE IN THE US

CDC uses two surveillance systems to track GAS:

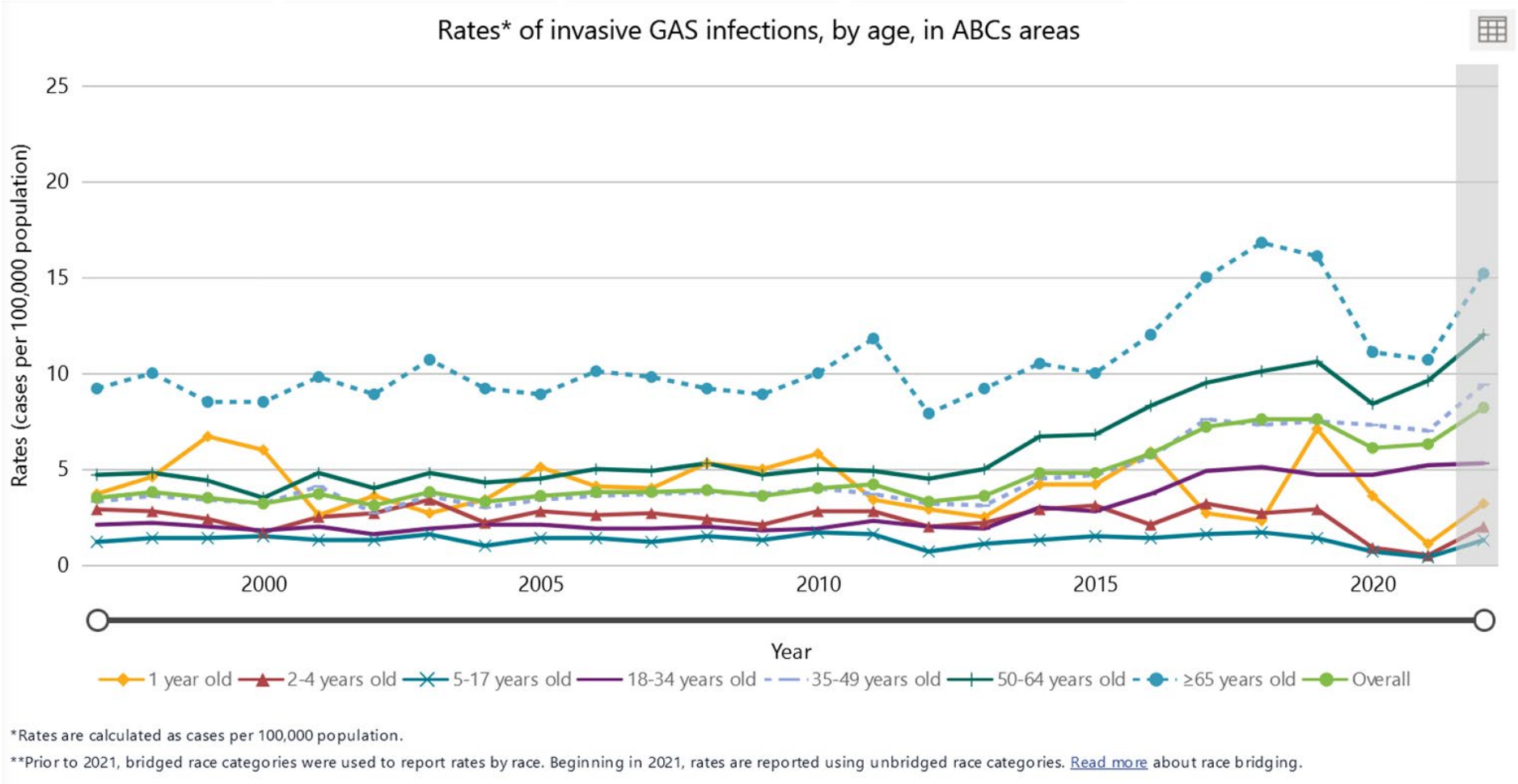
- Tracks Streptococcal Toxic Shock Syndrome via the National Notifiable Diseases Surveillance System (NNDSS)
- CDC collaboration with some state health departments and academic institutions to conduct GAS surveillance for invasive disease (Active Bacterial Core surveillance: ABCs)
  - This covers a total population of 45.5 million individuals



TRENDS IN INVASIVE GROUP A STREPTOCOCCUS

Overall, rates of invasive GAS have been increasing since 2014

Preliminary 2023 data indicate the number of serious infections caused by GAS reached a 20-year high



https://www.cdc.gov/abcs/bact-facts/data-dashboard.html

YOU MAY REMEMBER…

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Dear LSBME Licensees,

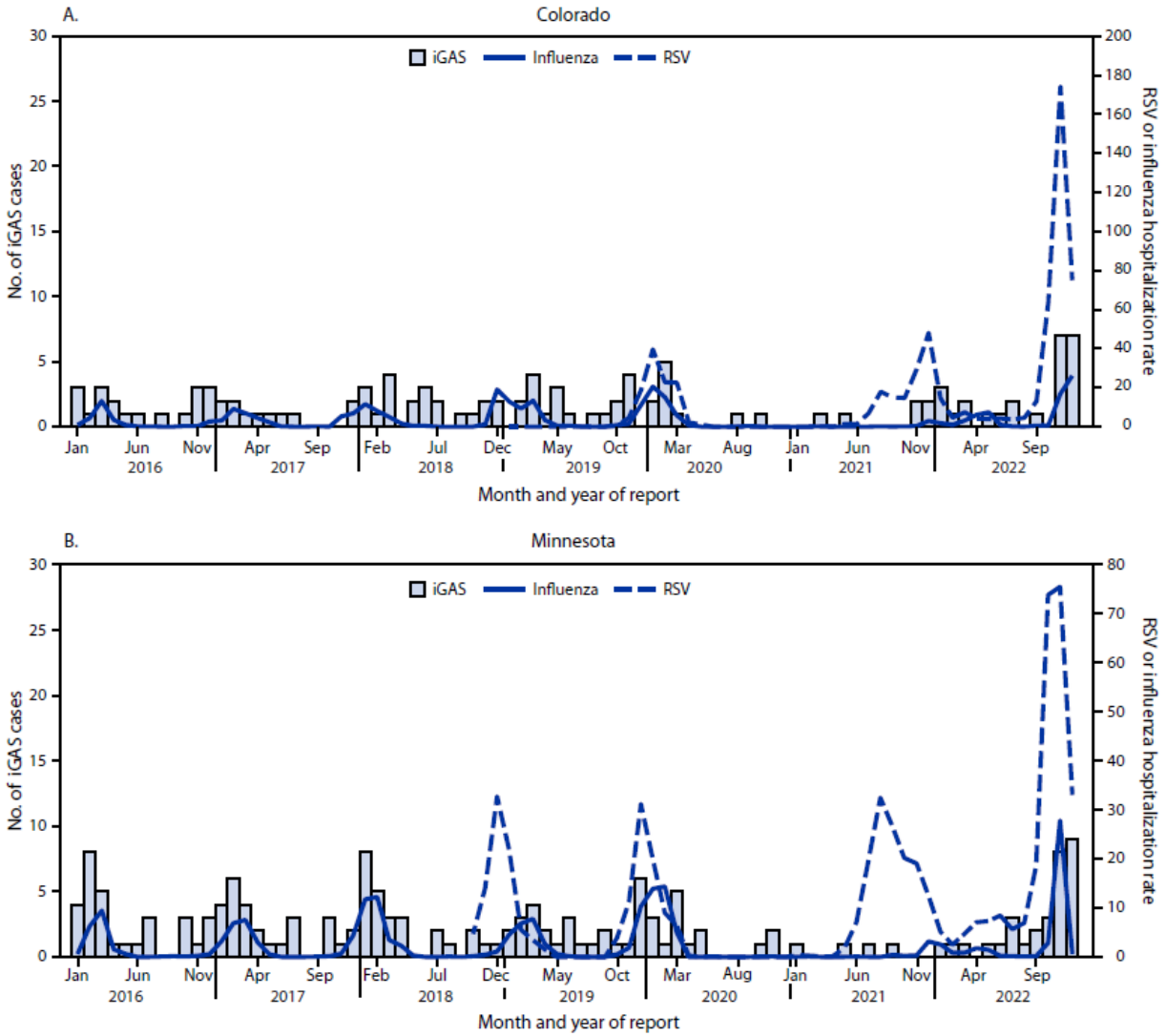
12/27/2022 04:29:29 PM
Message Urgency: HIGH

This message is being sent via the Louisiana Department of Health Emergency Operations Center's (LDH EOC) Louisiana Health Alert Network (LA HAN) for all LA HAN recipients. This message is from LDH regarding Increase in Pediatric Invasive Group A Streptococcal Infections . Please see the message below to share and distribute with relevant stakeholders and partners through your own distribution channels.

Increase in Pediatric Invasive Group A Streptococcal Infections

Summary
The Centers for Disease Control and Prevention (CDC) and the Louisiana Department of Health (LDH) are issuing this Health Alert Network (HAN) Health Advisory to notify clinicians and public health authorities of a recent increase in pediatric invasive group A streptococcal (iGAS) infections. In November 2022, CDC was notified of a possible increase in iGAS infections among children at a hospital in Colorado. Potential increases in pediatric iGAS cases in other states were subsequently noted by contributors to the Infectious Diseases Society of America's provider-based Emerging Infections Network and by certain jurisdictions participating in CDC's Active Bacterial Core Surveillance System (ABCs). A similar increase has been observed in Louisiana. The number of iGAS cases reported among pediatric patients in Louisiana remains relatively low. However, the number of cases reported year to date in 2022 is approximately 3 times higher than the average annual number of cases reported during the preceding 10 years.

FIGURE. Cases of invasive group A *Streptococcus* infections* and hospitalization rates† for influenza§ and respiratory syncytial virus¶ among children and adolescents aged <18 years — Colorado and Minnesota, January 2016–December 2022**



Barnes, Meghan. "Notes from the field: increase in pediatric invasive group A Streptococcus infections—Colorado and Minnesota, October–December 2022." *MMWR. Morbidity and Mortality Weekly Report* 72 (2023).

COLORADO SURGE

Fall of 2022 sharp rise in GAS hospitalizations in Colorado

Pneumonia dominated in ICU (15% pre-pandemic → 24% post-pandemic)

Peak illnesses corresponded with RSV and influenza

Table 1. Patient Characteristics, Clinical Presentations, and Outcomes Among 2022–2023 Colorado iGAS Outbreak Cases, by PICU Status

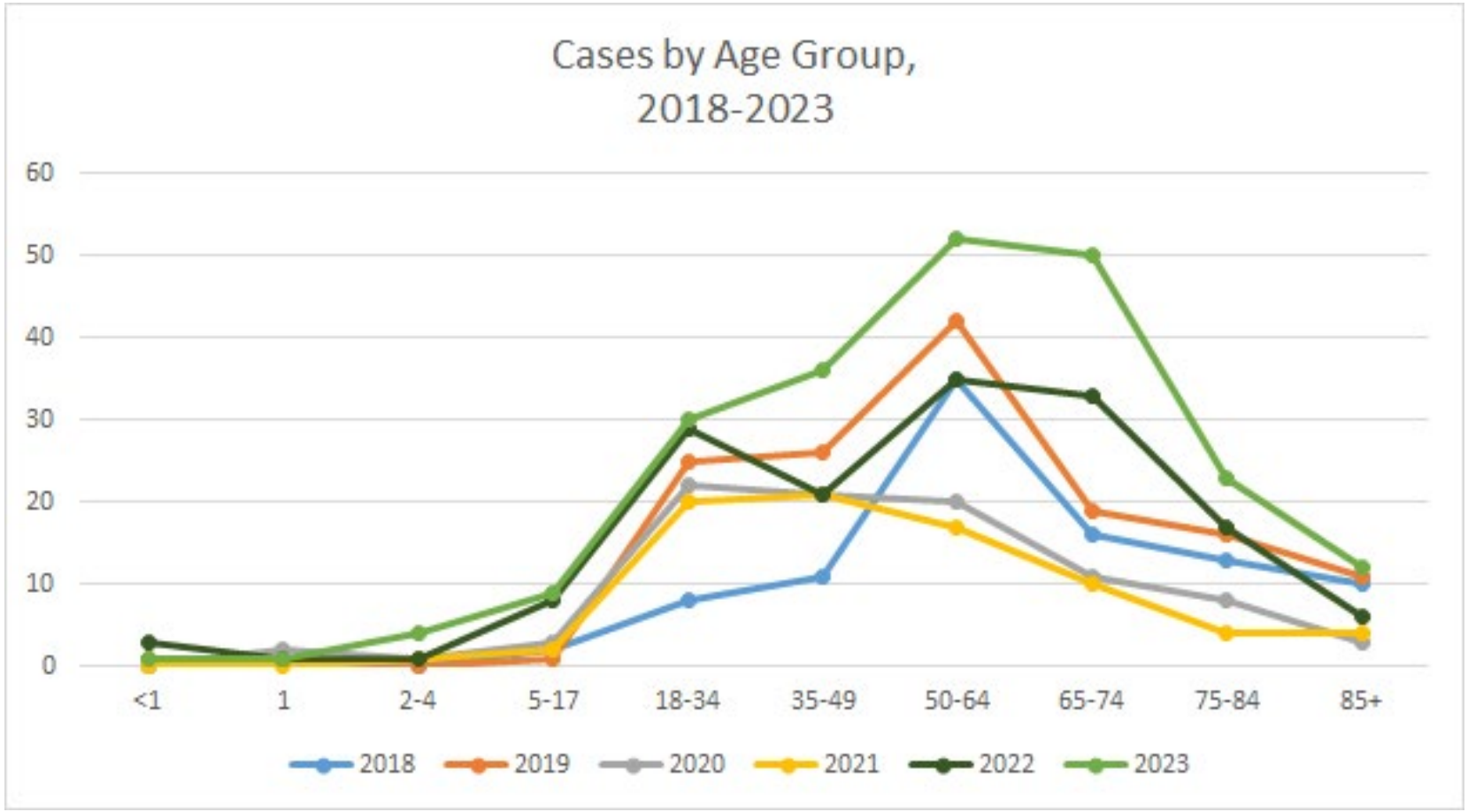
	N (%) or Median (IQR)		
	Total	PICU	Non-PICU
	(*N* = 96)	(*N* = 37)	(*N* = 59)
Patient characteristics			
Age (years)	5.7 (2.7–9.9)	6.2 (2.6–10.6)	5.7 (2.8–9.2)
Male sex	63 (66%)	25 (68%)	38 (64%)
Underlying medical condition, any	29 (30%)	14 (38%)	15 (25%)
Excluding asthma and eczema	21 (22%)	12 (32%)	9 (15%)
Immunocompromised status[a]	10 (10%)	5 (14%)	5 (8%)
Received annual influenza vaccine[b]	34 (35%)	17 (46%)	17 (29%)
Completed COVID-19 vaccine series[c]	14 (15%)	6 (16%)	8 (14%)
Laboratory findings			
C-reactive protein, initial (mg/dL)	7.7 (6.3–26.4)	15.5 (7–22.8)	6.4 (3.4–9.6)
C-reactive protein, peak (mg/dL)	19.4 (6.3–26.4)	25.2 (20.9–32.4)	8.4 (4.2–20.6)
WBC, initial (× 10^9/L)	14.1 (10–18.7)	11.9 (5.8–14.9)	15.6 (12.3–19.6)
Bandemia[d], initial	9 (9%)	8 (22%)	1 (2%)
Leukopenia[e], initial	9 (9%)	9 (24%)	0 (0%)
Predisposing and associated symptoms			
URI symptoms	57 (59%)	26 (70%)	31 (53%)
Positive viral testing, any[f]	29 (30%)	19 (51%)	10 (17%)
Positive for RSV, flu, or SARS-CoV-2[f]	14 (15%)	7 (19%)	7 (12%)
Sore throat without URI symptoms	4 (4%)	1 (3%)	3 (5%)
Received GAS RADT/throat culture	16 (17%)	8 (22%)	8 (14%)
RADT/throat culture positive	13/16 (81%)	7/8 (88%)	6/8 (75%)
Trauma, wound, skin lesions	13 (14%)	1 (3%)	12 (20%)
Clinical manifestations			
Toxic shock syndrome	10 (10%)	10 (27%)	0 (0%)
Necrotizing fasciitis	4 (4%)	4 (11%)	0 (0%)
Multifocal disease[g]	13 (14%)	10 (27%)	3 (5%)
Nonfocal bacteremia	5 (5%)	4 (11%)	1 (2%)
Pneumonia	23 (24%)	18 (49%)	5 (8%)
Musculoskeletal infection	31 (32%)	10 (27%)	21 (36%)
Skin and soft-tissue infection	7 (7%)	2 (5%)	5 (8%)
Head and neck infection	35 (36%)	7 (19%)	28 (47%)
Other	5 (5%)	3 (8%)	2 (3%)
Treatment and prophylaxis			
Beta-lactam antibiotic	96 (100%)	37 (100%)	59 (100%)
Adjunctive protein synthesis inhibitor	35 (36%)	26 (70%)	9 (15%)
PSI duration (days)	5 (3.5–11)	5 (4.3–10.5)	4 (2–11)
Adjunctive IVIG	18 (19%)	16 (43%)	2 (3%)
Household prophylaxis recommended	29 (30%)	17 (46%)	12 (20%)
Outcomes			
Hospital LOS (days)	5 (3–11)	11 (6–17)	4 (3–5.8)
PICU	37 (39%)	–	–
Surgical intervention[h]	76 (79%)	28 (76%)	48 (81%)
Death	4 (4%)	4 (11%)	0 (0%)

Ho, Erin C., et al. "Outbreak of invasive group a streptococcus in children—Colorado, October 2022–April 2023." *Journal of the Pediatric Infectious Diseases Society* 12.10 (2023): 540-548.

INVASIVE GROUP A STREPTOCOCCUS IN LOUISIANA, 2018-2023

Age (years)	2018	2019	2020	2021	2022	2023
<1	0	1	0	0	3	1
1	1	1	2	0	1	1
2-4	0	0	1	1	1	4
5-17	2	1	3	2	8	9
18-34	8	25	22	20	29	30
35-49	11	26	21	21	21	36
50-64	35	42	20	17	35	52
65-74	16	19	11	10	33	50
75-84	13	16	8	4	17	23
85+	10	11	3	4	6	12
Total	**96**	**142**	**91**	**79**	**154**	**218**

Source:
Infectious Disease Epidemiology, Louisiana Department of Health
Thank you Andrea Salinas, MPH, CIC



WHY IS THIS HAPPENING?

Multifactorial!

One hypothesis behind the jump in invasive GAS infections is a change in the dominant strain to a more toxigenic strain

Using isolates from the ABC surveillance, found an increase in the US of the hypertoxigenic $M1_{UK}$ strain from 1.7% to 11% - this strain also dominated in the described European surges in invasive GAS

Immune debt following COVID-19?

GAS taking advantage of surge in respiratory viral infections after the COVID-19 lockdown?

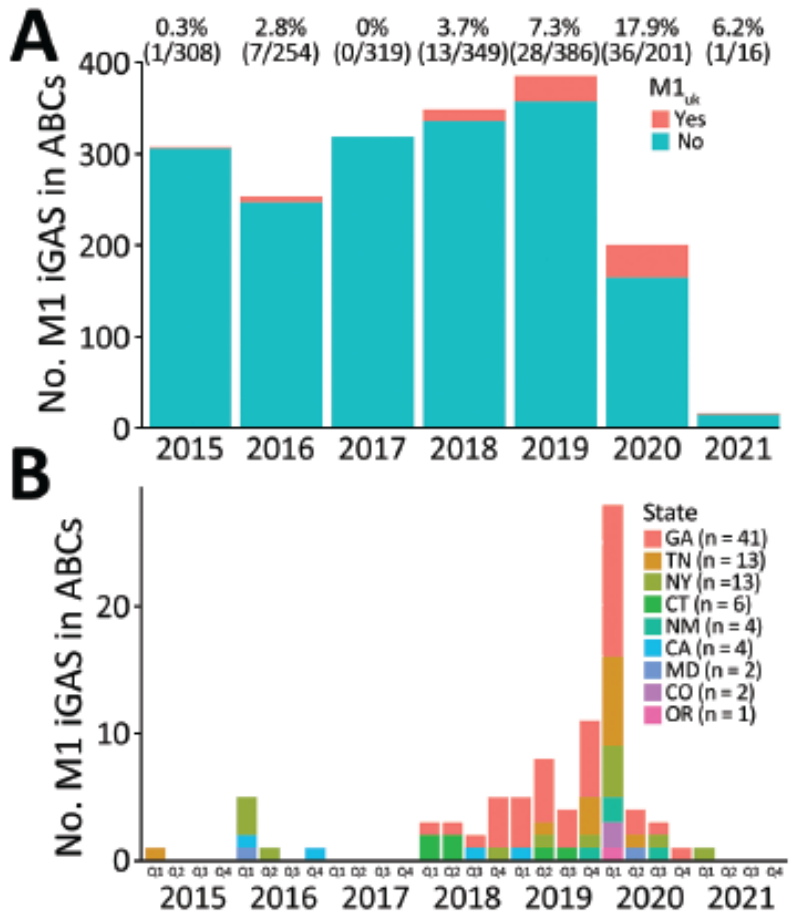


Figure 1. Expansion of $M1_{UK}$ lineage in serotype M1 iGAS in the United States, 2015–2021. A) Counts and percentages of $M1_{UK}$ isolates among M1 iGAS isolates in ABCs during 2015–2021. B) Number of $M1_{UK}$ infections over time in 9 states that are part of the ABCs system. Key shows total number of $M1_{UK}$ infections during 2015–2021 for each state. ABCs, Active Bacterial Core Surveillance System; iGAS, invasive group A *Streptococcus* disease; Q, quarter.

Li, Yuan, et al. "Expansion of invasive group A Streptococcus M1UK lineage in active bacterial core surveillance, United States, 2019–2021." *Emerging Infectious Diseases* 29.10 (2023): 2116.

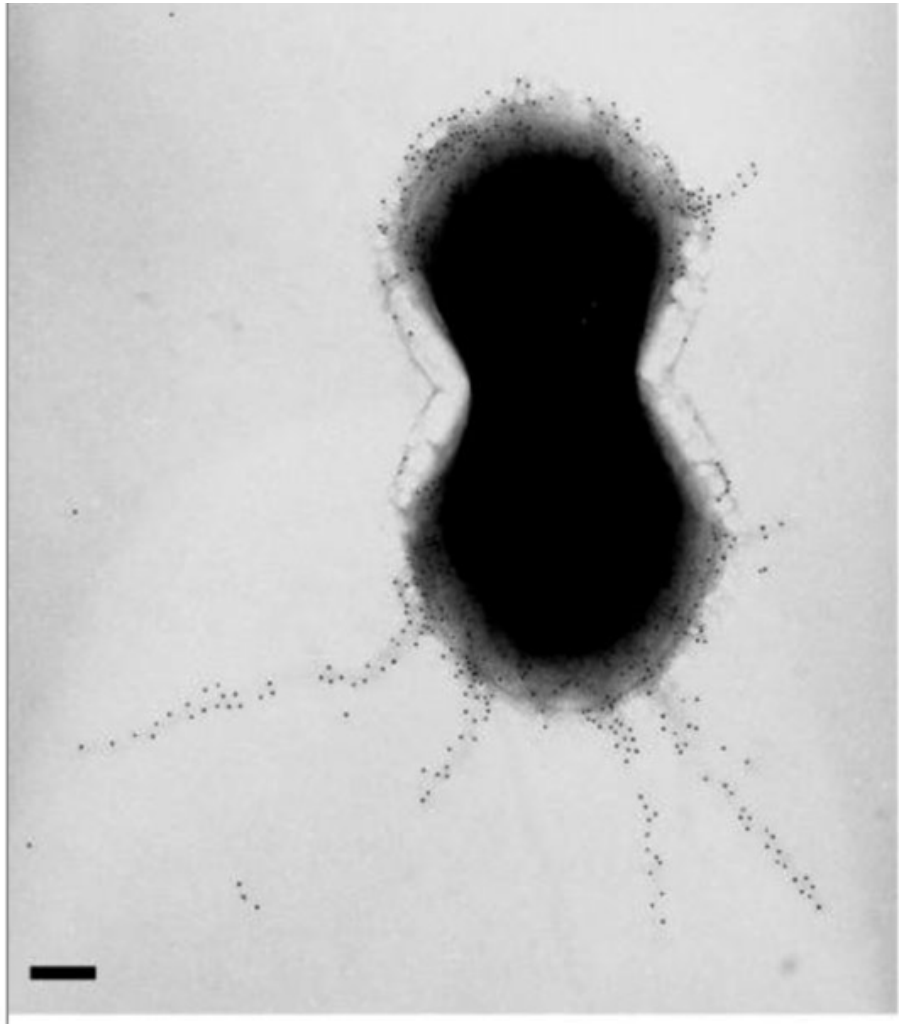
MECHANISMS OF VIRULENCE – NUMEROUS!

Cellular and Intracellular:

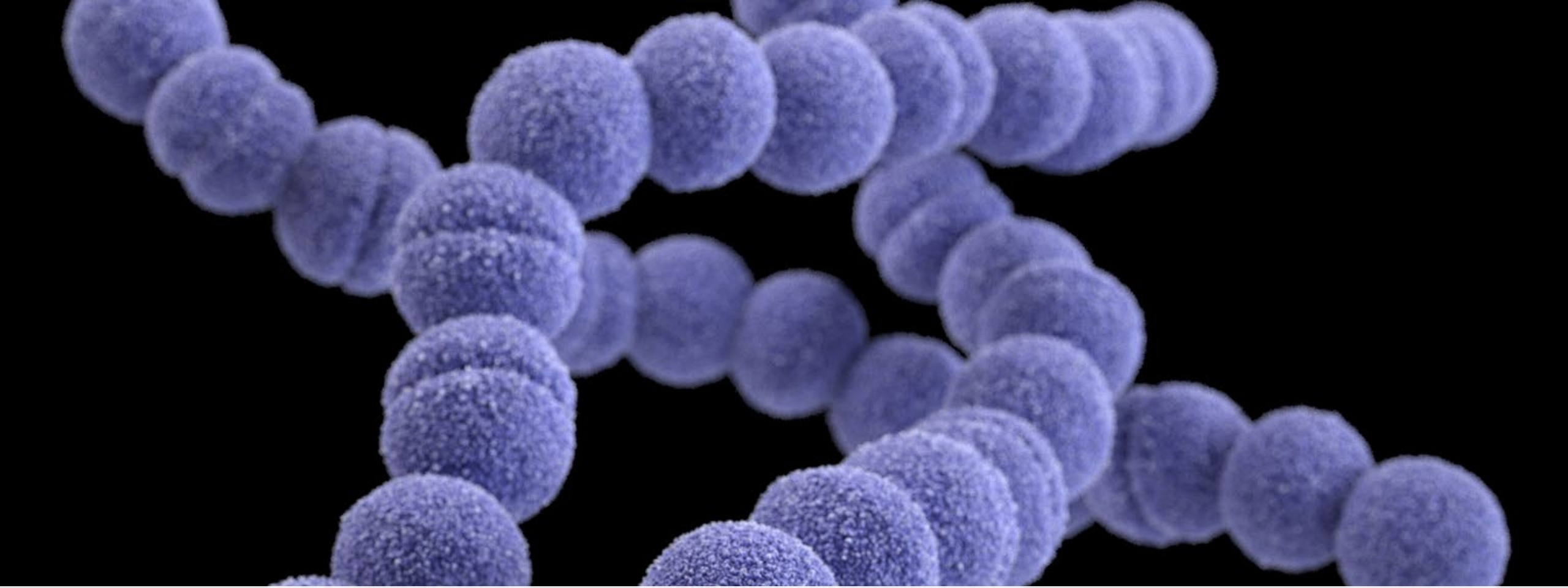
- Pili – mediate attachment specifically to human tonsillar epithelium and human keratinocytes
- Adhesins – allow GAS to hold on tight
- Thick hyaluronic capsule – immune evasion
- M protein – numerous functions, and the way we define strains

Extracellular:

- Leukocidins – variety of extracellular toxins which mediate immune responses
- Superantigens – “cytokine storm”
- Hemolysins
- Proteases
- NADases
- And so many more…

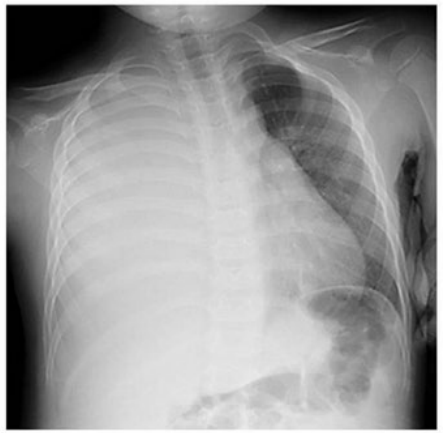


Mora, Marirosa, et al. "Group A Streptococcus produce pilus-like structures containing protective antigens and Lancefield T antigens." *Proceedings of the National Academy of Sciences* 102.43 (2005): 15641-15646.

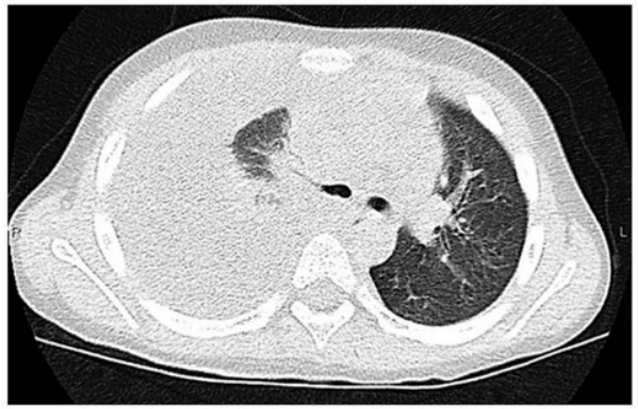


INVASIVE GROUP A STREPTOCOCCUS SYNDROMES

PNEUMONIA



(a)



(b)

TABLE 1. Patients' Demographic, Clinical and Laboratory Characteristics

Variable	Total n = 90	GAS n = 20	SP n = 70	*P*
Age, years (mean ± SD)	2.34 ± 0.88	2.49 ± 0.74	2.23 ± 1.11	0.79
Gender				
Male, n (%)	57 (63)	14 (70)	43 (61)	0.52
Female, n (%)	33 (37)	6 (30)	27 (39)	
Days of illness before hospitalization, mean (±SD)	4.54 ± 2.51	4.4 ± 2.23	5 ± 2.6	0.78
Underlying or concurrent conditions n (%)	17 (18.8)	5 (25)	12 (17.1)	0.49
Maximal temperature, °C (±SD)	39.4 ± 0.7	39.3 ± 0.73	39 ± 0.69	0.5
White blood cells/μL (mean ± SD)	17.8 ± 10.3	15.6 ± 10	18 ± 10.4	0.27
Platelets ($\times 10^3$/μL) (mean ± SD)	369 ± 181	355 ± 144	372 ± 191	0.7
CRP (mg/dL)	27.3 ± 9.7	25.4 ± 12.2	29 ± 7.1	0.32
Na (mEq/L) (mean ± SD)	132.7 ± 3.8	133.7 ± 4.1	132 ± 3.7	0.15
Positive culture				0.0057
Only blood, n (%)	40 (44.4)	2 (10)	38 (54.3)	
Pleural effusion, n (%)	43 (47.7)	17 (85)	26 (37.1)	
Both, n (%)	7 (7.8)	1 (5)	6 (8.6)	
Amount of pleural fluid				0.0003
Mild-mod, n (%)	41 (59)	4 (20)	37 (54)	
Large, n (%)	47 (69)	16 (80)	31 (46)	
Unknown, n (%)	2 (2)		2 (3)	
Need for oxygen, n (%)	49 (54)	11 (55)	38 (54)	0.96
Admission to ICU, n (%)	26 (29)	9 (45)	17 (24)	0.11
Mechanical ventilation, n (%)	4 (4.4)	3 (15)	1 (1.4)	0.02
Chest drain, n (%)	58 (64)	17 (85)	41 (59)	0.06
Length of hospital stay days (mean ± SD)	11.9 ± 5.2	13.9 ± 7.2	11 ± 4.4	0.05
Length of antibiotic treatment days (mean ± SD)	18.6 ± 5.13	20 ± 5.68	18 ± 4.94	0.18

Megged, Orli. "Characteristics of Streptococcus pyogenes versus Streptococcus pneumoniae pleural empyema and pneumonia with pleural effusion in children." *The Pediatric Infectious Disease Journal* 39.9 (2020): 799-802.

Ochi, Fumihiro, et al. "Sepsis and pleural empyema caused by streptococcus pyogenes after influenza a virus infection." *Case reports in pediatrics* 2018.1 (2018): 4509847.

NECROTIZING FASCIITIS

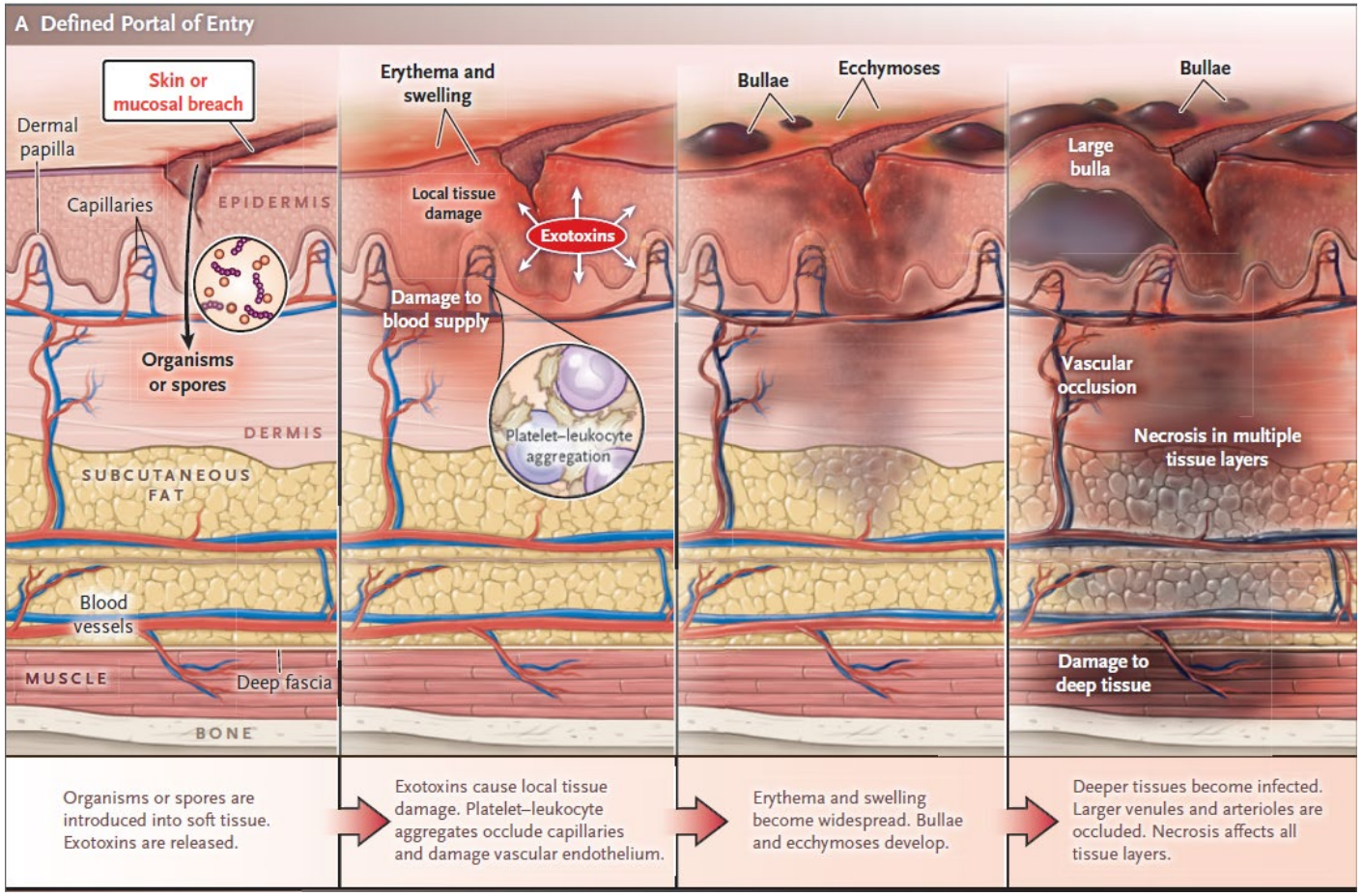
Begins as an innocuous lesion with **pain out of proportion** to physical exam findings

Rapid progression through fascial planes – proteases to damage tissue and vasculature – immune evasion + immune modulation rapid spread and tissue destruction

Infants may have profound irritability

Surgical debridement = most important

Antibiotic therapy = dual (beta-lactam/beta-lactamase + clindamycin/linezolid)



Stevens, Dennis L., and Amy E. Bryant. "Necrotizing soft-tissue infections." *New England Journal of Medicine* 377.23 (2017): 2253-2265.

PAIN OUT OF PROPORTION TO YOUR EXAM

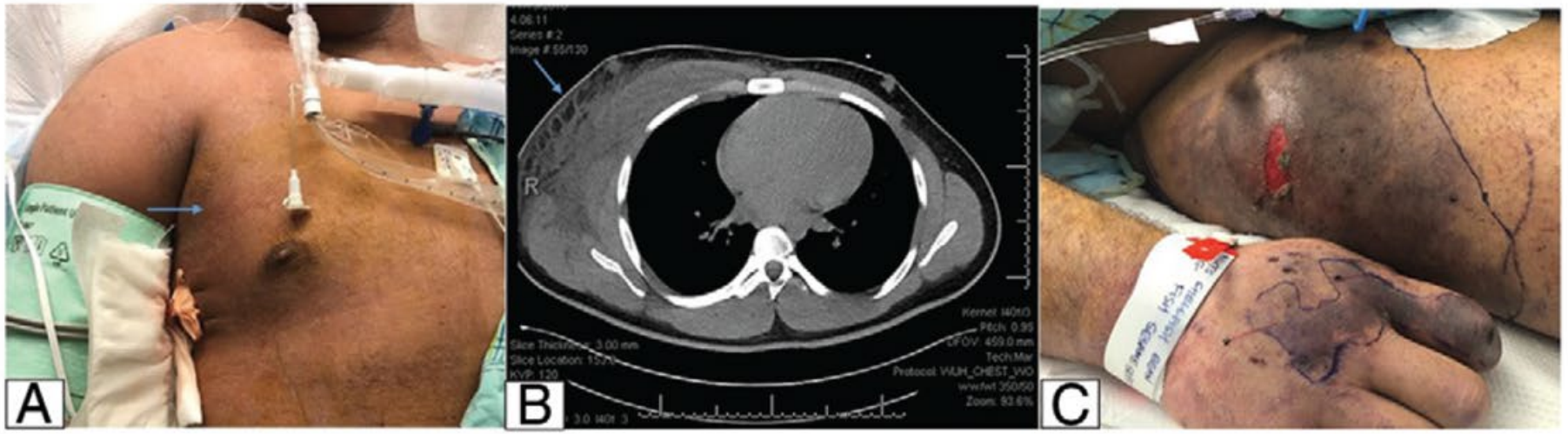
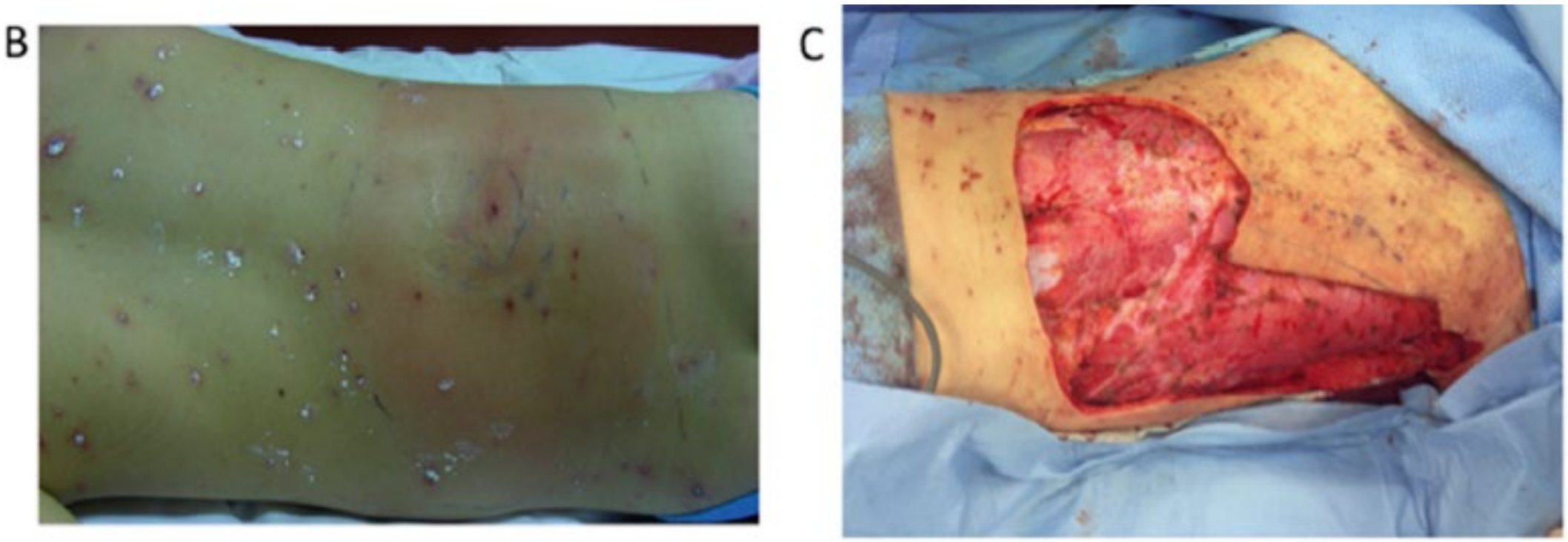


Figure. A 17-year-old athletic teenager with underlying eczema. A. Chest swelling with exquisite tenderness the day of presentation. B. Computed tomographic scan of the chest showing gas formation. C. Purplish dusky discoloration of the right upper and lower extremities 2 days later.

Noor, Asif, and Leonard R. Krilov. "Necrotizing fasciitis." (2021): 573-575.

PAIN OUT OF PROPORTION TO YOUR EXAM



B,**C**) Preoperative and intraoperatively findings
of necrotizing fasciitis following varicella infection on the back of a 5-year-old boy; Copyright by Pfeifle VA et al., J.EPSC, 2017 Copyright 2017, owner's Pfeifle, V.A.

Mercadante, Stefania, et al. "The Thousand Faces of Invasive Group A Streptococcal Infections: Update on Epidemiology, Symptoms, and Therapy." *Children* 11.4 (2024): 383.

Pfeifle, Viktoria A., et al. "Necrotizing fasciitis in children due to minor lesions." *Journal of pediatric surgery case reports* 25 (2017): 52-55.

STREPTOCOCCAL TOXIC SHOCK SYNDROME

GAS + hypotension and evidence of multi-organ failure

Can be seen with any infection – but usually skin or soft tissue

Pillars of treatment:

- Aggressive management of shock and organ failure
- Antibiotic therapy (dual)
- Consider IVIG

Table 3.60. Streptococcal Toxic Shock Syndrome: Clinical Case Definition[a]

I. Isolation of group A *Streptococcus (Streptococcus pyogenes)*
   A. From a normally sterile site (eg, blood, cerebrospinal fluid, peritoneal, joint, pleural, or pericardial fluid)
   B. From a nonsterile site (eg, throat, sputum, vagina, open surgical wound, or superficial skin lesion)

II. Clinical signs of severity
   A. Hypotension: systolic pressure 90 mm Hg or less in adults or lower than the fifth percentile for age in children <16 years of age

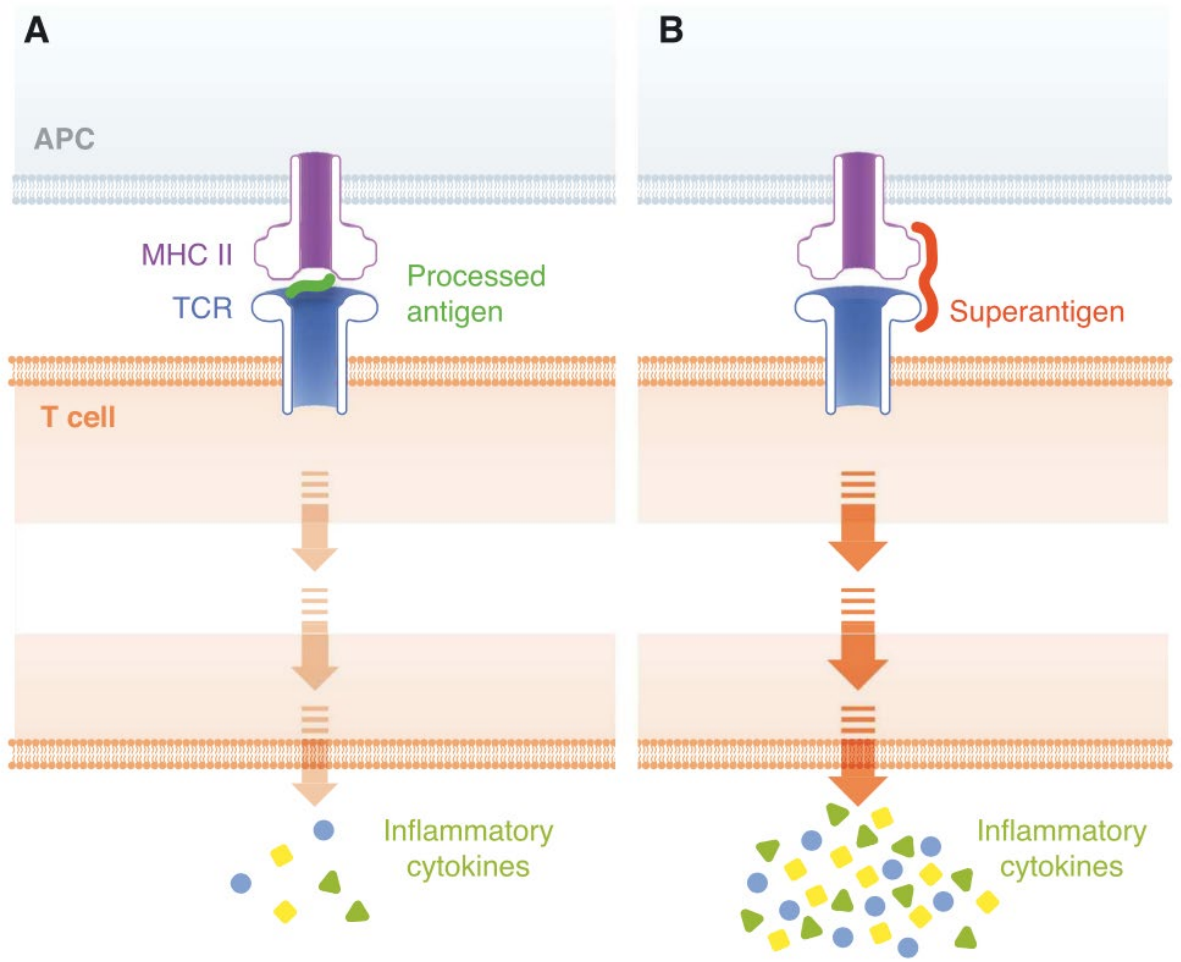
AND

   B. Two or more of the following signs of multiorgan involvement:
   - Renal impairment: creatinine concentration 177 µmol/L (2 mg/dL) or greater for adults or at least 2 times the upper limit of normal for age[b]
   - Coagulopathy: platelet count 100 000/mm^3 or less and/or disseminated intravascular coagulation defined by prolonged clotting times, low fibrinogen, and presence of fibrin degradation products
   - Hepatic involvement: elevated alanine aminotransferase, aspartate aminotransferase, or total bilirubin concentrations at least 2 times the upper limit of normal for age[b]
   - Acute respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in absence of cardiac failure or by evidence of diffuse capillary leak
   - A generalized erythematous macular rash that may desquamate
   - Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

Committee on Infectious Diseases, and American Academy of Pediatrics. "Red Book: 2024–2027 Report of the Committee on Infectious Diseases." (2024).

CYTOKINE STORM

Streptococcal “superantigens” – bypass the traditional process of immune activation, which requires a specific antigen presented to a T-cell by MHC-II – superantigens can bind non-specifically, resulting in an over-amplified T-cell response and “cytokine storm”

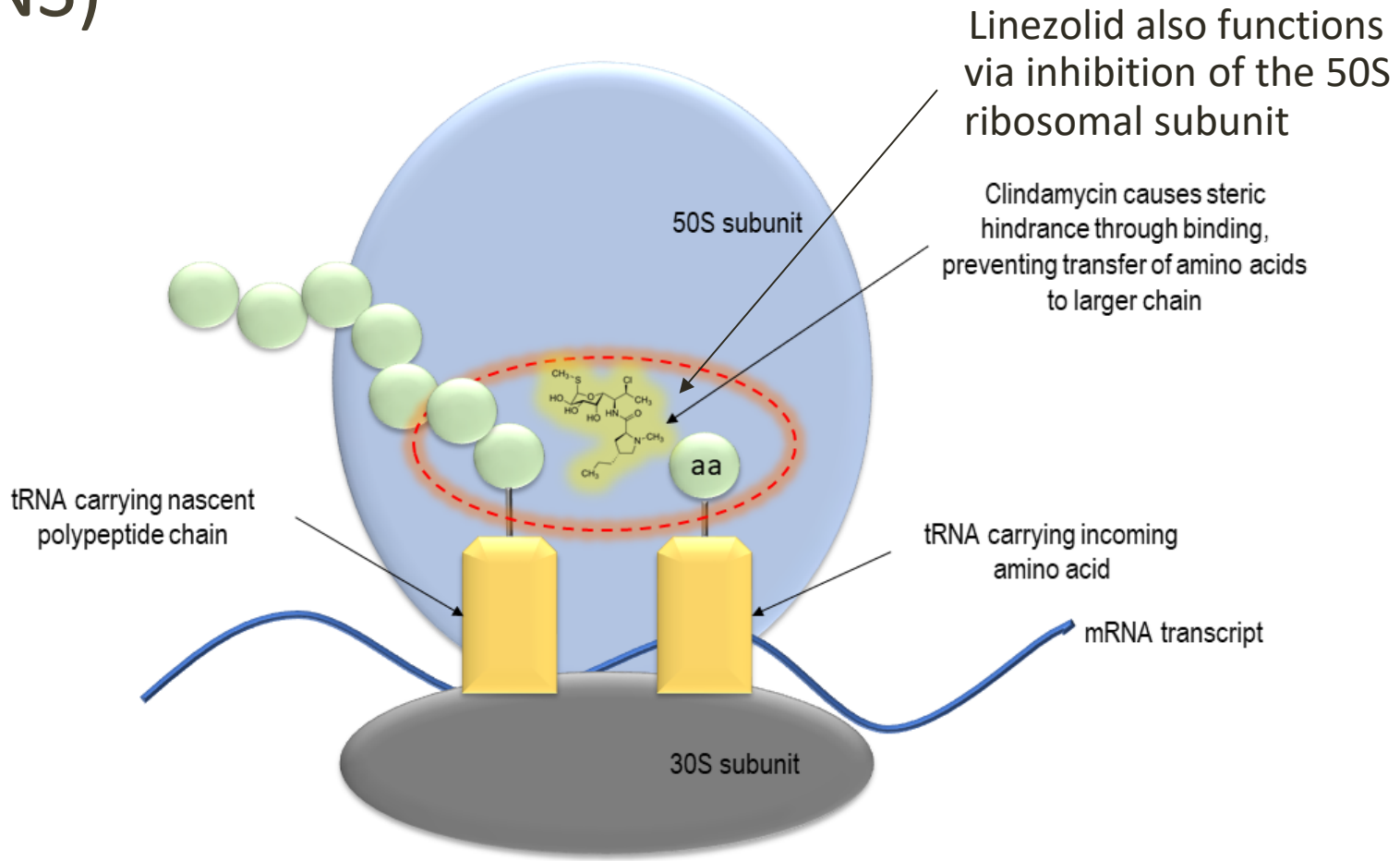


Barnett, Timothy C., et al. "Streptococcal toxins: role in pathogenesis and disease." *Cellular microbiology* 17.12 (2015): 1721-1741.

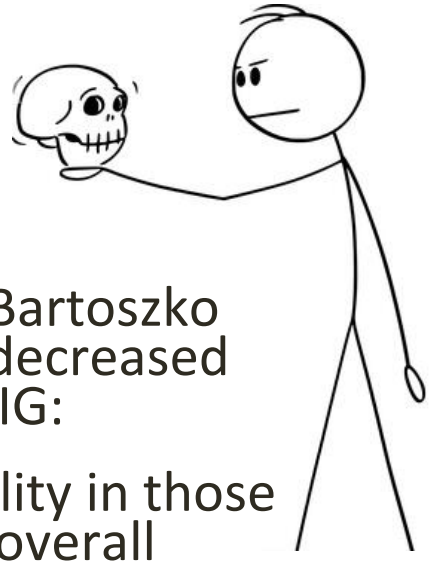
FUNCTION OF CLINDAMYCIN AND LINEZOLID IN STSS AND NF (NOT NECESSARILY ADDED IN OTHER INVASIVE INFECTIONS)

1. Group A Strep is an efficient factory producing virulence factors exquisitely targeted to humans
   - We add a ribosomal-targeting drug in an effort to shut down that factory

2. High bacterial burden may initially impede efficacy of beta-lactams
   - Adding a secondary agent can overcome this initially when bacterial burdens are high



TO IVIG OR NOT TO IVIG?



Good physiologic argument – IVIG can dampen cytokine release and neutralize superantigens/toxins, and provide passive immunity

Difficult to perform robust clinical trials due to ethical concerns – many would be unwilling to randomize into IVIG versus none, given the severity of the illness, and it is a relatively rare entity; different batches of IVIG may have different efficacy!

Majority of observational studies do not observe a statistically significant difference in outcome with use of IVIG

STSS: Two meta-analyses (Bartoszko 2022, Parks 2018) showed decreased mortality with the use of IVIG:

- Parks 2018: 30-day mortality in those given IVIG lower (RR 0.46), overall mortality 33.7% versus 15.7%

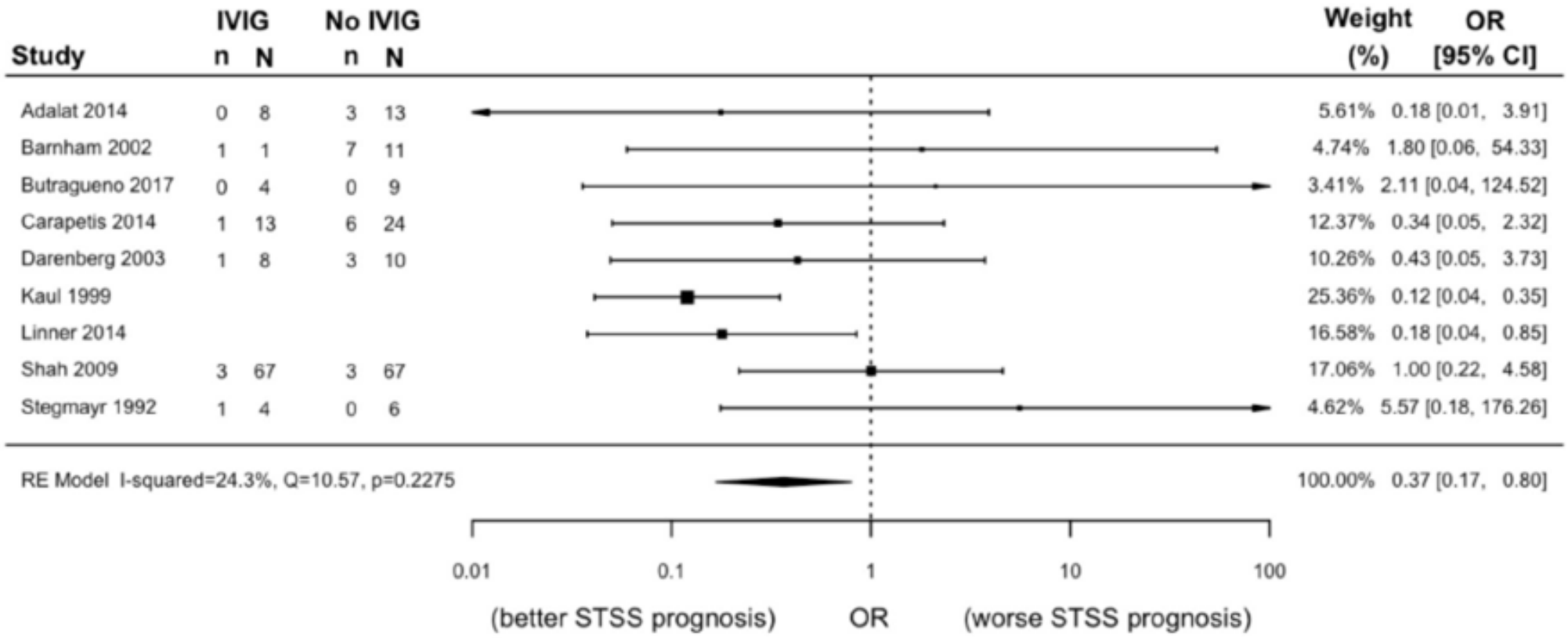
- Bartoszko 2022: Same studies as Parks, and some additional studies – OR 0.34

- Both studies acknowledged that certainty of evidence was low

Necrotizing fasciitis:

- Bruun 2021: Prospective observational trial - not receiving IVIG was associated with increased 90-day mortality (OR 2.98)

TO IVIG? PROBABLY

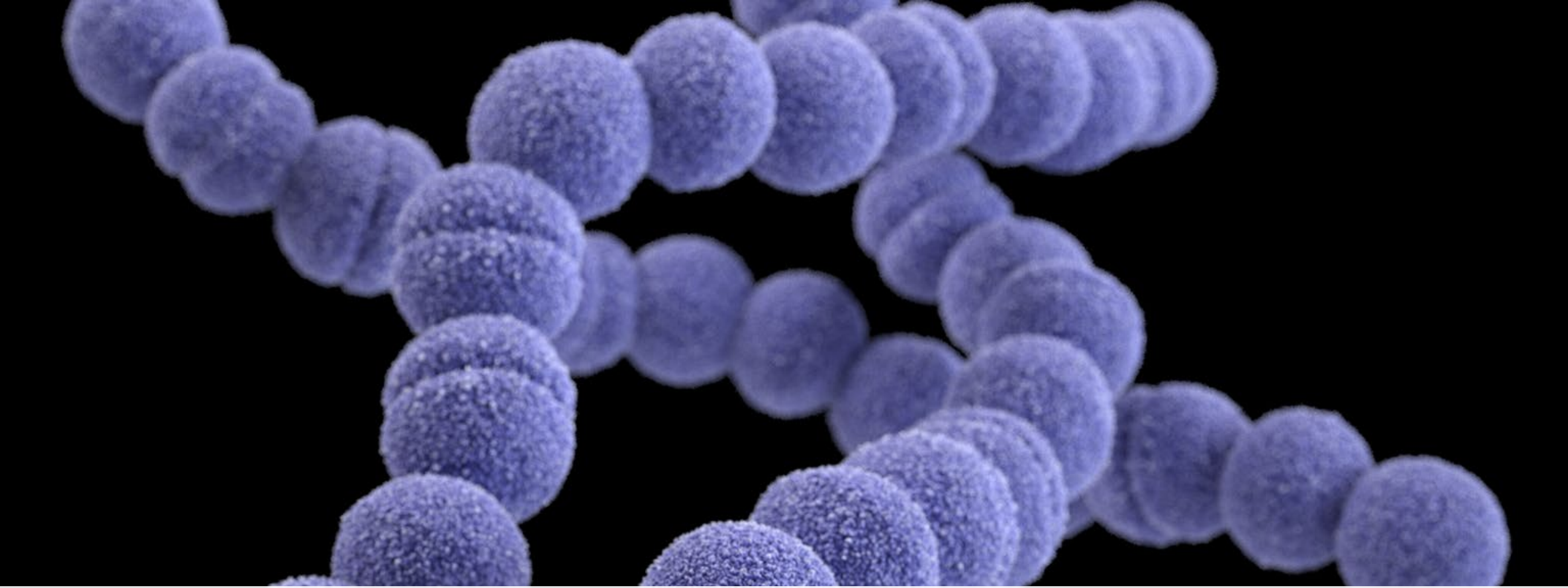


Bartoszko, Jessica J., et al. "Prognostic factors for streptococcal toxic shock syndrome: systematic review and meta-analysis." BMJ open 12.12 (2022): e063023.

HOUSEHOLD PROPHYLAXIS?

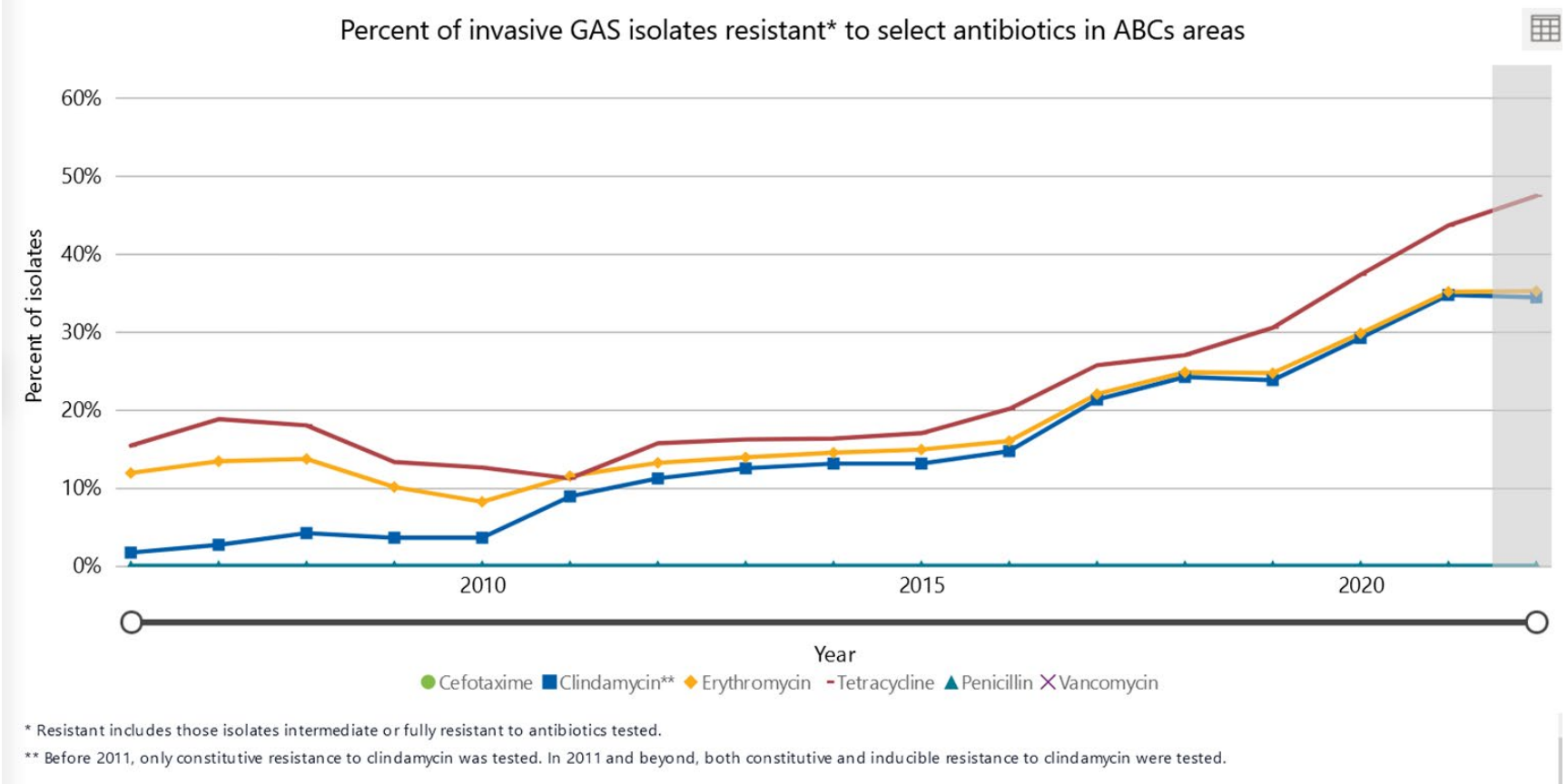
Household contacts of patients with severe invasive GAS disease, including STSS, are at some increased risk of developing severe invasive GAS disease compared with the general population. However, the risk is not sufficiently high to warrant routine testing for GAS colonization, and a clearly effective regimen has not been identified to justify routine chemoprophylaxis of all household contacts. Because of increased risk of sporadic, invasive GAS disease among certain populations (eg, people with human immunodeficiency virus [HIV] infection) and because of increased risk of death in those 65 years and older who develop invasive GAS disease, physicians may choose to offer targeted chemoprophylaxis to household contacts 65 years and older or to members of other high-risk populations (eg, people with HIV infection, varicella, or diabetes mellitus). Because of the rarity of secondary cases and the low risk of invasive GAS infections in children, chemoprophylaxis is generally not recommended in schools or child care facilities.

2024. "Group A Streptococcal Infections", Red Book: 2024–2027 Report of the Committee on Infectious Diseases, Committee on Infectious Diseases, American Academy of Pediatrics, David W. Kimberlin, MD, FAAP, Ritu Banerjee, MD, PhD, FAAP, Elizabeth D. Barnett, MD, FAAP, Ruth Lynfield, MD, FAAP, Mark H. Sawyer, MD, FAAP



CHALLENGES

RISING RATES OF RESISTANCE



Year	Clindamycin**	Erythromycin	Tetracycline	Penicillin
2006	1.7%	11.9%	15.4%	0.0%
2007	2.7%	13.4%	18.8%	0.0%
2008	4.2%	13.7%	18.0%	0.0%
2009	3.6%	10.1%	13.3%	0.0%
2010	3.6%	8.2%	12.6%	0.0%
2011	8.9%	11.5%	11.2%	0.0%
2012	11.2%	13.2%	15.7%	0.0%
2013	12.5%	13.9%	16.2%	0.0%
2014	13.1%	14.5%	16.3%	0.0%
2015	13.1%	14.9%	17.0%	0.0%
2016	14.7%	16.0%	20.1%	0.0%
2017	21.3%	22.0%	25.7%	0.0%
2018	24.2%	24.8%	27.0%	0.0%
2019	23.8%	24.7%	30.5%	0.0%
2020	29.2%	29.8%	37.3%	0.0%
2021	34.7%	35.1%	43.6%	0.0%
2022	34.4%	35.2%	47.4%	0.0%

- Variable fluoroquinolone resistance

- No documented beta-lactam resistance above clinical thresholds
  - Mechanism elucidated
  - Recent documentation of trains with higher MICs (lower susceptibility) BUT still not considered resistant

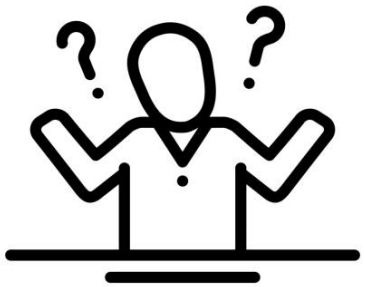
www.cdc.gov/abcs/bact-facts/data-dashboard.html

TAKE HOME POINT

Treatment of Group A Streptococcus should include a Beta-lactam antibiotic

Will GAS ever become penicillin resistant?

Maybe!

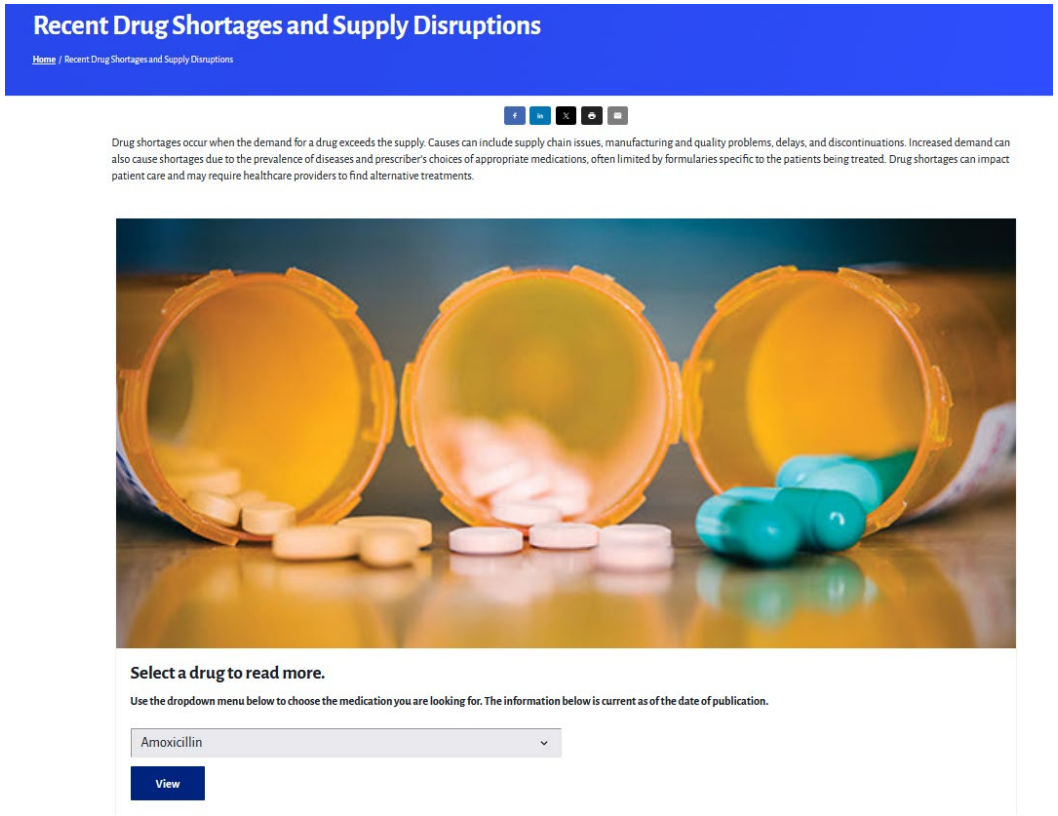


Is it now?

NO!

AMOXICILLIN SHORTAGE

https://www.aap.org/en/pages/drug-shortages/



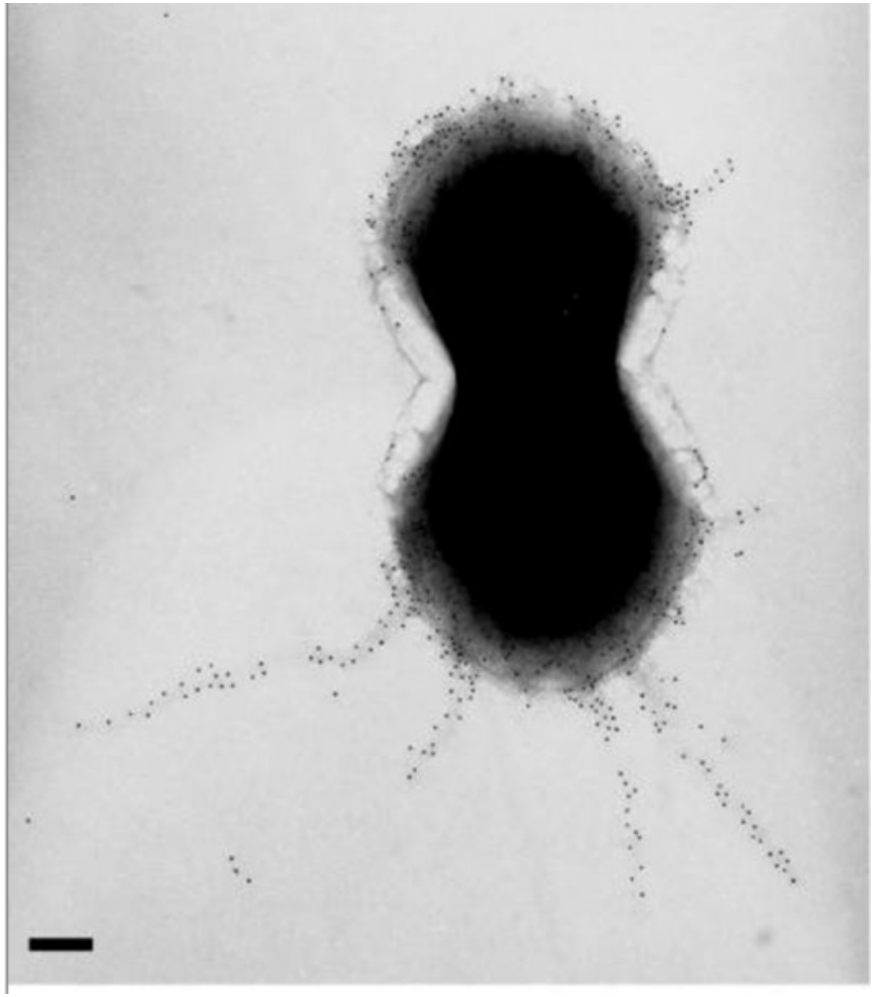
		5-7 days for sinusitis

Group A Streptococcus Pharyngitis	• Penicillin VK
	  ○ ≤27 kg: 250 mg BID
	  ○ >27 kg: 500 mg BID
	• IM penicillin G benzathine x 1
	  ○ ≤27 kg: 600,000 units
	  ○ > 27 kg: 1,200,000 units
	• Cephalexin (if PCN-allergic) 40mg/kg/day (max 500 mg/dose) divided BID
		• Treat for 10 days
		• Don't test children that have clear viral symptoms such as cough **and** rhinorrhea.
		• Don't test children for group A strep under the age of 3 unless there is a household member with group A strep pharyngitis

Asplenia	• Penicillin VK	

CONCLUSIONS

1. Invasive GAS infections have been on a steady rise since 2014, likely secondary to a shift to more toxigenic strains (in particular *emm1* strains)
2. Rapid drop in infections during COVID-19 lockdowns, with a bump afterwards likely a mix of more toxigenic strains + some “immune debt” + increased susceptibilities with surges in other respiratory viruses
3. Resistance to non-beta-lactam antibiotics is dramatically increasing



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