

Supplementary Table S1. Studies included EOS neonatal cases with of iGAS.

First author, publication year	Study type	Pa- tients (N)	Gesta- tional Age (weeks)	Birth weight (g)	Origin	Gen- der	Mode of De- livery	Length of Rup- ture of Mem- branes (hours)	Maternal symptoms	Ma- ternal GAS posi- tive Cul- tures	Neonatal positive cultures	Maternal Peripar- tum Anti- biotics	Clinical manifesta- tions	Diag- nosis	Microor- gan- ism(Strep A emm strains)	Complica- tions	Type of treatment	Treatmnt duration (days)	Neo- natal out- come
Middleton, 2014 [1]		1	33	1910	Nether- lands	Male	N/R	N/R	None	N/R	Skin, um- bilicus, ear, blood, pleural fluid	N/R	Respiratory distress, hy- potension	Sepsis, pneu- monia	N/R	N/R	Penicillin	N/R	Death
Crum, 2002 [2]	Case re- port	1	34	2216	USA	N/R	Cae- sarean section	0	Toxic shock syndrome (TSS)	Vagi- nal	N/A	gentami- cin, clindamy- cin	Cardiorespir- atory failure	respira- tory distress	N/R	Stage III hypoxic brain dam- age due to asphyxia at deliv- ery, grade IV intra- ventricular hemor- rhage, hy- drocephala- lus, and brainstem herniation	Ampicillin and cefo- taxime	N/R	Death
Mahieu, 1995 [3]	Case re- port	1	35	N/R	Belgium	Male	Vagi- nal	19	Tenderness of uterus	Pla- centa, um- bilical	Blood, bullae	Penicillin	Grunting, apnea, de- creased feed-	TSS	M1, T1, SOR-	Skin ne- crosis and formation of bullae,	Ampicillin, netilmycin → penicil- lin	21 days	Good

										cord, cer- vix, and amni- otic mem- branes			ing, brady- cardia, oligu- ria, hypoten- sion, respira- tory distress		cranial cel- lulitis, su- perior vena cava obstruc- tion				
Nieburg, 1975 [4]	Case series	1	36	2155	USA	Fe- male	N/R	4,5	Leucorrhea	Blood, and lochia	Blood, urine	N/R	Respiratory distress, pul- monary hemorrhage, circulatory collapse, bi- lateral ad- renal hemor- rhage	sepsis	emm type 12	N/R	N/R	N/R	Death
		1	36	2600	USA	Male	N/R	4,5	Fever, pelvic thrombo- phlebitis	Blood	Blood	N/R	Respiratory distress, pul- monary hemorrhage, circulatory collapse, bi- lateral ad- renal hemor- rhage	sepsis	emm type 12	N/R	N/R	N/R	Death
		1	38	3755	Nether- lands	Fe- male	N/R	N/R	Puerperal sepsis	N/R	Skin, ear, eye, um- bilicus, naso- pharynx	N/R	Fever, con- junctivitis, respiratory distress, hy- potension	Sepsis, pneu- monia	N/R	N/R	Penicillin	N/R	Good
Lequier 1998 [5]	Case series	1	38	2480	USA	Fe- male	N/R	N/R	N/R	Vagi- nal and blood	Blood	N/R	Pale and le- thargic	sepsis, empy- ema	emm type 1	Pleural empyema	Penicillin, empyema decortica- tion	N/R	Good

		1	39	3775	Netherlands	Male	N/R	N/R	TSLs	N/R	Skin, nasopharynx, umbilicus, blood	N/R	Respiratory distress, hypotension, skin rash	toxic shock-like syndrome (TSLs)	N/R	N/R	Penicillin, clindamycin	N/R	Good
Shinoda, 2020 [6]	Case series	1	39	3158	Japan	Female	Vaginal	N/R	N/R	blood	Blood, skin swabs, and cerebrospinal fluid	N/R	Fever	sepsis, meningitis	emm 80	N/R	Ampicillin, cefotaxime, and acyclovir	14 days	Good
		1	39	N/R	UK	Male	Caesarean section	N/R	Fever	Uterine cavity, placenta	Blood, umbilicus	N/R	Drowsy, jaundiced, fever, abdominal erythema and distension	sepsis	N/R	N/R	N/R	N/R	Good
Verboon-Macielek, 2000 [7]		1	40	3150	Netherlands	Male	N/R	N/R	Pharyngitis	N/R	Umbilicus, ascites fluid	N/R	Poor feeding, vomiting, distended abdomen, bloody stools	Peritonitis	N/R	N/R	Penicillin, laparotomy	N/R	Good
		1	40	3680	Netherlands	Male	N/R	N/R	Puerperal sepsis	N/R	Skin, ear, umbilicus, nasopharynx, blood	N/R	Fever, skin rash, respiratory distress, hypotension	TSLs	N/R	N/R	Penicillin, clindamycin	N/R	Good
Nohara, 2014 [8]	Case series	1	40	3144	Japan	Female	Vaginal	N/R	N/R	Vaginal	Throat, skin, head empyema, pleural fluid	N/R	Small empyema on the head, respiratory distress	pleural empyema	emm type 6	N/R	Ampicillin and cefotaxime	11	Good
		1	40	N/R	UK	Male	Vaginal	N/R	Sepsis	N/R	Blood, scalp wound swab,	N/R	Infected scalp wound,	sepsis	N/R	N/R	N/R	N/R	Good

											umbili- cus, nose, throat		cellulitis, oe- dema, gener- alised rash							
Miyairi, 2004 [9]	Case re- port	1	term	4800	USA	N/R	Vagi- nal	12	N/R	N/R	blood	N/R	Cardiorespir- atory arrest	sepsis	N/R	N/R	Ampicillin , gentamicin	N/R	Death	
Nutman, 1979 [10]	Case re- port	1	term	2700	Israel	Fe- male	Vagi- nal	14	N/R		Nose, cervix skin, CSF, blood	N/R	Erythema- tous lesion was ob- served on the right cheek, poor feeding, fever	sepsis, menin- gitis	type M52	N/R	Penicillin, gentamicin, and chlo- rampheni- col→ peni- cillin	N/R	Good	
Thaarup, 1997 [11]	Case re- port	1	term	3325	Den- mark	Fe- male	N/R	30 min	fever		blood, cervix and an in- fected peri- neal rup- ture	Pleural fluid	N/R	Tachypnea, costal retrac- tions, grunting and peripheral cyanosis	Pleural empy- ema	N/R	N/R	Ampicillin and netilmicin → Penicil- lin and netilmicin → ceftriax- one and netilmicin	28 days	Good
Ross, 2021 [12]	Case re- port	1	N/R	N/R	Aus- tralia	N/R	Vagi- nal	N/R	Abdominal pain		Vagi- nal, breast milk		N/R	Tachypnoea and grunt- ing, subga- leal haemor- rhage, hae- modynamic instability and fever	Sepsis	N/R	N/R	Ampicillin, gentamicin and cefo- taxime → ampicillin	14 days	Good
Sakata, 2013, 2014 [13,14]	Case series	1	N/R	N/R	Japan	Fe- male	N/R	N/R			N/R	Pleural fluid	N/R	N/R	Pyotho- rax	emm type 6	N/R	Ampicillin	N/R	Good
Timmis 2010 [15]	Case series	1	N/R	N/R	UK	Male	N/R	N/R			N/R	Blood	N/R	N/R	Definite strepto- coccal toxic shock	N/R	N/R	Cefotaxime gentamicin benzylpeni- cillin	N/R	Death

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Supplementary Table S2. Studies included LOS neonatal cases with of iGAS.

First author, publication year	Study type	Pa- tients (N)	Gesta- tional Age (weeks)	Birth weight (g)	Origin	Gender	Mode of De- livery	Length of Rup- ture of Mem- branes (hours)	Maternal symp- toms	Maternal GAS posi- tive Cul- tures	Neonatal positive cultures	Clinical manifes- tations	Diagno- sis	Microor- gan- ism(Strep A emm strains)	Com- plica- tions	Type of treatment	Treat- ment dura- tion (days)	Neonatal outcome
Middleton, 2014 [1]	Case series	1	30	N/R	Aus- tralia	Female	N/R	N/R	N/R	N/R	Peritoneal Fluid	Hypo- thermia, tachycar- dia, tach- ypnoea, grunting, hypoxia, hypoten- sion, cool peripher- ies, sunken fonta- nelle, ab- dominal disten- sion, bruish	TSLS	N/R	N/R	Ceftriaxone, gentamicin, metronida- zole → pipe- racillin-tazo- bactam, ex- ploratory laparotomy, surgical deb- ridement of the area of necrosis	14	Good
		1	30	N/R	Aus- tralia	Female	N/R	N/R	N/R	N/R	Blood	Cough, lethargy, de- creased	Sepsis	N/R	N/R	Ceftriaxone and flucloxa- cillin → pip- eracillin-	14	Good

												oral intake, hypothermia, hypoxia, poor peripheral perfusion, increased tissue turgor, sunken fontanelle, hypotension				tazobactam, vancomycin, azithromycin and oseltamivir→benzylpenicillin		
Barnham 2001 [16]	Case series	1	35	N/R	UK	Male	Vaginal	27 hours	N/R	N/R	Blood	Dusky, floppy, lethargy	sepsis	N/R	N/R	N/R	N/R	Good
		1	36	2550	Netherlands	Male	N/R	N/R	None	N/R	CSF, brain abscess	Fever, poor feeding, full anterior fontanelle, seizures	Meningitis, brain abscess	N/R	N/R	Penicillin	N/R	Death
Ventura 2019 [17]	Case report	1	36	N/R	Portugal	Female	Vaginal	3 hours	N/R	N/R	Blood	Feeding refusal and hyporeactivity, dry mucous membranes, depressed anterior	Sepsis	emm type STG7882	N/R	Cefotaxime, ampicillin,	N/R	Good

												fonta- nelle, and weight loss						
Saito, 2017 [18]	Case re- port	1	37	N/R	UK	Male	Vagi- nal	N/R	N/R	N/R	Blood	Poor feeding, irritabil- ity, vom- iting, loose stool and fever, ery- thema in umbili- cus, tach- ypnea, tachycar- dia	Sepsis	emm st28.0	N/R	Cefotaxime and amoxi- cillin	14 days	Good
Huber, 2014 [19]	Case re- port	1	39	N/R	Ger- many	Male	Cae- sarean sec- tion	N/R	N/R	N/R	Blood	Fever, lethargy and poor feed- ing, irrita- bility, pallor and mottling	sepsis	N/R	Celluli- tis-Ad- enitis	Ampicillin and gen- tamicin	14 days	Good
Verboon-Macielek, 2000 [7]	Case series	7	40	3350	Neth- er- lands	Male	N/R	N/R	None	N/R	Umbili- cus, ascites fluid	Poor feeding, vomit- ing, dis- tended abdomen, omphali- tis	Peritoni- tis	N/R	N/R	Penicillin, peritoneal puncture	N/R	Good
Bhutta, 1990 [20]	Case series	1	40	3000	Paki- stan	Male	N/R	N/R	N/R	N/R	Blood	Fever, poor feeding,	sepsis	N/R	Cardi- orespir- atory arrest	Cefotax- ime, amika- cin, cloxacil- lin	N/R	Death

Campbell, 1996 [21]	Retrospective cohort																	
		1	N/R	N/R	Pakistan	Female	N/R	N/R	N/R	N/R	Blood and pus from the lesions	respiratory difficulty Lethargy, 2 vesicular lesions in the left axilla and antecubital fossa	sepsis	N/R	N/R	No treatment	N/R	Good
		1	term	2800	Pakistan	Male	N/R	N/R	N/R	N/R	Blood	Icteric, periorbital oedema, vomiting, necrotic umbilicus	sepsis	N/R	Cardiorespiratory arrest	Cefotaxime, amikacin, cloxacillin	N/R	Death
		1	26	920	USA	N/R	N/R	N/R	N/R	N/R	Blood and throat	Apnea and poor perfusion	Sepsis	N/R	N/R	Ben-zathine penicillin G intramuscularly, intravenous clindamycin	14	Good
		1	28	560	USA	N/R	N/R	N/R	N/R	N/R	Blood	Apnea, bradycardia, hypotension, and toxic shock-like syndrome, necrotic scalp lesion	Sepsis	N/R	Seven days later, he had apnea, shock, neutropenia, disseminated intra-	14-day course of penicillin G (200,000 units/kg per day) and also received a single dose of benzathine penicillin G	14	Death

															vascu- lar co- ag- ulopa- thy, and,ne- crotiz- ing cel- lulitis of the right ear and scalp extend- ing to the oc- ciput.	(50,000 units/kg)		
Wilschanski, 1989 [22]	Case re- port	1	term	N/R	Israel	Male	Vagi- nal	N/R	N/R	N/R	Blood	Fever, poor feeding, erythem- atous rash in right cer- vix + pe- riorbital edema, focal sei- zure	Sepsis	3/13/B3264	N/R	Gentamicin, cefuroxime and ampicillin → Penicillin G	12 days	Good
Cartwright, 1977 [23]	Case re- port	1	term	4080	Eng- land	Male	Vagi- nal	N/R	N/R	N/R	Blood	Erythem- atous le- sion, swollen cheek, oe- dematous eye	Sepsis	N/R	N/R	Penicillin, hydrocorti- sone	14	Good

Barnham, 1989 [24]	co-hort study	1	preterm	N/R	UK	Male	N/R	Pro-longed	N/R	N/R	Blood	Jaundice, sepsis	Sepsis	N/R	N/R	N/R	N/R	Good
Umadevi, 2013 [25]	Case re-port	1	term	3200	Neth-er-lands	Male	Cae-sarean sec-tion	N/R	N/R	N/R	Arthritic fluid	Swelling on his right el-bow and reduced move-ments of the right forearm	septic ar-thritis, sepsis	N/R	N/R	Ampicillin, cloxacillin and amika-cin → Oral ampicillin and erythro-mycin	10 days	Good
Coulter, 1984 [26]	Case series	1	term	N/R	UK	Female	N/R	N/R	N/R	N/R	Blood, CSF, and umbilicus	Snuffles, irritabil-ity, poor feeding, bleeding from the tongue, and a transient rash on the face and trunk.	sepsis, meningi-tis	N/R	N/R	Penicillin, cefuroxime	N/R	Death
		1	term	N/R	UK	Male	N/R	N/R	N/R	Vaginal swab	CSF, paronych-iae, um-bilicus, nose, and nasogas-tric aspi-rate	Fever, opis-thoto-nous, sei-zures, fontanelle disten-sion.	meningi-tis	N/R	Hydro-cepha-lus	Gentamicin and cefurox-ime → peni-cillin	N/R	Good
Martic, 2010 [27]	Case re-port	1	N/R	N/R	Serbia	Male	N/R	N/R	superfi-cial pyo-derma	Skin	Blood	Fever , lethargy, poor feeding, erythema	sepsis	emm type 53.2	N/R	Vancomycin, amikacin → penicillin G	N/R	Good

Sakata, 2013, 2014 [13,14]	Case series	1	N/R	N/R	Japan	Female	N/R	N/R		N/R	Blood	N/R	Sepsis	emm type 1	N/R	Ampicillin	N/R	Good
		1	N/R	N/R	Japan	Male	N/R	N/R		N/R	Blood	N/R	Sepsis	emm type 1	N/R	Ampicillin	N/R	Good
		1	N/R	N/R	Japan	Female	N/R	N/R		N/R	Blood	N/R	sepsis , necrotizing fasciitis	N/R	N/R	N/R	N/R	N/R
Santos, 2009 [28]	Case series	1	N/R	N/R	Brazil	Female	N/R	N/R		N/R	CSF	N/R	meningitis	emm type 39,1	N/R	N/R	N/R	N/R
		1	N/R	N/R	Brazil	Female	N/R	N/R		N/R	CSF	N/R	meningitis	emm type 92	N/R	N/R	N/R	N/R
Shanks, 1986 [29]	Case report	1	N/R	N/R	USA	Male	Caesarean section	N/R	Fever, chills, vaginal hemorrhage	Vaginal	Tunica vaginalis pus	Irritability, scrotal swelling, fever, yellow exudate of umbilicus	hydrocele infection	N/R	N/R	Nafcillin, gentamycin	N/R	Good
Torres-Martinez 1992 [30]	Case series	1	N/R	N/R	UK	Female	N/R	N/R		N/R	Blood, peritoneal fluid	Fever, rash, abdominal distension, hypotension, shock	Peritonitis, sepsis	N/R	N/R	Penicillin	14 days	Good
Givner, 1991 [31]	Case series	1	N/R	N/R	Canada	Female	N/R	N/R		N/R	Blood	N/R	Sepsis, osteomyelitis	N/R	N/R	N/R	N/R	N/R
Johnson, 1990 [32]	Case report	1	N/R	N/R	USA	N/R	N/R	N/R		N/R	Blood	N/R	sepsis	N/R	N/R	N/R	N/R	Good
Lehtonen, 1987 [33]	Case series	1	N/R	N/R	Turkey	Female	N/R	N/R		N/R	Blood	Febrile , irritable, lethargic,	sepsis	N/R	N/R	Metronidazole-cephalothin	N/R	Good

											abdomen disten- sion and rash							
		1	N/R	N/R	Tur- key	Female	N/R	N/R		N/R	Blood	Fever,ir- ritable, lethargic, abdomen disten- sion and rash	sepsis	N/R	N/R	Metronida- zole-cepha- lothin	N/R	Good
Leonard, 2019 [34]	Ret- ro- spec- tive study	12	N/R	N/R	UK	N/R	4 cae- sarean sec- tion,3 vagi- nal deliv- ery, 5 N/R	N/R		N/R	Blood	5 fever, 2 respira- tory dis- tress , 2 infections of the umbilicus or ear, 1 hypoxic ischaemic encepha- lopathy, 2 N/R	sepsis	N/R	N/R	N/R	N/R	Good

Supplementary Table S3. Studies included neonatal cases of iGAS with no data regarding the time of disease onset.

First author, publication year	Study type	Pa- tients (N)	Gesta- tional Age (weeks)	Birth weight (g)	Origin	Gen- der	Mode of De- livery	Length of Rup- ture of Mem- branes (hours)	Maternal symptoms	Mater- nal GAS positive Cultures	Neona- tal posi- tive cul- tures	Maternal peripar- tum anti- biotics	Clinical mani- festa- tions	Diagno- sis	Microor- gan- ism(Strep A emm strains)	Compli- cations	Type of treatment	Ttreat- ment du- ration (days)	Neonatal Outcome
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Siti Hafsyah, 2021 [35]	Case re-report	1	37	2460	Malaysia	Female	Vaginal	N/R	Vaginal itchiness and discharge, fever, chills	Vaginal	Peritoneal fluid, pleural fluid and blood	N/R	Lethargic and grunting, cardiopulmonary arrest	Sepsis	N/R	N/R	N/R	N/R	Death
Davey 2006 [36]	Case re-report	1	term	3560	Canada	Female	vaginal	4 hours		Vaginal	Skin cultures	Cefazolin	Fever, erythematous scalp lesion, irritable and fed poorly	Cellulitis	type M11 T non-typeable	Acute renal failure, respiratory distress syndrome, perforated necrotizing enterocolitis (requiring resection of necrotic bowel, a jejunos-tomy, and distal ileal mucous fistula), recurrent infections, failure to thrive,	Ampicillin, cefuroxime, → gentamicin, meropenem and clindamycin → penicillin G	20 days	Good

																			and cho- lestatic jaundice
Pius, 2016 [37]	Original arti- cle	5	N/R	N/R	Nigeria	N/R	N/R	N/R		N/R	Blood	N/R	N/R	Sepsis	N/R	N/R	N/R	N/R	2 deaths
Wheeler, 1991 [38]	Case series	1	N/R	N/R	USA	Male	N/R	N/R		N/R	N/R	N/R	N/R	Pneumo- nia	N/R	N/R	N/R	N/R	Good
		1	N/R	N/R	USA	Male	N/R	N/R		N/R	CSF	N/R	N/R	Meningi- tis	N/R	N/R	N/R	N/R	Good
		1	N/R	N/R	USA	Male	N/R	N/R		N/R	N/R	N/R	N/R	Pneumo- nia	N/R	N/R	N/R	N/R	Good
		1	N/R	N/R	USA	Fe- male	N/R	N/R		N/R	N/R	N/R	N/R	Pneumo- nia	N/R	N/R	N/R	N/R	Good
		1	N/R	N/R	USA	Male	N/R	N/R		N/R	Skin les- sion	N/R	N/R	Cellulitis	N/R	N/R	N/R	N/R	N/R
Seale, 2016 [39]	ob- serva- tional study	94	N/R	N/R	Kenya	N/R	N/R	N/R		N/R	Blood, (2.3%) CSF, (54.7%) swab sample (wound, skin breach, or pus), (2.0%) joint as- pirates, (1.5%) urine	N/R	Skin or soft tis- sue in- fection (69.9%); fol- lowed by se- vere pneu- monia in (23.3%), of which (69%) were compli- cated by sepsis; then	Sepsis, meningi- tis	N/R	N/R	N/R	N/R	12.2% mor- tality

bactere-
mia
without
focus in
(14.4%),
(4.6%)
bone
and
joint in-
fections,
(3.0%)
menin-
gitis,
(1.6%)
urinary
tract in-
fection,
(0.5%)
acute
glomer-
ulone-
phritis,
(0.3%)
endocar-
ditis,
(0.3%)
nonspe-
cific
ab-
dominal
signs,
(0.3%)
necrotiz-
ing
fasciitis.
A
total of
(5.1%)

												met the criteria for strepto- coccal toxic shock syn- drome						
Givner, 1991 [31]	1	N/R	N/R	Canada	Male	N/R	N/R		Endo- metrium	Blood	N/R	N/R	Sepsis	N/R	N/R	N/R	N/R	N/R
Lehtonen, 1987 [33]	1	N/R	N/R	Turkey	N/R	N/R	N/R		N/R	Skin les- sion	N/R	N/R	Pyo- derma	N/R	N/R	Metroni- dazole- cepha- lothin	N/R	Good
	1	N/R	N/R	Turkey	N/R	N/R	N/R		N/R	Ompha- lus	N/R	N/R	Ompha- litis and conjunc- tivitis.	N/R	N/R	Metroni- dazole- cepha- lothin	N/R	Good
	17	N/R	N/R	Turkey	N/R	N/R	N/R		N/R	Ompha- lus	N/R	N/R	Ompha- litis	N/R	N/R	Metroni- dazole- cepha- lothin	N/R	Good

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