Title: Impact of Adjunctive Clindamycin in Invasive β-hemolytic Streptococcal Infections: A Retrospective Cohort Analysis of 1956 β-lactam Treated Patients from 118 US Hospitals, 2000-2015

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Online data supplement

Appendix Tables

e-Appendix 1: Methods: *Case Selection*

The *Cerner Healthfacts*™ Database was queried for inpatients with any positive clinical cultures between 2000 and 2015 which grew βHS species of interest (see below) and received a β-lactam antibiotic (Supplementary data Table E5) within ±3 days of culture sampling. This group was then queried for patients who also received clindamycin within ±3 days of culture sampling. Patient's with polymicrobial growth in culture and missing variables were excluded.

"Proven" iβHS infection was defined as isolation of βHS from a normally sterile body sites, or as per the U.S. Centers of Diseases Control and Prevention [1] definitions, isolation of βHS from a deep wound in conjunction with International Classification of Diseases Version 9 (ICD-9) code of STSS (040.82*)* or NF (728.86, 0.40) [1]. "Probable" iβHS infection was defined as isolation of βHS from a non-sterile site with ICD codes for lower respiratory, genitourinary, skin and soft tissue and musculoskeletal, intra-abdominal or other deep-seated infections as was the source of secondary bacteremia cases. (Supplementary data Table E1).

Culture sterility was deemed by using guidance from CDC definitions. Culture sterility designation was based on culture collection source and culture procedure name in Cerner data set and coded as such by AB and reviewed independently by and JS and SK.

Invasive β-Hemolytic Streptococcus Species included in Analysis (N=1956)

Group A *streptococci* (GAS):

Streptococcus pyogenes (Group A *Streptococcus*) (N=1079)

Non-group A, non-group B β-hemolytic streptococci (NABS):

β-hemolytic streptococci, Group G (N=511)

β-hemolytic streptococci, Group C (N=281)

β-hemolytic streptococci, not Grp A,B (N=32)

Streptococcus dysgalactiae (N=27)

Streptococcus equi (ss equi) (N=2)

Streptococcus equi ss zooepidemicus (N=1)

Streptococcus equisimilis (N=22)

Streptococcus iniae (N=1)

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Table E1: Infection Site ICD-9-CM Codes

Clinical Syndrome/Variable	ICD 9 codes
Necrotizing soft tissue infection/Necrotizing Fasciitis	728.86, 0.40,
Shock	785.52, 785.50
Streptococcal toxic shock syndrome (STSS)	*040.82*
Respiratory Infection	020.3 020.4 020.5 021.2 022.1 039.1 052.1 055.1 073.0, 079.6, 464.1x (464.10, 464.11), 466x (466.0 466.1 466.11 466.19, 480x (480.0-480.3, 480.8, 480.9), 481, 482x (482.0-482.3, 482.30-482.32, 482.39, 482.40-482.42, 482.49, 482.81-482.84 , 482.89, 482.9), 483x(483.0, 483.1 483.8) 484x (484.1, 484.3, 484.5, 484.6, 484.7, 484.8) 485, 486, 487x (487.0,487.1, 487.8), 488x (488.01, 488.02,488.09,488.11, 488.12,488.19, 488.8,488.81,488.82,488.89), 490.0, 507.0 510.x(510.0,510.9), 513x (513.0, 513.1) , 997.3x (997.31, 997.32)
SSTI/MSK	035, 039.0, 373.0x (373.00, 373.01, 373.02) 373.4, 376.01 566, 680.0-686.9 (680.0, 680.1, 680.2, 680.3 680.4 680.5 680.6 680.7 680.8 680.9 681.00 681.01 681.02 681.10 681.11 681.9 682.0 682.1 682.2 682.3 682.4 682.5 682.6 682.7 682.8 682.9 684, 685.0 685.1 686.0 686.00 686.01 686.09 686.1 686.8 686.9) , 695.3, 910.1, 910.3, 910.5, 910.7, 910.9, 911.1, 911.3, 911.5, 911.5, 911.7, 911.9, 912.1, 912.3, 912.5, 912.7, 912.7, 912.9, 913.1, 913.3, 913.5, 913.7, 913.9, 914.1, 914.3, 914.5, 914.7, 914.9, 915.1, 915.3, 915.3, 915.5, 915.7, 915.9, 916.1, 916.3, 916.5, 916.7, 916.9, 917.1, 917.3, 917.5, 917.7, 917.9, 919.1, 919.3, 919.5, 919.7, 919.9 , 997.62, 998.51, 036.82, 376.01, 376.02, 376.03,,711.0x (711.00-711.09), 711.4x (711.40-711.49), 711.8x (711.90-711.89), 711.9x (711.90-711.99) , 730.0x (730.00-730.09), 726.3x (726.30, 726.31, 726.32, 726.33, 726.39) 726.6x (726.60-726.69), 726.7x (726.70-726.79) 728.0, 729.4, 730.1x (730.10-730.19), 730.2x (730.20-730.29), 730.3x(730.30-730.39), 730.8x (730.80-730.89), 730.9x (730.90-730.99), 996.66, 996.67

Genitourinary/Puerperal sepsis	597x (597.0-597.89),601x (601.0-601.9), 603.1, 604x (604.0-604.99), 614x (614.0-614.9), 615x (615.0-615.9), 639.0, 646.x (646), 670x (670.0-670.8)
CNS Infections	027.0, 036.0, 047x (047.1, 047.8, 047.9), 049.x (049.0, 049.1, 049.8, 049.9) , 053.0, 072.1, 100.81, 112.83, 114.2, 115.01, 115.11, 115.91, 320.x (320.0-320.9), 321x (321.0-321.4, 321.8) 0- 322.0, 322.9, 323.4, 324x (324.0, 324.1, 324.9), 325
Intra-abdominal Infection	009x (009.0–009.3), 540x (540.0-540.9) 541, 542, 562.01 562.03 562.11 562.13 567x (567.0-567.9), 569.83, 569.5, 569.61, 569.71, 572x (572.0-572.8), 574.0x(574.00-574.01), 574.1x (574.10-574.11), 574.3x (574.30-574.31), 574.4x (574.40-574.41), 574.6(574.60-574.61), 574.7x(574.70-574.91), 574.8x (574.80-574.81), 575.0, 575.1x (575.10-575.12), 575.4, 576.1, 590x(590.0-590.9), 996.68
Other Deep infection/Abscess*	513.1, 527.3, 519.2, 604.9, 567.38, 478.22, 522.5, 475, 478.24
Primary Bacteremia	036.42, 421x (421.0-421.9), 422.92, 423.8, 423.9, 424.9x(425.90-91), All other codes

* Other deep infections:

a. Mediastinitis
b. Orchitis/epididymitis
c. Parapharyngeal abscess
d. Periapical abscess
e. Peritonsillar abscess
f. Retropharyngeal abscess
g. Abscess of Mediastinum
h. Abscess of Salivary Gland

e-Appendix 2: Methods: *Study Comorbidities and Conditions of Interest*

The Elixhuaser was score calculated using ICD-9-CM codes [2]

Table E2: ICD-9-CM Codes for Comorbidities/Conditions of Interest

Comorbidities/Conditions of interest	ICD codes
DM	250.0–250.3, 250.4–250.9
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x
Atherosclerotic Heart disease	410.x, 412.x
Chronic Lung Disease	416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8
Moderate to Severe Liver Disease	456.0–456.2, 572.2–572.8
Malignancy	140.x–172.x, 174.x–195.8, 196.x–199.x 200.x–208.x, 238.6 (doesn't include skin malignancy)
CKD/ESRD	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Cerebrovascular disease	362.34, 430.x–438.x
Obesity	278.0
Smoking/Tobacco use	V15.82, 305.1
Alcohol abuse	265.2, 291.1–291.3, 291.5–291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0– 571.3, 980.x, V11.3
Drug Abuse	292.x, 304.x, 305.2– 305.9, V65.42
Obesity	278.0

Acute Skin Breakdown		
Burns	906.5, 906.6, 906.7, 906.8, 906.9, 941.0, 941.1, 941.2, 941.3, 941.4, 941.5, 942.0, 942.1, 942.2, 942.3, 942.4, 942.5, 943.0, 943.1, 943.2, 943.3, 943.4, 943.5, 944.0, 944.1, 944.2, 944.3, 944.4, 944.5, 945.0, 945.1, 945.2, 945.3, 945.4, 945.5, 946.0, 946.1, 946.2, 946.3, 946.4, 946.5, 948.0, 948.1, 948.2, 948.3, 948.4, 948.5, 948.6, 948.7, 948.8, 948.9, 949.0, 949.1, 949.2, 949.3, 949.4, 949.5	
Blunt/Penetrating Trauma[3]	Head/face/neck	873(.0–.1,.8–.9), 941.x6, 951, 959.01, 802, 830, 848(.0–.1), 872, 873(.2–.7), 941(.x1,.x3–.x5,.x7) , 807(.5–.6), 848.2, 874, 925.2, 941.x8, 953.0, 954.0 900, 910, 920, 925.1, 941(.x0, .x9), 947.0, 957.0, 959.09. 870–871, 918, 921, 940, 941.x2, 950(.0,.9)
	Chest /Abdomen/ Trunk/Back	807(.0–.4), 839(.61,.71), 848(.3–.4), 860–862, 875, 879(.0–.1), 901, 922(.0–.1,.33), 926.19, 942(.x1–.x2), 953.1 , 863–866, 868, 879(.2–.5), 902(.0–.4), 922.2,942.x3, 947.3, 953(.2,.5) , 809, 879(.6–.7), 911, 922(.8–.9), 926(.8–.9), 942(.x0,.x9), 954(.1,.8–.9), 959.1 , 847.9, 876, 922(.31–.32), 926.11, 942.x4
	Upper Extremity	810–812, 831, 840, 880, 887(.2–.3), 912,923.0, 927.0, 943(.x3–.x6) ,959.2, 813, 832, 841, 881(.x0–.x1), 887(.0–.1), 923.1, 927.1, 943(.x1–.x2), 814–817, 833–834, 842,881.x2, 882, 883, 885–886, 914–915, 923(.2–.3) ,927(.2–.3), 944 ,959(.4–.5) , 818, 884, 887(.4–.7), 903, 913, 923(.8–.9), 927(.8–.9), 943(.x0,.x9), 953.4, 955, 959.3
	Lower Extremity	820, 835, 843, 924.01, 928.01 , 821, 897(.2–.3), 924.00, 928.00, 945.x6 822, 836, 844(.0–.3), 924.11, 928.11, 945.x5, 823–824, 837, 845.0, 897(.0–.1), 924(.10,.21), 928(.10,.21), 945(.x3–.x4), 825–826, 838, 845.1, 892–893,

		895–896, 917, 924(.3,.20), 928 (.3,.20), 945 (.x1–.x2), 827,844(.8–.9), 890–891, 894, 897(.4–.7), 904(.0–.8), 916, 924(.4–.5), 928(.8–.9), 945(.x0,.x9), 959(.6–.7)
	Unspecified or Multiple sites	819, 828, 902(.87,.89), 947(.1–.2), 953.8, 956, 829, 839(.8–.9), 848(.8–.9), 869, 879(.8–.9), 902.9, 904.9, 919, 924(.8–.9), 929, 946, 947(.8–.9), 948, 949, 953.9, 957(.1,.8–.9), 959(.8–.9)
Varicella	052.9, 052.7, 052.8	
Chronic Skin breakdown		
Psoriasis	696.1	
Eczema, Atopic or Contact Dermatitis	692.9, 691.8	
Decubitus Ulcers	707.00–707.09, 707.20–707.25	
HIV/AIDs	042.x–044.x	
Hematological Malignancy	200.0-208.9 (200x, 201x, 202x, 203x, 204x, 205x, 206x, 207x, 208x), 238.4-238.79	

Immunosuppression Algorithm

Patients were deemed immunosuppressed if they fulfilled on of the below three criteria

1- ICD 9 code for HIV/AIDs OR Hematologic Malignancy OR Other Immune Conditions (Table E4)

2-Metastatic Cancer, Solid/System/Neuroendocrine Tumor without Metastasis, Organ Transplant, Organ complications present on admission for transplant, Rheumatology (Table E4) + Chemo or Immune-Modulating Agent (Table E5)

3- Chronic Steroids ICD 9 code (V58.65) + Systemic Steroids (table E5)

Table E3: ICD-9-CM Codes for Immunosuppressed Algorithm

Condition	ICD 9- code	
HIV/AIDs	042.x–044.x	
Hematological Malignancy	200.0-208.9 (200x, 201x, 202x, 203x, 204x, 205x, 206x, 207x, 208x), 238.4-238.79	
Other Immune Conditions		
Sickle Cell Disease	282.41, 282.42, 282.6x,	
Asplenia	759.0	
Nephrotic syndrome	581.9, 581.0, 581.1, 581.2, 581.3, 581.81	
Immunoglobulin deficiency	279.00, 279.03, 279.2, 279.04, 279.06, 279.11, 279.02	
Myelofibrosis	289.83	
WBC Diseases	288.1, 288.2, 288.5, 288.8, 288.9	
Neutropenia	288.04, 288.00	
Other Immunosuppressive conditions of Interest		
Metastatic Cancer	196-199.0 (196x, 197x, 198x, 199.0)	
Solid or Neuroendocrine Tumor without Metastasis	140.x–195.8, 209.0x-209.3x, 235.0-238.5, 238.8-239.0	
Rheumatological/Inflammatory	135, 277.3x (277.30, 277.31, 277.39) 340x, 341.0, 357.0, 446x 495.9, 555.6x, 695.4, 696x, 710x, 712x, 714x, 720x, 725x	
Solid Organ transplant (w and w/out complication)	**Kidney**	V42.0, 55.61, 55.69
	Heart	V42.1, 37.51
	Liver	V42.7, 50.51, 50.59
	Lung	V42.6, 33.50, 33.51, 33.52, 33.6
	Pancreas	V42.83, 52.8-x

	Intestine	V42.84 , 46.97, 996.87
Hematopoietic cell transplantation	**Peripheral stem cells**	V42.82, Z94.84, 41.01, 41.04, 41.07, 41.09, 41.02, 41.03, 41.05, 41.06, 41.08
	Bone Marrow	V42.81, 41.00, 41.01, 41.09, 41.02, 41.03

Debridement codes

Debridement within three days was included in sensitivity analysis as a variable to control for when examining mortality among SSTI/MSK subgroup of patients. Debridement was determined by ICD 9/10 codes.

Table E4: ICD-9 Procedure Codes for Surgical Debridement and/or Amputation

Diagnosis	ICD-9 Code
Abdominal Wall Incision	54.0
Destruction of Abdominal Wall Lesion	54.3
Scrotal Lesion Destruction	61.3
Amputation Stump Revision	84.3
Other Local Destruction Skin	86.3
Myotomy	83.02
Soft Tissue Incision not elsewhere classified	83.09
Fasciotomy	83.14
Soft Tissue Division not elsewhere classified	83.19
Open Biopsy Soft Tissue	83.21
Excision of Soft Tissue Lesion not elsewhere classified	83.39
Other Fasciectomy	83.44
Other Myectomy	83.45
Other Soft Tissue Excision	83.49
Muscle or Fascia Graft	83.82
Toe Amputation	84.11
Amputation Through Foot	84.12
Below Knee Amputation not elsewhere classified	84.15
Above Knee Amputation	84.17
Other Skin & Subcutaneous Incision & Drainage	86.04
Excisional debridement of wound, infection, or burn	86.22
Non-excisional debridement of wound, infection or burn	86.28
Heterograft to Skin	86.65
Homograft to Skin	86.66
Dermal Regeneration Graft	86.67
Free Skin Graft not elsewhere classified	86.69
Dressing of Wound not elsewhere classified	93.57
Wound Irrigation not elsewhere classified	96.59

eAppendix 3. Methods: *Study Medications*

For purposes of case-finding criteria we included the defined below list of antibiotics as β-lactams. Antibiotics were deemed within window if administered within 3 days of culture sampling. Patients who received other toxin inhibitor antibiotics were excluded (Figure 1).

We only included intravenous administrations of vasopressors. The five vasopressors of interest were Norepinephrine, Epinephrine, Dopamine, Vasopressin, and Phenylephrine.

Immunosuppressive medication where considered as part of our immunosuppression algorithm if patient received medication during index admission.

Table E5: Study Medication

Medication	Name
β-lactams	aztreonam amoxicillin amoxicillin/clavulanate ampicillin ampicillin/sulbactam cloxacillin cefepime ceftazidime ceftazidime/avibactam ceftaroline cefaclor cefadroxil cefamandole cefazolin cefotetan cefoxitin cefprozil cefuroxime cefdinir cefditoren cefixime cefoperazone cefotaxime cefpodoxime ceftibuten

	ceftizoxime ceftriaxone cephalexin cephapirin dicloxacillin piperacillin/tazobactam ticarcillin/clavulanate doripenem ertapenem meropenem ticarcillin cinoxacin mezlocillin nafcillin oxacillin penicillin piperacillin
Clindamycin	clindamycin
Other toxin inhibitor antibiotics	linezolid , tedizolid
Vasopressor	norepinephrine, phenylephrine, epinephrine, dopamine, vasopressin
Immunosuppressive medication	
Monoclonal antibodies:	alemtuzumab; bevacizumab; cetuximab; gemtuzumab; ibritumomab; ipilimumab; ofatumumab; panitumumab; pertuzumab; rituximab; tositumomab and iodine; trastuzumab.
Chemotherapy : Alkylating Agents	busulfan; dacarbazine; estramustine phos sodium; altretamine; bendamustine hydrochloride; thiotepa; chlorambucil; cyclophosphamide; ifosfamide; ifosfamide/mesna; mechlorethamine; melphalan; uracil mustard; carmustine; lomustine; streptozocin.
Chemotherapy : antibiotics	amsacrine; daunorubicin; daunorubicin citrate liposome; doxorubicin; doxorubicin hcl liposome; epirubicin; idarubicin; bleomycin sulfate; dactinomycin; mitomycin; plicamycin
Other	mitoxantrone; brentuximab vedotin; arsenic trioxide; bortezomib; carfilzomib; everolimus; mitotane; porfimer; pralatrexate; sipuleucel-t; sorafenib; temozolomide; vorinostat; erlotinib; gefitinib; tretinoin; romidepsin; dasatinib; imatinib; lapatinib; nilotinib; pazopanib; sunitinib; temsirolimus; bexarotene; aldesleukin; denileukin diftitox; levamisole; amifostine;

	dexrazoxane; mesna; azacitidine; decitabine; nelarabine; irinotecan; topotecan; asparaginase; pegaspargase; etoposide.
Chemotherapy: Antimitotics	eribulin mesylate; ixabepilone; cabazitaxel; docetaxel; paclitaxel; vinblastine; vincristine; vinorelbine. amsacrine; daunorubicin; daunorubicin citrate liposome; doxorubicin; doxorubicin hcl liposome; epirubicin; idarubicin; bleomycin sulfate; dactinomycin; mitomycin; plicamycin.
Systemic Steriods	betamethasone; budesonide; dexamethasone; methylprednisolone; methylprednisolone; prednisolone; prednisone; triamcinolone
Anti-metabolites	methotrexate; pemetrexed; cladribine; clofarabine; fludarabine phos; mercaptopurine; pentostatin; thioguanine; capecitabine; cytarabine [4]; cytarabine (lipo); floxuridine; fluorouracil; gemcitabine.
Immune modulating agents	belimumab; denosumab; eculizumab; palivizumab; auranofin; aurothioglucose; gold sodium thiomalate; leflunomide; abatacept; adalimumab; anakinra; certolizumab pegol; etanercept; fingolimod; golimumab; infliximab; interferon alfa-2a; interferon alfa-2b; interferon alfa-n3; interferon alfacon-1; interferon beta-1a; interferon beta-1b; interferon gamma-1b; lenalidomide; natalizumab; peginterferon alfa-2a; peginterferon alfa-2b; thalidomide; tocilizumab; ustekinumab; pegademase bovine; alefacept; azathioprine; basiliximab; belatacept; cyclosporine; daclizumab; efalizumab; glatiramer acetate; muromonab-c; tacrolimus; mycophenolate mofetil; mycophenolic acid sodium; sirolimus; rapamycin; thymoglobulin

e-Appendix 4: Methods: *Sequential Organ Failure Assessment (SOFA) score*

SOFA scores were calculated as previously described [5]

e-Appendix 5: Methods: *Analysis*

For the comparison of baseline characteristics between clindamycin and non-clindamycin groups, the p-values for categorical variables were computed by chi-squared tests (or in the case of expected frequencies <5, Fisher's exact test) and for continuous variables by Wilcoxon rank sum test. For the matched data, Friedman's test was used to compare the continuous variables and the Cochran-Mantel-Haenszel test was used to compare the categorical variables between treatment groups.

To estimate the effect of clindamycin on mortality, propensity score matching was carried out using the *R* package Matchit. Specifically, Propensity scores were calculated from a logistic regression model that is relating clindamycin group status as a binary outcome to the matching variables as predictors. All variables in Table 1, except specific β-lactam therapy received, were included in the model. Age, Sequential Organ Failure Assessment (SOFA) and Elixhuaser scores were included as continuous variables.

Clindamycin patients were matched 2:1 to a non-clindamycin patient with a similar logit of the propensity scores by nearest neighbor method with a caliper of 0.2 in the two cohorts (group A streptococcus [GAS] and non-group A, non-group B β-hemolytic streptococcus [NABS])[6]. Specifically, a non-clindamycin patient was randomly selected as the match if its logit of the propensity score falls within 0.2 of the standard deviation of the logit of the propensity scores from a clindamycin patient. Propensity score matching was executed in concert with exact matching for the following prioritized variables to enrich selection of cases with iβHS disease of clinical importance: presence of ICD-9 code of necrotizing fasciitis; (See Table E2 for list of ICD-9 codes), vasopressor use (Table E3), ICU stay and proven iβHS.

For the primary outcome measure, in-hospital mortality, logistic regression analysis was performed on the matched data to examine the effect of clindamycin and other risk covariates. Odds ratio (OR) and the associated 95% confidence intervals for clindamycin vs. Non-clindamycin mortality were reported.

Seven subset sensitivity analyses were conducted to examine the effect of clindamycin on mortality in a subset of clinically relevant patients in the matched cohort. The subset sensitivity analyses included patients: Subgroup analyses in both cohorts were performed on patients with proven infections alone; probable infections alone; (3) skin/soft tissue /musculoskeletal (SST/MSK) infections—adjusted for source control or debridement; (4) ICU stay; (5) vasopressor use within 1 day of index culture; (6) necrotizing fasciitis; [7] neither vasopressor-dependent shock nor necrotizing fasciitis (8) early clindamycin use (i.e. within ±1 day of culture sampling) and; (9) > 1, >2 and >3 days of clindamycin .

Primarily the matched data was analyzed with logistic regression models without adjusting for the matching nature of the data.[8,9] However, matched approaches such as conditional logistic regression or the generalized estimating equations (GEE)[10] are also proposed to account for the dependence among the subjects within each propensity score matched block. Thus, we further conducted sensitivity analysis utilizing the GEE approach. This approach was found relatively more efficient handling data with incomplete matching blocks[11], which was the case in our data.

Based on the matched cohort, secondary outcome of length of stay was compared between the two treatment groups in both cohorts (GAS and NABS) with the Wilcoxon rank sum test with continuity correction.

All analysis was conducted were performed using Rstudio [12]

e-Appendix 6: Results: *Overall Cohort Baseline Characteristics*

Table E6: Baseline Characteristics of All Patients with Invasive β-hemolytic Streptococcal Infection

Variable (%)	Included patient Non- Clindamycin Group (n=1497)	Included patients Clindamycin Group (n=459)	p-Value	Excluded patients (n=3915)
Age (Median[IQR])	56 [40,71]	49 [31,64]	<0·001	44 [24, 62]
Male Sex	941 (62·9)	265 (57·7)	0·06	2155 (55.0)
Caucasian Ethnicity	1143 (76·4)	319 (69·5)	<0·05	2653 (67.8)
Elixhauser Index * (Median[IQR])	2·0 [1·0, 4·0]	2·0 [0·0, 3·0]	<0·05	1·0 [0·0, 3·0]
Baseline SOFA Score ^ (Median[IQR])	1·0 [0·0, 3·0]	1·0 [0·0, 3·5]	0·05	1·0 [0·0, 3·0]
Proven iβHS	828 (55·3)	257 (56·0)	0·84	768 (19.6)
iβHS pathogen type			<0·001	
GAS	736 (49·2)	343 (74·7)		2282 (58.3)
NABS	761 (50·80)	116 (25·3)		2201 (49.1)
Site			<0·001	
MSK/SSTI	500 (33·4)	177 (38·6)		519 (36.4)
Respiratory	212 (14·2)	32 (7·0)		187 (13.1)
Other Deep Infection Site**	50 (3·3)	16 (3·5)		47 (3.3)
Primary Bacteremia	204 (13·6)	44 (9·6)		188 (13.1)
Secondary Bacteremia:	531 (35·3)	190 (41·4)		485 (34.0)

Necrotizing Fasciitis	14 (0·9)	46 (8·7)	<0·001	50 (1.3)
ICU Stay	251 (16·8)	121 (26·4)	<0·001	556 (14.2))
IVIG therapy	8 (0·5)	29 (6·3)	<0·001	25 (0.6)
Vasopressor‡	162 (10·8)	94 (20·5)	<0·001	285 (7.3)
Debridement within 3 days	240 (16·0)	127 (27·7)	<0·001	425 (10.9)
Immunocompromised†	118 (7·9)	39 (8·5)	0·75	291 (7.4)
Obesity	177 (11·8)	59 (12·9)	0·61	352 (9.0)
Community Onset	1411 (94·3)	437 (95·2)	0·51	4071 (90.8)
Academic Hospital	994 (66·4)	307 (66·9)	0·89	2993 (66.8)
Urban Hospital	1225 (81·8)	386 (84·1)	0·30	3023 (77.2)
Year of Infection			0·35	
Prior to 2005	141 (9·4)	39 (8·5)		495 (12.6)
2005-2009	539 (36·0)	182 (39·7)		1103 (28.2)
2010-2015	817 (54·6)	238 (51·9)		2317 (59.2)
Geographic Region			<0·05	
Midwest	356 (23·8)	81 (17·6)		850 (21.7)
Northeast	506 (33·8)	146 (31·8)		1226 (31.3)
South	412 (27·5)	138 (30·1)		1389 (35.5)
West	223 (14·9)	94 (20·5)		450 (11.5)
Hospital Bed Capacity			0·89	
Small (<200 beds)	347 (23·2)	105 (22·9)		884 (22.6)
Medium (200-500 beds)	847 (56·6)	265 (57·7)		2034 (52.0)

Large (>500 beds)	303 (20·2)	89 (19·4)	997 (25.5)

Abbreviations: βHS: β-hemolytic streptococci, CNS: central nervous system, GAS: Group A *Streptococcus* , GU: genitourinary, ICU: intensive care unit, IQR: interquartile range, IVIG: intravenous immunoglobulin, iβHS: invasive β-hemolytic streptococci, MSK: musculoskeletal, NABS: non-group A or B β-hemolytic streptococci, SSTI: skin and soft tissue infection, SOFA: Sequential Organ Failure Assessment

Data presented as No. (%) unless otherwise indicated. Wilcoxon ranked sum test was used to compare continuous variables and chi-square test was used to compare the categorical variables.

* The Elixhuaser was score calculated using ICD-9-CM codes (Supplementary Table-E3). Adapted from: Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data. Med Care. 2005 Nov;43(11):1130-9

^ Using an electronic health record-based adaption of the original Sequential Failure Assessment (SOFA) (Supplementary Table E8)

† Based on ICD 9 codes, algorithm can be found in supplementary document

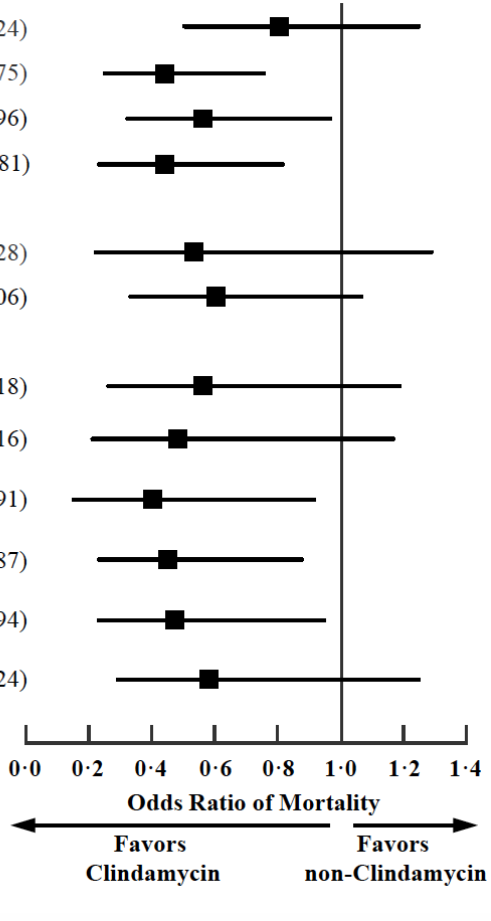
‡Norepinephrine, epinephrine, phenylephrine, dopamine within (+/-) 24 hours of culture

Other deep infections: include mediastinitis, orchitis/epididymitis, parapharyngeal abscess, periapical abscess, peritonsillar abscess, retropharyngeal abscess, abscess of mediastinum, abscess of salivary gland

e-Appendix 7: Results: Sensitivity Analysis, Odds Ratio of In-Hospital Mortality Using Generalized Estimating Equations

Figure E1: GAS Cohort

Groups	Clindamycin cases No.	Clindamycin cases Mortality (%)	Non-Clindamycin cases No.	Non-Clindamycin cases Mortality (%)	*p* Value	Odd Ratio of Mortality (95% CI)
Primary Analysis						
Unmatched, unadjusted	343	28 (8·2)	736	74 (10·1)	0·32	0·80 (0·50-1·24)
Unmatched, adjusted					<0·05	0·44 (0·25-0·75)
Matched (1:2), unadjusted	277	18 (6·5)	500	55 (11·0)	0·04	0·56 (0·32-0·96)
Matched (1:2), adjusted*					0·01	0·44 (0·23- 0·81)
Subgroup Analysis						
Matched early Clindamycin†	97	6 (6·2)	500	55 (11·0)	0·16	0·53 (0·22-1·28)
Matched, proven iβHS†	153	18 (11·8)	282	51 (18·1)	0·09	0·60 (0·33-1·06)
Matched, probable iβHS†	124	0 (0·0)	218	4 (1·8)	1·00	**
Matched, ICU patients†	55	13 (23·6)	90	32 (35·6)	0·13	0·56 (0·26-1·18)
Matched, vasopressor-dependent shock†	37	12 (32·4)	57	28 (49·1)	0·11	0·48 (0·21-1·16)
Matched, without shock nor necrotizing fasciitis†	239	6 (2·6)	442	27 (6·1)	0·04	0·40 (0·15-0·91)
Matched, Clindamycin > 1 day†	226	12 (5·3)	500	55 (11·0)	0·02	0·45 (0·23-0·87)
Matched, Clindamycin > 2 days†	183	10 (5·5)	500	55 (11·0)	0·03	0·47 (0·23-0·94)
Matched, Clindamycin > 3 days†	122	9 (6·9)	500	55 (11·0)	0·17	0·58 (0·29-1·24)



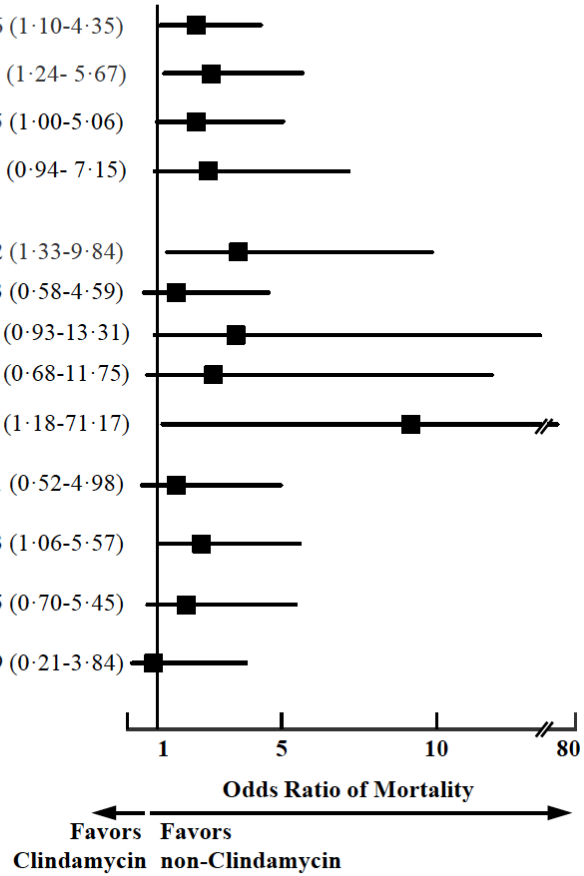
Abbreviations: CI: confidence intervals, GAS: group A *Streptococcus*, ICU: intensive care unit, iβHS: invasive β-hemolytic streptococci, OR: odds ratio

* primary analysis adjusted for proven iβHS, vasopressor-dependent shock and ICU status

Figure E1 Legend: The figure reports the odds ratios (ORs) of in-hospital mortality and 95% confidence intervals in the unmatched and unadjusted analysis, matched and unadjusted analysis, and primary analysis conducted using generalized estimating equations (GEE)[10] (matched and by logistic regression), as well as subgroup analysis on propensity matched pairs of the GAS cohort.

Figure E2: NABS Cohort

Groups	Clindamycin cases No.	Clindamycin cases Mortality (%)	Non-Clindamycin cases No.	Non-Clindamycin cases Mortality (%)	*p* Value	Odd Ratio of Mortality (95% CI)
Primary Analysis						
Unmatched, unadjusted	116	12 (10·3)	761	37 (5·1)	0·02	2·26 (1·10-4·35)
Unmatched, adjusted					0·01	2·73 (1·24- 5·67)
Matched (1:2), unadjusted	102	10 (9·8)	193	9 (4·6)	0·05	2·25 (1·00-5·06)
Matched (1:2), adjusted*					0·06	2·63 (0·94- 7·15)
Subgroup Analysis						
Matched, early Clindamycin†	39	6 (15·4)	193	9 (4·6)	0·01	3·62 (1·33-9·84)
Matched, proven iβHS†	57	5 (8·7)	106	6 (5·7)	0·35	1·63 (0·58-4·59)
Matched, probable iβHS†	45	5 (11·1)	87	3 (3·5)	0·06	3·53 (0·93-13·31)
Matched, ICU patients†	19	5 (26·3)	36	4 (11·1)	0·15	2·83 (0·68-11·75)
Matched, vasopressor-dependent shock†	7	5 (71·4)	14	3 (21·4)	0·03	9·17 (1·18-71·17)
Matched, without shock nor necrotizing fasciitis†	95	5 (5·3)	177	6 (3·4)	0·41	1·61 (0·52-4·98)
Matched, Clindamycin > 1 day†	85	9 (10·6)	193	9 (4·6)	0·08	2·43 (1·06-5·57)
Matched, Clindamycin > 2 days†	69	6 (8·7)	193	9 (4·6)	0·27	1·95 (0·70-5·45)
Matched, Clindamycin > 3 days†	47	2 (4·3)	193	9 (4·6)	0·87	0·89 (0·21-3·84)



Abbreviations: CI: confidence intervals, ICU: intensive care unit, iβHS: invasive β-hemolytic *streptococci*, NABS: Non-group A/B β-hemolytic *streptococci*, OR: odds ratio

* primary analysis. Adjusted for proven iβHS, vasopressor-dependent shock and ICU status

† subgroup analysis

Figure E2 Legend: The figure reports the odds ratios (ORs) of in-hospital mortality and 95% confidence intervals in the unmatched and unadjusted analysis, matched and unadjusted analysis, and primary analysis conducted using generalized estimating equations (GEE)[10] (matched and by logistic regression), as well as subgroup analysis on propensity matched pairs of the NABS cohort

e-Appendix 8: Results: *Mortality over time*

Table E7: Mortality Over Time Among Invasive β-hemolytic Streptococcal Infection

Time Period	GAS		NABS	
	Non-Clindamycin n=500	Clindamycin n=277	Non-Clindamycin n=193	Clindamycin n=102
2000-2005	5 (10·4)	3 (10·7)	0 (0)	0 (0)
2005-2009	17 (9·8)	7 (6·7)	5 (5·6)	5 (10·4)
2010-2015	33 (11·8)	8 (5·5)	4 (4·3)	5 (10·6)

Percentages are reported in parenthesis. Abbreviations GAS: group A *Streptococcus,* NABS: non-group A/B β-hemolytic streptococci

e-Appendix 9: Results: *Clindamycin Resistance*

Susceptibility testing results were available for 20% (n=[1172/5953]; GAS: 19% (496/2570), NABS:20% [676/3383]). Of those tested, 13% (156/1172) exhibited resistance or intermediate susceptibility to clindamycin and were removed from further analysis. Within the cohort whom underwent matching (n=1956) susceptibility testing results was present for 24% (469/1956) of patients (GAS: 25% [276/1079], NABS: 22% [196/877])

Among excluded patients with isolates which exhibited resistance or intermediate susceptibility bases (n=156), rates of resistance were significantly higher in NABS isolates compared to GAS isolates (16% [80/492] *vs.* 11% [76/669], p=0.02). Among NABS the percentage of resistance isolates increased significantly over the three time periods (3% [1/33] *vs.*11% [11/93] *vs.* 19% [68,/286]; p=0·01), which was not the case for GAS (2000-2005: 7%[4/54] *vs*. 2005-2010: 9% [14/140] *vs.* 2010-2015: 13% [58/399]; p=0·25)

Crude mortality among those with resistance/intermediate isolates compared to susceptible isolates was similar among both GAS (3% (10/76) vs. 10% 60/593, p=0·54) and NAB 5% (4/80) vs 7% (30/412), p=0·62)

e-Appendix 10: Table E8: Studies Examining Clinical Efficacy of Adjunctive Clindamycin in iβHS

Study	Study Design	Case definition	Cases	Deaths/Poor outcome		Univariate or crude OR/RR [95% CI]	Multivariate or adjusted OR/RR [95% CI]	Additional Information
				Clindamycin	Non-clindamycin			
Group A *Streptococcus*								
Kaul et al (1997)[13]	Observational prospective surveillance	Necrotizing fasciitis	77^	12/47 (26%)	14/30 (47%)	0·55 [0·23-1·02]	-	Clindamycin not retained in multivariable model
Kaul et al (1999)[14]	Comparative observational prospective surveillance	STSS (IVIG treated vs non IVIG treated)	53*	15/37 (41%)	12/15 (80%)	0·21 [0·07-1·00]	-	Adjunctive clindamycin use data missing for one patient. Clindamycin not retained in multivariable model
Zimbelman et al (1999)[15]	Retrospective cohort	iGAS	19†	2/12 (17%)	6/7 (86%)	-	-	Results reported for all protein synthesis inhibitors (n=45, of which 39 received clindamycin).
Mulla et al (2003) [16]	Observational prospective surveillance		195	-	-	1·05 [0·49-2·28]	0·58 [0·20-1·74]	Among 33 patients with necrotizing fasciitis clindamycin showed statistically significant benefit (aOR 0.11 [0.01-0.89]) but not among 162 patients without necrotizing fasciitis (aOR 1.01 [0.31-3.33]
Mehta et al (2006)[17]	Observational prospective surveillance	iGAS (ICU patients)	62	-	-	Not significant (data not shown)	-	Clindamycin was not a predictor of mortality in univariate model (ORs not reported) and not included in the multivariate model

Carapetis et al (2014)[18]	Observational prospective surveillance	Severe iGAS (necrotizing fasciitis/ STSS/ septic shock/ cellulitis + hypotension)	84	8/53 (15%)	12/31 (39%)	0·28 [0·10-0·80]	0·31 [0·09-1·12]	
Linner et al (2014)[19]	Observational prospective surveillance	STSS	67	-	-	0·13 [0·04-0·50]	0·12 [0·03-0·56]	
Couture-Cossette et al (2018)[20]	Retrospective cohort	iβHS	249	5/128 (4%)	15/128 (12%)	0·2 [0·04-0·90]**	0·04 [0·003-0·55]**	ORs are for patient receiving clindamycin within 24hs (mortality: 2/77 (3%))
Non-group A β-hemolytic streptococci								
Couture-Cossette et al (2018)[20]	Retrospective cohort	iβHS	304	1/23 (4·3%)	23/281 (8·2%)	0·51 [0·07-3·96]	-	

Abbreviations: CI: confidence intervals, iβHS: invasive β-hemolytic streptococci, iGAS: invasive group A *Streptococcus*, STSS: streptococcal toxic syndrome OR: odds ratio, RR: relative risk

- missing data

^ Two patients had Group A *Streptococcus* + *S. aureus* isolated. Authors used stepwise backward regression. Model included variables associated with mortality on univariate analysis (including clindamycin). Non-significant variables were eliminated from the MV model, this included adjunctive clindamycin.

* Adjunctive clindamycin use data missing for one patient

† Overall cases: n=56, deep infection: n=19 (these included bacteremia, osteomyelitis, arthritis, pyomyositis, necrotizing cellulitis or fasciitis). Reported results for protein synthesis antibiotics. In overall cohort the protein synthesis antibiotic used was clindamycin in 39/45 cases. Reported *p* value for favorable outcomes with protein synthesis antibiotic *p*=0.006

^^ Among 33 patients with necrotizing fasciitis clindamycin showed statistically significant benefit (aOR 0.11 [0.01-0.89]) but not among 162 patients without necrotizing fasciitis (aOR 1.01 [0.31-3.33]

** OR for patient receiving clindamycin within 24hs (mortality: 2/77 (3%))

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