Landon State Office Building
900 SW Jackson Street, Room 1031
Topeka, KS 66612-1228

Kansas
Board of
Emergency Medical Services

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Dr. Joel E Hornung, Chair
Joseph House, Executive Director

Laura Kelly, Governor

MEDICAL ADVISORY COUNCIL

June 3, 2021 ***10:00 AM CDT***

Landon State Office Building – Room 509
900 SW Jackson; Topeka, KS 66612
(Virtual Attendance is Available – Information on Page 2)

TENTATIVE AGENDA

1. Introduction and Welcome: Dr. Jacobsen
2. Roll-call: Dr. Jacobsen
3. Review of meeting notes from December 2020: Dr. Jacobsen.
4. Business/Discussion
    a. Medication List Additions
        i. Addition of Ketorolac to the AEMT Medication List
            1. Kansas EMS Ketorolac Administration Data (attached)
            2. Ketorolac Monograph for Professionals (attached)
        ii. Addition of IN administration route for Glucagon - (Baqsimi®)
            1. https://www.baqsimi.com/hcp/adult
            2. https://www.baqsimi.com/hcp/pediatrics
            3. Prescribing Information Highlights (attached)

    b. Consideration of addition of Point-of-Care ultrasound (POCUS) as an approved activity for all levels of EMS provider
        i. https://www.ems1.com/ems-products/defibrillators-and-monitors/articles/prehospital-ultrasound-emerging-technology-for-ems-7ZSxlEn7qHIMZOdQ/ (attached)
        ii. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7383635/ (attached)
        iii. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6019293/ (attached)
        iv. Webinar: https://www.pocus.org/resources/the-pocus-certification-academy-webinar-series-episode-3/
        v. http://www.naemsp-blog.com/emsmed/2017/1/20/the-new-12-lead-prehospital-point-of-care-ultrasound

    c. Discussion regarding conflicts between off-line and on-line medical direction

    d. Election of Chair (done at first meeting of odd years)

5. Parking Lot (no action / discussion unless active issue presents)
    a. Credentialing Exam Presentation – Deryk Ruddle (Sedgwick County)
6. Upcoming meeting dates (mark your calendars now)
    a. 2021 – August 5th; September 30th; December 2nd
7. Adjournment

Virtual Attendance Information:

Computer, tablet or smartphone: https://global.gotomeeting.com/join/802688829

Phone only: +1 (571) 317-3122 **Access Code:** 802-688-829

Attachment(s):

1. December 2020 Meeting Notes
2. Kansas EMS Ketorolac Administration Data
3. Ketorolac Monograph for Professionals (Source: drugs.com)
4. Baqsimi® Prescribing Highlights
5. POCUS – EMS1
6. POCUS – NIH-PMC7383635
7. POCUS – NIH-PMC6019293

MEDICAL ADVISORY COUNCIL
KS Board of Emergency Medical Services

Date of Meeting: December 3, 2020

Minutes Prepared By: Joe House

1. Purpose of Meeting

- The purpose of this virtual only, bi-monthly meeting was to discuss adding the administration of vaccinations to the authorized activities of an EMS Provider (EMR, EMT, AEMT, and/or Paramedic).

2. Attendance at Meeting

Members	*Company*	
Dr. Ryan Jacobsen	MAC – Chair	Present
Dr. James Longabaugh	MAC – Vice Chair	Absent
Dr. Dennis Allin	MAC Member	Present
Dr. Paige Dodson	MAC Member	Present
Dr. John Gallagher	MAC Member	Present
Dr. Sean Herrington	MAC Member	Absent
Dr. Michael Machen	MAC Member	Absent
Dr. Martin Sellberg	MAC - KBEMS Board Member	Present
Dr. Tim Stebbins	MAC Member	Present
Dr. Caleb Trent	MAC Member	Present
Dr. Carolina Pereira	MAC Member	Present
Dr. Paul Bogner	MAC Member	Present

3. Meeting Notes, Decisions, Issues

- Dr. Jacobsen introduced guests - Ally Briggs, a 2nd year emergency medicine resident with KU that is doing an EMS elective as well as Dr. Bryan Beaver, a KU EMS Physician and potential future appointment to the council.

- Review of Meeting Notes
  - Dr. Jacobsen asked if there were any issues or comments on the minutes from the October 2020 meeting. Dr. Gallagher asked for a revision to the top of page 2 to assist with completing the thought. Director House stated he would make that change.
    Dr. Gallagher made a motion to approve the minutes with the noted change. The motion was seconded by Dr. Pereira. No discussion and the motion carried with none opposed.

- Business/Discussion
  - Adding the administration of vaccinations to the authorized activities of an EMS provider

- Clarification was provided that this is already allowed at the paramedic level making the question more along the lines of the EMR, EMT, and AEMT levels.
- Initial thought provided that there was no real downside as long as training existed, medical director approved, etc.
- Concern was brought forth upon going all the way to the EMR and perhaps restricting to just EMT and AEMT citing no concern with the act of IM administration, but rather a lack of training related to decision making and recognition of untoward effects.
- It was noted that this would not authorize an EMT or AEMT to independently administer these immunizations, it would still be authorized, directed, and oversight provided by a physician, but that these individuals would be able to assist with the manpower necessary to undertake mass vaccination as is expected with the COVID-19 and influenza vaccination plans.
- Discussion was further had regarding how long this should be in effect and how broad it would encompass. Discussion revolved around the need seems to exist to vaccinate the entire population in a very short period of time, therefore, the manpower necessary to execute this plan would require additional assistance beyond that which is typically available. That would limit itself to COVID-19 and influenza as both are 'global' populations that would require vaccination of large quantities of people in short time.
- It was noted that perhaps a more in-depth consideration of vaccinations as a permanent grouping be a future discussion as the impact upon other potential vaccination populations may also be impacted by this pandemic.
- Dr. Stebbins made a motion to recommend to the Board that EMTs and AEMTs be allowed to administer COVID-19 and Influenza vaccines. The motion was seconded by Dr. Gallagher. No further discussion and the motion carried with none opposed.

Having no further business before the council, the meeting was adjourned at 10:33am.

4. Action Items

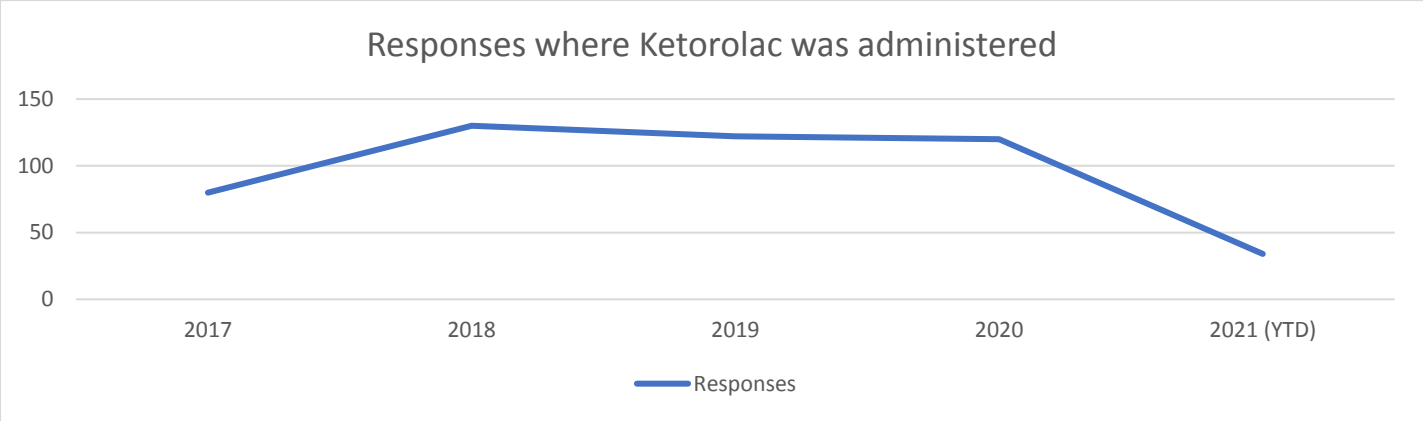
Action	*Assigned to*	*Due Date*	*Status*
Recommend to the Board the allowance of COVID-19 and Influenza vaccines at the EMT and AEMT levels	House	December	Done

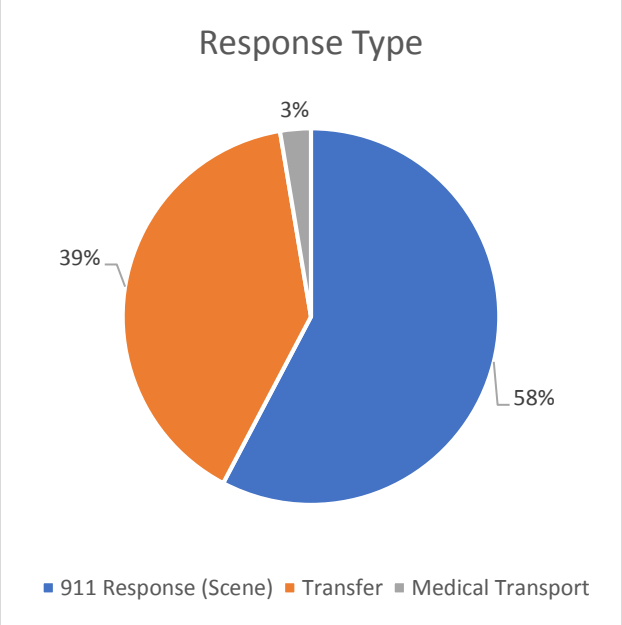
5. Next Meeting

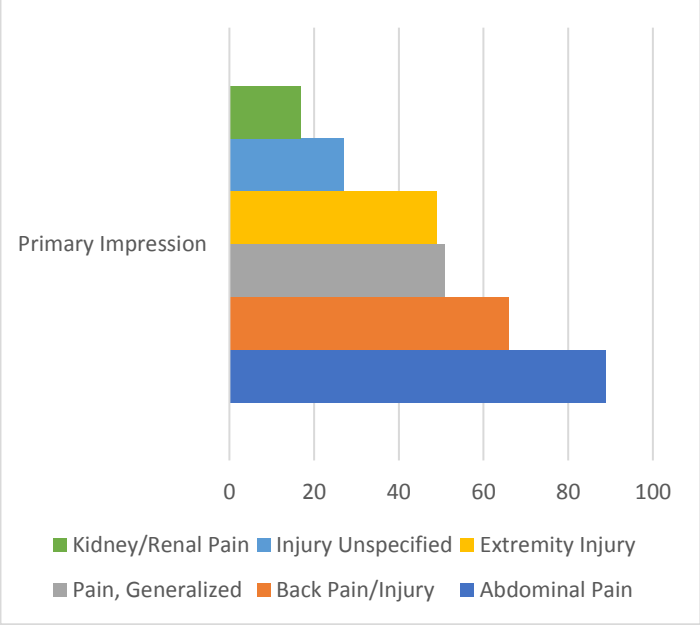
Date:	*February 4, 2021*	*Time:*	10:00AM	*Location:*	*Landon State Office Building; Room 509*
Objectives:	Continued discussion on credentialing as a CE pathway. Continued discussion on Kansas's Emergency First Responders legislation of adding dispatchers. Continued discussion on breadth of vaccinations that could be allowed.				

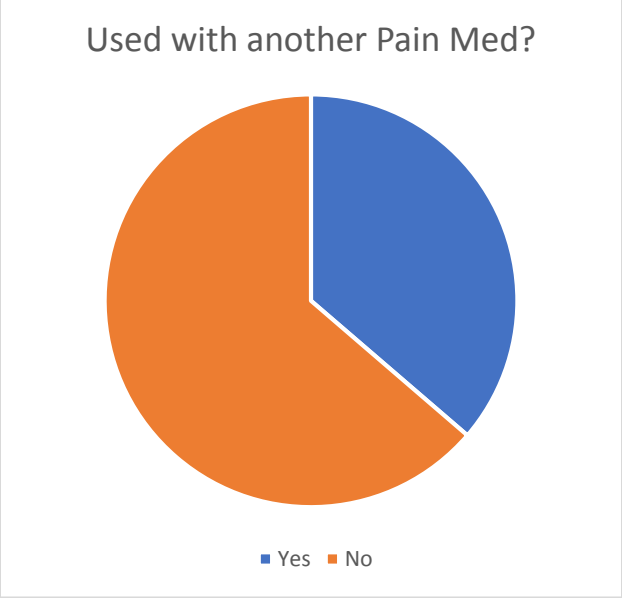
Ketorolac Administration Snapshot – Kansas EMS

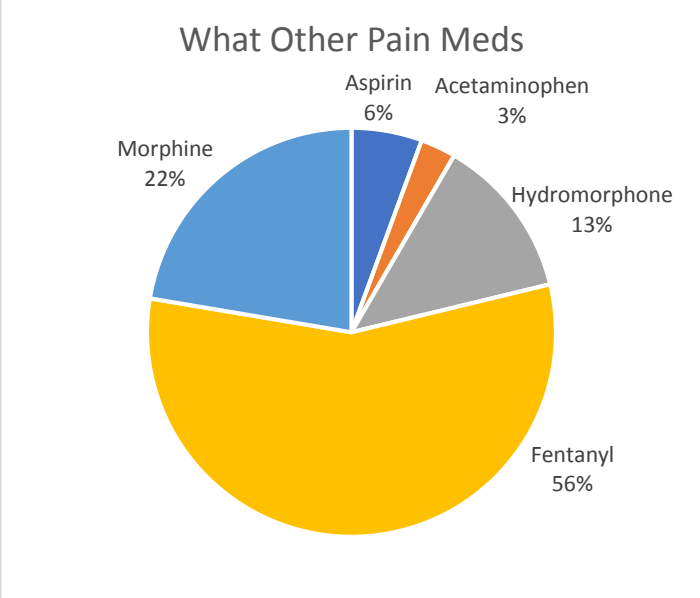
Data gathered from information submitted to KEMSIS v3 through 10:30am – 05/13/2021. No service, patient, or EMS provider can be identified from this aggregated information.

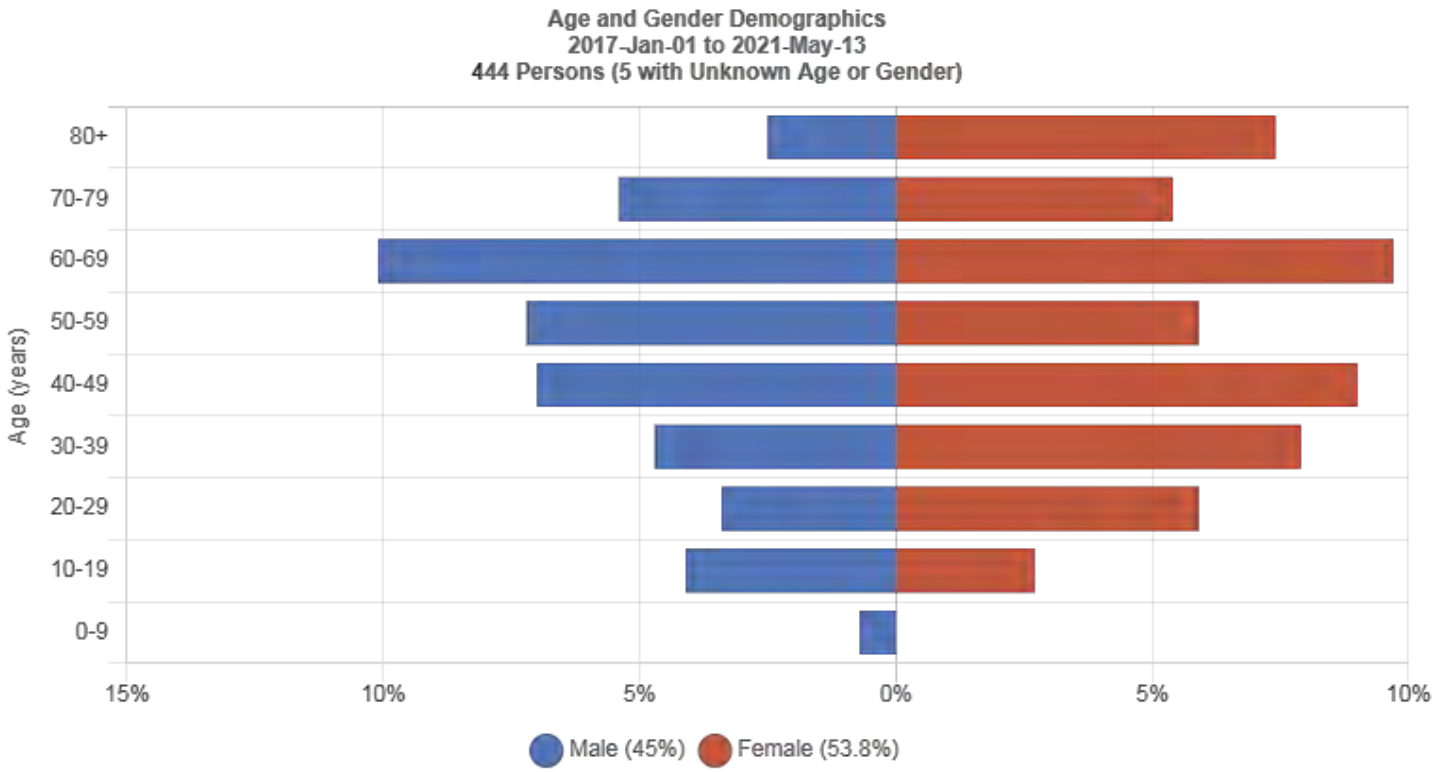












Usage in 53 of 105 counties during this time frame.

Usage in 21 of 105 counties for 911 Responses.

The Medical Advisory Council of the Board is being asked to consider whether the Board should approve Ketorolac administration for the Advanced Emergency Medical Technician (AEMT) level.

History: Services are reporting that hospitals are increasing their use of Ketorolac for non-opioid pain control primarily in traumatic patients. Currently, the administration of Ketorolac is limited to the Paramedic level (for EMS providers). Current pain management medications approved for use by the AEMT include: Opioids and Aspirin. The medication list is currently within the revision process to implement the addition of Nitrous Oxide at the AEMT level.

Drugs.com
Know more. Be sure.

Ketorolac (Systemic)

Class: Other Nonsteroidal Anti-inflammatory Agents
VA Class: CN103
Chemical Name: (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid compd. with 2-Amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
Molecular Formula: $C_{15}H_{13}O_3 \cdot C_4H_{11}NO_3$
CAS Number: 74103-07-4

Medically reviewed by Drugs.com. Last updated on Nov 9, 2020.

Warning

Special Alerts:

[Posted 10/15/2020]

AUDIENCE: Consumer, Patient, Health Professional, Pharmacy

ISSUE: FDA is warning that use of NSAIDs around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications.

For prescription NSAIDs, FDA is requiring changes to the prescribing information to describe the risk of kidney problems in unborn babies that result in low amniotic fluid.

For over-the-counter (OTC) NSAIDs intended for use in adults, FDA will also update the Drug Facts labels, available at: [Web]. These labels already warn to avoid using NSAIDs during the last 3 months of pregnancy because the medicines may cause problems in the unborn child or complications during delivery. The Drug Facts labels already advise pregnant and breastfeeding women to ask a health care professional before using these medicines.

BACKGROUND:

NSAIDs

- are a class of medicines available by prescription and OTC. They are some of the most commonly used medicines for pain and fever.

- are used to treat medical conditions such as arthritis, menstrual cramps, headaches, colds, and the flu.

- work by blocking the production of certain chemicals in the body that cause inflammation.

- are available alone and combined with other medicines. Examples of NSAIDs include aspirin, ibuprofen, naproxen, diclofenac, and celecoxib.

Common side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

RECOMMENDATION:

Consumers/Patients

- If you are pregnant, do not use NSAIDs at 20 weeks or later in pregnancy unless specifically advised to do so by your health care professional because these medicines may cause problems in your unborn baby.

- Many OTC medicines contain NSAIDs, including those used for pain, colds, flu, and insomnia, so it is important to read the Drug Facts labels, available at: [Web], to find out if the medicines contain NSAIDs.

- Talk to your health care professional or pharmacist if you have questions or concerns about NSAIDs or which medicines contain them.

- Other medicines, such as acetaminophen, are available to treat pain and fever during pregnancy. Talk to your pharmacist or health care professional for help deciding which might be best.

Health Care Professionals

- FDA recommends that health care professionals should limit prescribing NSAIDs between 20 to 30 weeks of pregnancy and avoid prescribing them after 30 weeks of pregnancy. If NSAID treatment is determined necessary, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours and discontinue the NSAID if oligohydramnios is found. FDA is warning that use of NSAIDs around 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

- These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

- Oligohydramnios is often, but not always, reversible with treatment discontinuation.

- Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

- If NSAID treatment is deemed necessary between 20 to 30 weeks of pregnancy, limit use to the lowest effective dose and shortest duration possible. As currently described in the NSAID labels, avoid prescribing NSAIDs at 30 weeks and later in pregnancy because of the additional risk of premature closure of the fetal ductus arteriosus.

- The above recommendations do not apply to low-dose 81 mg aspirin prescribed for certain conditions in pregnancy.

- Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs and follow up according to clinical practice.

For more information visit the FDA website at: [Web] and [Web].

Warning

Appropriate Use

- Indicated for short-term (≤5 days in adults) management of moderately severe acute pain that requires analgesia at opiate level. Not indicated for use in minor or chronic painful conditions.

- A potent NSAIA; administration associated with risks. Serious NSAIA-related adverse effects can occur in patients in whom the drug is indicated, especially when the drug is used inappropriately. Increasing the dose beyond the recommended dose will not result in improved efficacy and increases the risk of serious adverse effects.

GI Effects

- Can cause peptic ulcers, GI bleeding, and/or perforation. Contraindicated in patients with active peptic ulcer disease, recent GI bleeding or perforation, or a history of peptic ulcer disease or GI bleeding.

- Serious GI events can occur at any time and may not be preceded by warning signs and symptoms. Geriatric individuals are at greater risk for serious GI events. (See GI Effects under Cautions.)

Renal Effects

- Contraindicated in patients with advanced renal impairment and those at risk of renal failure because of volume depletion.

Hematologic Effects

- Inhibits platelet function. Contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis and in patients at a high risk of bleeding.

- Contraindicated as prophylactic analgesic before major surgery; contraindicated as intraoperative analgesic during procedures where hemostasis is critical. Increased risk of bleeding in these patients.

Cardiovascular Risk

- Increased risk of serious (sometimes fatal) cardiovascular thrombotic events (e.g., MI, stroke). Risk may occur early in treatment and may increase with duration of use. (See Cardiovascular Thrombotic Effects under Cautions.)

- Contraindicated in the setting of CABG surgery.

Sensitivity Reactions

- Hypersensitivity reactions (e.g., bronchospasm, anaphylactic shock) reported; appropriate counteractive measures must be available when administering the first dose. Contraindicated in patients with known hypersensitivity to ketorolac, aspirin, or other NSAIAs.

Intrathecal or Epidural Administration

- Contraindicated for intrathecal or epidural administration because of alcohol content in parenteral formulation.

Labor and Delivery

- Contraindicated during labor and delivery. (See Pregnancy under Cautions.)

Lactation

- Contraindicated in nursing women.

Concomitant Use with NSAIAs

- Contraindicated in patients receiving aspirin or other NSAIAs because of cumulative risk of serious adverse effects.

Dosage and Administration

- Oral formulation is used as continuation therapy in adults; total combined duration of parenteral and oral therapy in adults should not exceed 5 days because of increased risk of serious adverse effects.

- Maximum daily oral dosage (40 mg) is lower than the maximum daily parenteral dosage (120 mg).

Special Populations

- Adjust dosage in patients ≥65 years of age, adults weighing <50 kg, and those with moderately increased S_{cr}. Daily parenteral dosage should not exceed 60 mg in these patients. (See Dosage and Administration.)

- Administer only a single parenteral dose in children; maximum 30 mg IM or 15 mg IV.

Introduction

Prototypical NSAIA; pyrrolizine carboxylic acid derivative; structurally related to tolmetin and indomethacin.

Uses for Ketorolac (Systemic)

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Pain

Consider potential benefits and risks of ketorolac therapy as well as alternative therapies before initiating therapy with the drug. Use lowest effective dosage and shortest duration of therapy consistent with the patient's treatment goals.

Short-term (i.e., up to 5 days) management of moderately severe, acute pain that requires analgesia at opiate level in adults; mainly used in the postoperative setting.

Management of moderately severe, acute pain in children 2–16 years of age (single IV or IM dose); studies usually have evaluated pain in the postoperative setting (e.g., pain following tonsillectomy). Limited data available to support administration of >1 parenteral dose in pediatric patients.

Parenteral ketorolac has been used concomitantly with opiate agonist analgesics (e.g., meperidine, morphine) for the management of moderate to severe postoperative pain without apparent adverse drug interactions. Combined use can result in reduced opiate analgesic requirements. (See Syringe Compatibility under Stability.)

Ketorolac (Systemic) Dosage and Administration

General

- Current principles of pain management indicate that analgesics, including ketorolac, should be administered at regularly scheduled intervals, although the drug also has been administered on an as-needed basis (i.e., withholding subsequent doses until pain returns).

- Consider potential benefits and risks of ketorolac therapy as well as alternative therapies before initiating therapy with the drug.

Administration

Administer IV, IM, or orally in adults; administer IV or IM in children 2–16 years of age.

Initiate therapy in adults with parenteral (IV or IM) ketorolac; oral formulation is used as continuation therapy, as required. Administer IV or IM as a single dose or every 6 hours; administer orally every 4–6 hours.

In children 2–16 years of age, administer as a single IV or IM dose.

Switch patients to alternate analgesic therapy as soon as clinically possible.

Oral Administration

Manufacturer makes no specific recommendations regarding administration with meals; high-fat meal may decrease rate but not extent of absorption and reduce peak plasma concentrations.

IV Administration

For solution and drug compatibility information, see Compatibility under Stability.

Rate of Administration

Administer over ≥15 seconds.

IM Administration

Administer IM slowly and deeply into the muscle.

For drug compatibility information, see Compatibility under Stability.

Dosage

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Available as ketorolac tromethamine; dosage expressed in terms of the salt.

To minimize the potential risk of adverse cardiovascular and/or GI events, use lowest effective dosage and shortest duration of therapy consistent with the patient’s treatment goals. Adjust dosage based on individual requirements and response; attempt to titrate to the lowest effective dosage.

For breakthrough pain, supplement with low doses of opiate analgesics (unless contraindicated) as needed rather than higher or more frequent doses of ketorolac.

Pediatric Patients

Pain

Single Dose

IV

Children 2–16 years of age: One dose of 0.5 mg/kg (maximum 15 mg).

IM

Children 2–16 years of age: One dose of 1 mg/kg (maximum 30 mg).

Adults

Pain

Oral

When switching from parenteral to oral therapy, the first oral dose is 20 mg, followed by 10 mg every 4–6 hours (maximum 40 mg in a 24-hour period).

Weight <50 kg: When switching from parenteral to oral therapy, 10 mg every 4–6 hours (maximum 40 mg in a 24-hour period).

Single Dose

IV

30 mg.

Weight <50 kg: 15 mg.

IM

60 mg.

Weight <50 kg: 30 mg.

Multiple Dose

IV or IM

30 mg every 6 hours.

Weight <50 kg: 15 mg every 6 hours.

Prescribing Limits

Pediatric Patients

Pain

Only a single parenteral dose is recommended.

Single Dose

IV

15 mg.

IM

30 mg.

Adults

Pain

Total combined duration of parenteral and oral therapy should not exceed 5 days.

Oral

All adults: Maximum 40 mg in a 24-hour period.

Multiple Dose

IV or IM

Maximum 120 mg in a 24-hour period.

Weight <50 kg: Maximum 60 mg in a 24-hour period.

Special Populations

Hepatic Impairment

Need for dosage adjustment not fully established; evidence in patients with cirrhosis suggests that dosage adjustment may not be necessary.

Renal Impairment

Pain

Safety not established in patients with S_{cr} >5 mg/dL and/or those undergoing dialysis.

Oral

When switching from parenteral to oral therapy, 10 mg every 4–6 hours (maximum 40 mg in a 24-hour period).

Single Dose

IV

15 mg.

IM

30 mg.

Multiple Dose

IV or IM

15 mg every 6 hours. Maximum 60 mg in a 24-hour period.

Geriatric Patients

Dosage recommendations are the same as those for patients with moderately increased S_{cr} or for those weighing <50 kg.

Detailed Ketorolac dosage information

Cautions for Ketorolac (Systemic)

Contraindications

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

- Peptic ulcer disease, recent GI bleeding or perforation, or history of peptic ulcer disease or GI bleeding.
- Advanced renal impairment or risk of renal failure secondary to volume depletion.
- Labor and delivery.
- Nursing women.
- Known hypersensitivity to ketorolac or any ingredient in the formulation.
- History of asthma, urticaria, or other sensitivity reactions precipitated by aspirin or other NSAIAs.
- Use as a prophylactic analgesic before major surgery; intraoperative use when hemostasis is critical.
- In the setting of CABG surgery.
- Suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis; high risk of bleeding.
- Concomitant use with aspirin or NSAIAs.
- Neuraxial (epidural or intrathecal) administration.
- Concomitant use with probenecid.

Warnings/Precautions

Warnings

Duration of Therapy

Total combined duration of parenteral and oral therapy in adults should not exceed 5 days.

Only single doses of parenteral ketorolac are recommended in pediatric patients.

Cardiovascular Thrombotic Effects

NSAIAs (selective COX-2 inhibitors, prototypical NSAIAs) increase the risk of serious adverse cardiovascular thrombotic events (e.g., MI, stroke) in patients with or without cardiovascular disease or risk factors for cardiovascular disease.

Findings of FDA review of observational studies, meta-analysis of randomized controlled trials, and other published information indicate that NSAIAs may increase the risk of such events by 10–50% or more, depending on the drugs and dosages studied.

Relative increase in risk appears to be similar in patients with or without known underlying cardiovascular disease or risk factors for cardiovascular disease, but the absolute incidence of serious NSAIA-

associated cardiovascular thrombotic events is higher in those with cardiovascular disease or risk factors for cardiovascular disease because of their elevated baseline risk.

Increased risk may occur early (within the first weeks) following initiation of therapy and may increase with higher dosages and longer durations of use.

In controlled studies, increased risk of MI and stroke observed in patients receiving a selective COX-2 inhibitor for analgesia in first 10–14 days following CABG surgery.

In patients receiving NSAIAs following MI, increased risk of reinfarction and death observed beginning in the first week of treatment.

Increased 1-year mortality rate observed in patients receiving NSAIAs following MI; absolute mortality rate declined somewhat after the first post-MI year, but the increased relative risk of death persisted over at least the next 4 years.

Some systematic reviews of controlled observational studies and meta-analyses of randomized studies suggest naproxen may be associated with lower risk of cardiovascular thrombotic events compared with other NSAIAs. FDA states that limitations of these studies and indirect comparisons preclude definitive conclusions regarding relative risks of NSAIAs.

Use NSAIAs with caution and careful monitoring (e.g., monitor for development of cardiovascular events throughout therapy, even in those without prior cardiovascular symptoms) and at the lowest effective dosage for the shortest duration necessary.

Some clinicians suggest that it may be prudent to avoid NSAIA use, whenever possible, in patients with cardiovascular disease. Avoid use in patients with recent MI unless benefits of therapy are expected to outweigh risk of recurrent cardiovascular thrombotic events; if used, monitor for cardiac ischemia. Contraindicated in the setting of CABG surgery.

No consistent evidence that concomitant use of low-dose aspirin mitigates the increased risk of serious adverse cardiovascular events associated with NSAIAs. (See Specific Drugs under Interactions.)

GI Effects

Serious GI toxicity (e.g., bleeding, ulceration, perforation) can occur with or without warning symptoms; increased risk in those with a history of GI bleeding or ulceration, geriatric patients, smokers, those with alcohol dependence, those in poor general health, and those receiving >90 mg of parenteral ketorolac tromethamine daily. (See Contraindications under Cautions.)

Hematologic Effects

May inhibit platelet aggregation and prolong bleeding time. Use with caution and careful monitoring in patients with coagulation disorders. (See Contraindications under Cautions.)

Hematomas and other signs of wound bleeding reported in patients receiving the drug perioperatively; undertake postoperative administration with caution when hemostasis is critical. (See Contraindications under Cautions.)

Increased risk of intramuscular hematoma following IM administration in patients receiving anticoagulants.

Administer with caution in patients receiving therapeutic doses of anticoagulants (e.g., heparin, warfarin). Concurrent use with prophylactic low-dose heparin (2500–5000 units every 12 hours), warfarin, or dextrans not studied extensively, but also may be associated with increased risk of bleeding. Administer with caution when the potential benefits justify the possible risks. (See Specific Drugs under Interactions.)

Increased risk of bleeding following tonsillectomy in pediatric patients. Consider the increased risk when using ketorolac in pediatric patients undergoing tonsillectomy.

Renal Effects

Direct renal injury, including renal papillary necrosis, reported in patients receiving long-term NSAIA therapy. Interstitial nephritis and nephrotic syndrome reported in patients receiving ketorolac.

Potential for overt renal decompensation. Increased risk of renal toxicity in patients with renal or hepatic impairment or heart failure; in patients with volume depletion; in geriatric patients; and in those receiving a diuretic, ACE inhibitor, or angiotensin II receptor antagonist. (See Renal Impairment and also Contraindications under Cautions, and Renal Impairment under Dosage and Administration.)

Correct hypovolemia before initiating ketorolac therapy.

Hypertension

Hypertension and worsening of preexisting hypertension reported; either event may contribute to the increased incidence of cardiovascular events. Use with caution in patients with hypertension; monitor BP.

Impaired response to ACE inhibitors, angiotensin II receptor antagonists, β-blockers, and certain diuretics may occur. (See Specific Drugs under Interactions.)

Heart Failure and Edema

Fluid retention and edema reported.

NSAIAs (selective COX-2 inhibitors, prototypical NSAIAs) may increase morbidity and mortality in patients with heart failure.

NSAIAs may diminish cardiovascular effects of diuretics, ACE inhibitors, or angiotensin II receptor antagonists used to treat heart failure or edema. (See Specific Drugs under Interactions.)

Manufacturer recommends avoiding use in patients with severe heart failure unless benefits of therapy are expected to outweigh risk of worsening heart failure; if used, monitor for worsening heart failure.

Some experts recommend avoiding use, whenever possible, in patients with reduced left ventricular ejection fraction and current or prior symptoms of heart failure.

Sensitivity Reactions

Hypersensitivity Reactions

Anaphylactoid reactions (e.g., anaphylaxis, angioedema) reported.

Immediate medical intervention and discontinuance for anaphylaxis.

Avoid in patients with aspirin triad (aspirin sensitivity, asthma, nasal polyps); caution in patients with asthma.

Dermatologic Reactions

Serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis) reported; can occur without warning. Discontinue at first appearance of rash or any other sign of hypersensitivity (e.g., blisters, fever, pruritus).

General Precautions

Hepatic Effects

Severe reactions including jaundice, fatal fulminant hepatitis, liver necrosis, and hepatic failure (sometimes fatal) reported rarely with NSAIAs.

Elevations in ALT or AST reported.

Monitor for symptoms and/or signs suggesting liver dysfunction; monitor abnormal liver function test results. Discontinue ketorolac if associated with abnormal liver function test results.

Specific Populations

Pregnancy

Category C. Avoid use in the third trimester because of possible premature closure of the ductus arteriosus. May inhibit uterine contractions during labor and delivery. (See Contraindications under Cautions.)

Lactation

Distributed into milk; contraindicated in nursing women.

Pediatric Use

Safety and efficacy of parenteral ketorolac administered as a single dose established in children 2–16 years of age. Safety and efficacy not established in children <2 years of age.

Bleeding reported following tonsillectomy. (See Hematologic Effects under Cautions.)

Geriatric Use

Geriatric patients appear to tolerate NSAIA-induced adverse effects less well than younger adults. Fatal adverse GI effects reported more frequently in geriatric patients than younger adults.

Caution and reduced dosages advised. (See Geriatric Patients under Dosage and Administration.)

Hepatic Impairment

Severe hepatic reactions possible. Use with caution in patients with hepatic impairment or a history of liver disease. (See Hepatic Impairment under Dosage and Administration.)

Renal Impairment

Use with caution in patients with renal impairment or a history of kidney disease; monitor closely. (See Contraindications under Cautions.)

Clearance may be decreased. Dosage adjustment necessary in patients with moderately elevated S_{cr}. (See Renal Impairment under Dosage and Administration.)

Patients with underlying renal insufficiency are at risk of developing acute renal failure; consider risks and benefits before instituting therapy in these patients.

Common Adverse Effects

Headache, somnolence or drowsiness, dizziness, dyspepsia, nausea, GI pain, diarrhea, edema.

Interactions for Ketorolac (Systemic)

Does not induce or inhibit hepatic enzymes involved in drug metabolism; unlikely to alter its own metabolism of that or other drugs metabolized by CYP isoenzymes.

Protein-bound Drugs

Could be displaced from binding sites by, or could displace from binding sites, some other protein-bound drugs.

Drugs Affecting Hemostasis

Possible increased risk of bleeding complications; carefully monitor patients receiving therapy that affects hemostasis.

Specific Drugs

Drug	Interaction	Comments
ACE inhibitors	Increased risk of renal impairment Reduced BP response to ACE inhibitor	Monitor BP
Acetaminophen	No alteration in the protein binding of ketorolac	
Angiotensin II receptor antagonists	Reduced BP response to angiotensin II receptor antagonist Possible deterioration of renal function in individuals with renal impairment	Monitor BP
Antacids	No effect on the extent of oral ketorolac absorption	
Anticonvulsants	Seizures reported in patients receiving	

	carbamazepine or phenytoin Phenytoin does not alter the protein binding of ketorolac	
CNS agents (alprazolam, fluoxetine, thiothixene)	Hallucinations reported in patients receiving fluoxetine, thiothixene, or alprazolam	
Dextrans	Possible increased risk of bleeding	Carefully monitor patients
Digoxin	No alteration in the protein binding of either drug	
Diuretics (furosemide, thiazides)	Reduced natriuretic effect	
Heparin	Increased risk of bleeding complications Increased bleeding time when administered with heparin 5000 units; concurrent use with heparin 2500–5000 units sub-Q every 12 hours not studied extensively	Extreme caution advised in patients receiving therapeutic doses of heparin; carefully monitor patients
Lithium	Increased plasma lithium concentrations	Monitor for lithium toxicity
Methotrexate	Increased plasma methotrexate concentrations in patients receiving other NSAIAs; studies with ketorolac have not been undertaken	Caution advised
Nondepolarizing skeletal muscle relaxants	May potentiate the effects of the muscle relaxant resulting in apnea	
NSAIAs	NSAIAs including aspirin: Potential for increased risk of GI toxicity Aspirin: No consistent evidence that low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIAs Therapeutic anti-inflammatory concentrations of salicylates (300 mcg/mL) may displace ketorolac from binding sites; ibuprofen, naproxen, or piroxicam does not alter the protein binding of ketorolac	Concomitant use contraindicated
Probenecid	Increased plasma concentrations and AUC of ketorolac	Concomitant use contraindicated

Thrombolytic agents	Possible increased risk of bleeding	Carefully monitor patients
Tolbutamide	No alteration in the protein binding of ketorolac	
Warfarin	Increased risk of bleeding complications; concurrent use not studied extensively Possible slight displacement of warfarin (but not ketorolac) from binding sites; other pharmacokinetic interactions unlikely	Extreme caution advised in patients receiving therapeutic doses of warfarin; carefully monitor patients

Ketorolac drug interactions (more detail)

Ketorolac (Systemic) Pharmacokinetics

Absorption

Bioavailability

Rapidly and completely absorbed following IM administration.

Rapid and almost completed absorbed following oral administration; bioavailability reported to be 80–100%.

Onset

IM administration: Onset in 10 minutes, with peak analgesia at 75–150 minutes.

Oral administration: Onset in 30–60 minutes, with peak analgesia at 1.5–4 hours.

Duration

Oral or IM administration: 6–8 hours.

Food

Food decreases rate but not extent of absorption.

Special Populations

Rate of absorption from GI tract may be decreased in patients with hepatic or renal impairment and in geriatric individuals.

Distribution

Extent

Not distributed widely. Crosses the blood-brain barrier poorly.

Crosses the placenta; distributed into milk.

Plasma Protein Binding

>99%.

Elimination

Metabolism

Metabolized in the liver by hydroxylation; also undergoes conjugation with glucuronic acid.

Elimination Route

Excreted in urine (92%) as parent drug (60%) or metabolites (40%) and in feces (6%).

Half-life

4–6 hours in adults; 3.8–6.1 hours in pediatric patients.

Special Populations

Hepatic impairment (e.g., cirrhosis) does not appear to substantially affect half-life. In patients with cirrhosis, half-life of about 4.5–5.4 hours reported.

Renal impairment: Half-life is about 9–10 hours (range: 3.2–19 hours); in patients undergoing dialysis, half-life of about 13.6 hours (range: 8–39.1 hours) reported.

Geriatric individuals: Half-life is about 5–7 hours (range: 4.3–8.6 hours).

Stability

Storage

Oral

Tablets

15–30°C.

Parenteral

Injection

15–30°C; protect from light.

Compatibility

For information on systemic interactions resulting from concomitant use, see Interactions.

Parenteral

Solution CompatibilityHID

Compatible
Dextrose 5% in sodium chloride 0.9%

Dextrose 5% in water
Plasma-Lyte A, pH 7.4
Ringer’s injection
Ringer’s injection, lactated
Sodium chloride 0.9%

Drug Compatibility

Syringe Compatibility1HID
Compatible
Sufentanil citrate
Incompatible
Haloperidol lactate
Hydroxyzine HCl
Meperidine HCl
Morphine Sulfate
Nalbuphine
Prochlorperazine edisylate
Promethazine HCl
Thiethylperazine maleate
Variable
Diazepam
Hydromorphone HCl

Ketorolac tromethamine 1 mg/mL tested.

Y-Site CompatibilityHID

Compatible
Dexmedetomidine HCl
Fentanyl citrate
Hetastarch in lactated electrolyte injection (Hextend)
Hydromorphone HCl
Methadone HCl
Morphine sulfate
Remifentanil HCl
Sufentanil citrate
Incompatible
Azithromycin
Fenoldopam mesylate

Actions

- Inhibits cyclooxygenase-1 (COX-1) and COX-2.
- Pharmacologic actions similar to those of other prototypical NSAIAs; exhibits anti-inflammatory, analgesic, and antipyretic activity.

Advice to Patients

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

- Importance of reading the medication guide for NSAIAs that is provided each time the drug is dispensed.
- Risk of serious cardiovascular events (e.g., MI, stroke).
- Risk of GI bleeding and ulceration.
- Risk of bleeding following tonsillectomy.
- Risk of serious skin reactions. Risk of anaphylactoid and other sensitivity reactions.
- Risk of hepatotoxicity.
- Risk of kidney failure.

- Importance of seeking immediate medical attention if signs and symptoms of a cardiovascular event (chest pain, dyspnea, weakness, slurred speech) occur.
- Importance of notifying clinician if signs and symptoms of GI ulceration or bleeding, unexplained weight gain, or edema develops.
- Importance of discontinuing ketorolac and contacting clinician if rash or other signs of hypersensitivity (blisters, fever, pruritus) develop. Importance of seeking immediate medical attention if an anaphylactic reaction occurs.
- Importance of discontinuing therapy and contacting clinician immediately if signs and symptoms of hepatotoxicity (nausea, fatigue, lethargy, pruritus, jaundice, upper right quadrant tenderness, flu-like symptoms) occur.
- Risk of heart failure or edema; importance of reporting dyspnea, unexplained weight gain, or edema.
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. Importance of avoiding ketorolac in late pregnancy (third trimester).
- Importance of not exceeding recommended duration of therapy.
- Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs.
- Importance of informing patients of other important precautionary information. (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Please refer to the ASHP Drug Shortages Resource Center for information on shortages of one or more of these preparations.

* available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Ketorolac Tromethamine				
Routes	**Dosage Forms**	**Strengths**	**Brand Names**	**Manufacturer**
Oral	Tablets, film-coated	10 mg*	Ketorolac Tromethamine Tablets	
Parenteral	Injection, for IM or IV use	15 mg/mL*	Ketorolac Tromethamine Injection	
		30 mg/mL*	Ketorolac Tromethamine Injection	

	Injection, for IM use	30 mg/mL*	Ketorolac Tromethamine Injection	

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Show article references

Frequently asked questions

- How long does ketorolac (Toradol) stay in your system?

BAQSIMI- glucagon powder
Eli Lilly and Company

Close All Sections

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BAQSIMI safely and effectively. See full prescribing information for BAQSIMI.
BAQSIMI (glucagon) nasal powder
Initial U.S. Approval: 1960

INDICATIONS AND USAGE

BAQSIMI™ is an antihypoglycemic agent indicated for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes ages 4 years and above. (1)

DOSAGE AND ADMINISTRATION

- BAQSIMI is for intranasal use only. (2.1)
- The recommended dose of BAQSIMI is 3 mg administered as one actuation of the intranasal device into one nostril. (2.2)
- Administer BAQSIMI according to the printed instructions on the shrink-wrapped tube label and the Instructions for Use. (2.1)
- Administer the dose by inserting the tip into one nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled. (2.1)
- Call for emergency assistance immediately after administering the dose. (2.1)
- When the patient responds to treatment, give oral carbohydrates. (2.1)
- Do not attempt to reuse BAQSIMI. Each BAQSIMI device contains one dose of glucagon and cannot be reused. (2.1)
- If there has been no response after 15 minutes, an additional 3 mg dose may be administered while waiting for emergency assistance. (2.2)

DOSAGE FORMS AND STRENGTHS

Nasal powder: intranasal device containing one dose of glucagon 3 mg (3)

CONTRAINDICATIONS

- Pheochromocytoma (4)
- Insulinoma (4)
- Known hypersensitivity to glucagon or to any of the excipients (4)

WARNINGS AND PRECAUTIONS

- *Substantial Increase in Blood Pressure in Patients with Pheochromocytoma*: Contraindicated in patients with pheochromocytoma because BAQSIMI may stimulate the release of catecholamines from the tumor. (4, 5.1)
- *Hypoglycemia in Patients with Insulinoma*: In patients with insulinoma, administration may produce an initial increase in blood glucose; however, BAQSIMI may stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of BAQSIMI, give glucose orally or intravenously. (4, 5.2)
- *Hypersensitivity and Allergic Reactions*: Allergic reactions have been reported and include generalized rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension. (4, 5.3)
- *Lack of Efficacy in Patients with Decreased Hepatic Glycogen*: BAQSIMI is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for BAQSIMI to be effective. Patients with these conditions should be treated with glucose. (5.4)

ADVERSE REACTIONS

Most common (≥10%) adverse reactions associated with BAQSIMI are nausea, vomiting, headache, upper respiratory tract irritation (i.e., rhinorrhea, nasal discomfort, nasal congestion, cough, and epistaxis), watery eyes, redness of eyes, itchy nose, throat and eyes. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Beta-blockers*: Patients taking beta-blockers may have a transient increase in pulse and blood pressure. (7.1)
- *Indomethacin*: In patients taking indomethacin BAQSIMI may lose its ability to raise glucose or may produce hypoglycemia. (7.2)
- *Warfarin*: BAQSIMI may increase the anticoagulant effect of warfarin. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2020

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FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Hide

1 INDICATIONS AND USAGE

BAQSIMI™ is indicated for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes ages 4 years and above.

Hide

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

BAQSIMI is for intranasal use only.

Instruct patients and their caregivers on the signs and symptoms of severe hypoglycemia. Because severe hypoglycemia requires help of others to recover, instruct the patient to inform those around them about BAQSIMI and its Instructions for Use. Administer BAQSIMI as soon as possible when severe hypoglycemia is recognized.

Instruct the patient or caregiver to read the Instructions for Use at the time they receive a prescription for BAQSIMI. Emphasize the following instructions to the patient or caregiver:

- Do not push the plunger or test the device prior to administration.
- Administer BAQSIMI according to the printed instructions on the shrink-wrapped tube label and the Instructions for Use.
- Administer the dose by inserting the tip into one nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled.
- Call for emergency assistance immediately after administering the dose.
- When the patient responds to treatment, give oral carbohydrates to restore the liver glycogen and preve recurrence of hypoglycemia.

- Do not attempt to reuse BAQSIMI. Each BAQSIMI device contains one dose of glucagon and cannot be reused.

2.2 Dosage in Adults and Pediatric Patients Aged 4 Years and Above

The recommended dose of BAQSIMI is 3 mg administered as one actuation of the intranasal device into one nostril.

If there has been no response after 15 minutes, an additional 3 mg dose of BAQSIMI from a new device may be administered while waiting for emergency assistance.

Hide

3 DOSAGE FORMS AND STRENGTHS

Nasal Powder:
- 3 mg glucagon: as a white powder in an intranasal device containing one dose of glucagon

Hide

4 CONTRAINDICATIONS

BAQSIMI is contraindicated in patients with:
- Pheochromocytoma because of the risk of substantial increase in blood pressure *[see Warnings and Precautions (5.1)]*
- Insulinoma because of the risk of hypoglycemia *[see Warnings and Precautions (5.2)]*
- Known hypersensitivity to glucagon or to any of the excipients in BAQSIMI. Allergic reactions have been reported with glucagon and include anaphylactic shock with breathing difficulties and hypotension *[see Warnings and Precautions (5.3)]*

Hide

5 WARNINGS AND PRECAUTIONS

5.1 Substantial Increase in Blood Pressure in Patients with Pheochromocytoma

BAQSIMI is contraindicated in patients with pheochromocytoma because glucagon may stimulate release of catecholamines from the tumor *[see Contraindications (4)].* If the patient develops a substantial increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure.

5.2 Hypoglycemia in Patients with Insulinoma

In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose; however, BAQSIMI administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. BAQSIMI is contraindicated in patients with insulinoma *[see Contraindications (4)].* If a patient develops symptoms of hypoglycemia after a dose of BAQSIMI, give glucose orally or intravenously.

5.3 Hypersensitivity and Allergic Reactions

Allergic reactions have been reported with glucagon, these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. BAQSIMI is contraindicated in patients with a prior hypersensitivity reaction *[see Contraindications (4)].*

5.4 Lack of Efficacy in Patients with Decreased Hepatic Glycogen

BAQSIMI is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for BAQSIMI administration to be effective. Patients with these conditions should be treated with glucose.

Hide

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Hypersensitivity and Allergic Reactions *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trial Data

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of BAQSIMI cannot be directly compared with rates in clinical trials of other drugs and may not reflect the rates observed in practice.

Adverse Reactions in Adult Patients

Two similarly designed comparator-controlled trials, Study 1 and Study 2, evaluated the safety of a single dose of BAQSIMI compared to a 1 mg dose of intra-muscular glucagon (IMG) in adult patients with diabetes *[see Clinical Studies (14)]*.

Table 1 presents adverse reactions that occurred with BAQSIMI at an incidence of ≥2% in a pool of Study 1 and Study 2.

Table 1: Pooled Adverse Reactions (≥2%) in Adult Patients with Type 1 and Type 2 Diabetes in Study 1 and Study 2

Adverse Reaction	BAQSIMI 3 mg (N=153) %
Nausea	26.1
Headache	18.3
Vomiting	15.0
Upper Respiratory Tract Irritation[a]	12.4

[a] Upper Respiratory Tract Irritation: rhinorrhea, nasal discomfort, nasal congestion, cough, and epistaxis.

Nasal and ocular symptoms with BAQSIMI were solicited through a patient questionnaire in Study 1 and 2 and these adverse reactions are presented in Table 2.

Table 2: Solicited Nasal and Non-Nasal Adverse Reactions in Adult Patients with Type 1 and Type 2 Diabetes Pooled from Study 1 and 2

Adverse Reaction[a]	BAQSIMI 3 mg (n=153) %
	Any increase in symptom severity[a]
Watery eyes	58.8
Nasal congestion	42.5
Nasal itching	39.2
Runny nose	34.6
Redness of eyes	24.8
Itchy eyes	21.6
Sneezing	19.6
Itching of throat	12.4
Itching of ears	3.3

[a] Subjects were asked to report whether they have the symptom, as well as severity (mild, moderate, severe) at baseline, and after glucagon administration.

Adverse Reactions in Pediatric Patients Aged 4 Years and Above

A single dose of BAQSIMI was compared to weight-based doses of 0.5 mg or 1 mg of IMG in pediatric patients with type 1 diabetes in Study 3 *[see Clinical Studies (14)]*.

Table 3 presents adverse reactions that occurred with BAQSIMI in pediatric patients at an incidence of ≥2% in Study 3.

Table 3: Adverse Reactions (≥2%) Occurring in Pediatric Patients with Type 1 Diabetes in Study 3

Adverse Reaction	BAQSIMI 3 mg (n=36) %
Vomiting	30.6
Headache	25.0
Nausea	16.7
Upper Respiratory Tract Irritation[a]	16.7

[a] Upper Respiratory Tract Irritation: nasal discomfort, nasal congestion, sneezing.

Nasal and ocular symptoms with BAQSIMI were solicited through a patient questionnaire in pediatric patients in Study 3 and these adverse reactions are presented in Table 4.

Table 4: Solicited Nasal and Non-Nasal Adverse Reactions in Pediatric Patients with Type 1 Diabetes in Study 3

Adverse Reaction[a]	**BAQSIMI 3 mg (n=36) %**
	Any increase in symptom severity[a]
Watery eyes	47.2
Nasal congestion	41.7
Nasal itching	27.8
Runny nose	25.0
Sneezing	19.4
Itchy eyes	16.7
Redness of eyes	13.9
Itching of throat	2.8
Itching of ears	2.8

[a] Subjects were asked to report whether they have the symptom, as well as severity (mild, moderate, severe) at baseline, and after glucagon administration.

Other Adverse Reactions in Adult and Pediatric Patients

Other observed adverse reactions with BAQSIMI-treated patients across clinical trials were, dysgeusia, pruritus, tachycardia, hypertension, and additional upper respiratory tract irritation events (nasal pruritus, throat irritation, and parosmia).

6.2 Immunogenicity

As with all therapeutic peptides, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to BAQSIMI with the incidences of antibodies to other products may be misleading.

In 3 clinical trials, 3/124 (2%) of BAQSIMI-treated patients had treatment-emergent anti-drug antibodies as detected by an affinity capture elution (ACE) ligand-binding immunogenicity assay. No neutralizing antibodies were detected.

Hide

7 DRUG INTERACTIONS

7.1 Beta-blockers

Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given BAQSIMI.

7.2 Indomethacin

In patients taking indomethacin, BAQSIMI may lose its ability to raise blood glucose or may even produce hypoglycemia.

7.3 Warfarin

BAQSIMI may increase the anticoagulant effect of warfarin.

Hide

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and a small number of observational studies with glucagon use in pregnant women over decades of use have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Multiple small studies have demonstrated a lack of transfer of pancreatic glucagon across the human placental barrier during early gestation. In a rat reproduction study, no embryofetal toxicity was observed with glucagon administered by injection during the period of organogenesis at doses representing up to 40 times the human dose, based on body surface area (mg/m^2) *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant rats given animal sourced glucagon twice-daily by injection at doses up to 2 mg/kg (up to 40 times the human dose based on body surface area extrapolation, mg/m^2) during the period of organogenesis, there was no evidence of increased malformations or embryofetal lethality.

8.2 Lactation

Risk Summary

There is no information available on the presence of glucagon in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. However, glucagon is a peptide and would be expected to be broken down to its constituent amino acids in the infant's digestive tract and is therefore, unlikely to cause harm to an exposed infant.

8.4 Pediatric Use

The safety and effectiveness of BAQSIMI for the treatment of severe hypoglycemia in patients with diabetes have been established in pediatric patients ages 4 years and above. Use of BAQSIMI for this indication is supported by evidence from a study in 48 pediatric patients from 4 to <17 years of age with type 1 diabetes mellitus. *[see Clinical Studies (14.2)]*.

The safety and effectiveness of BAQSIMI have not been established in pediatric patients younger than 4 years of age.

8.5 Geriatric Use

Clinical studies of BAQSIMI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Limited clinical trial experience has not identified differences in responses between the elderly and younger patients.

Hide

10 OVERDOSAGE

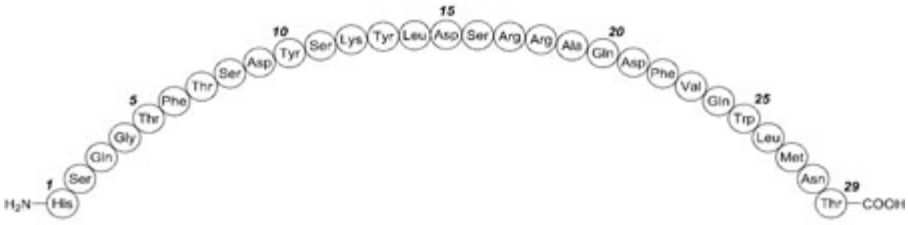
If overdosage occurs, the patient may experience nausea, vomiting, inhibition of GI tract motility, increase in blood pressure and pulse rate. In case of suspected overdosing, serum potassium levels may decrease and should be monitored and corrected if needed. If the patient develops a dramatic increase in blood pressure, phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed.

Hide

11 DESCRIPTION

BAQSIMI contains glucagon, an antihypoglycemic agent used to treat severe hypoglycemia. Glucagon is a single-chain polypeptide containing 29 amino acid residues and has a molecular weight of 3483, and is identical to human glucagon.

Its molecular formula is $C_{153}H_{225}N_{43}O_{49}S$, with the following molecular structure:



BAQSIMI is a preservative-free, white powder for intranasal administration in an intranasal device containing one dose of 3 mg glucagon. BAQSIMI contains glucagon as the active ingredient and betadex, and dodecylphosphocholine as the excipients.

Hide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect.

12.2 Pharmacodynamics

After administration of BAQSIMI in adult patients with diabetes, the mean maximum glucose increase from baseline was 140 mg/dL (Figure 1).

In pediatric patients with type 1 diabetes (4 to <17 years), the mean maximum glucose increase from baseline was 138 mg/dL (4 to <8 years), 133 mg/dL (8 to <12 years), and 102 mg/dL (12 to <17 years) (Figure 2).

Sex and body weight had no clinically meaningful effects on the pharmacodynamics of BAQSIMI.

Common cold with nasal congestion tested with or without use of decongestant did not impact pharmacodynamics of BAQSIMI.

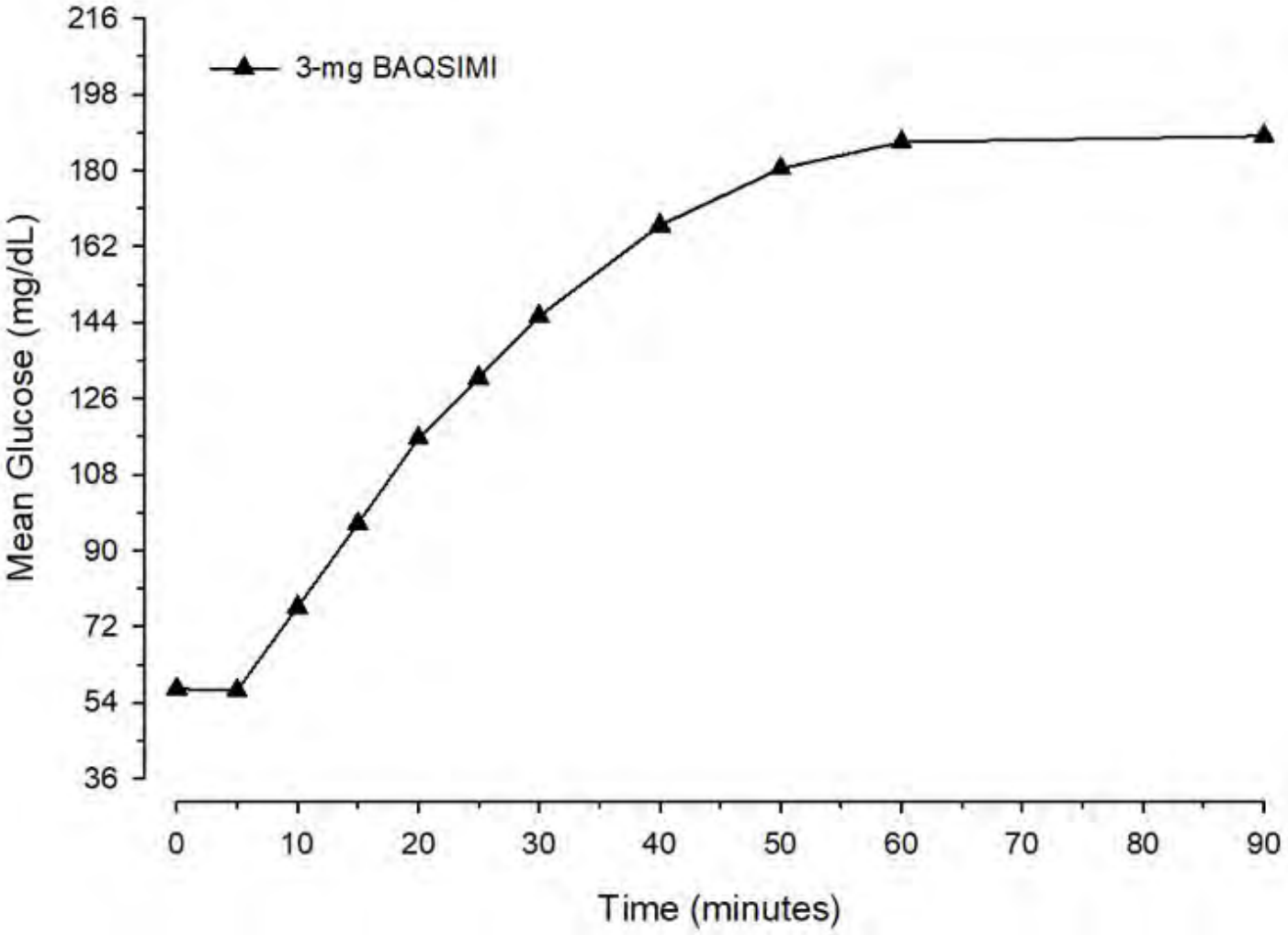


Figure 1 Mean glucose concentration over time after glucagon dose in adult Type 1 Diabetes patients with insulin-induced hypoglycemia.

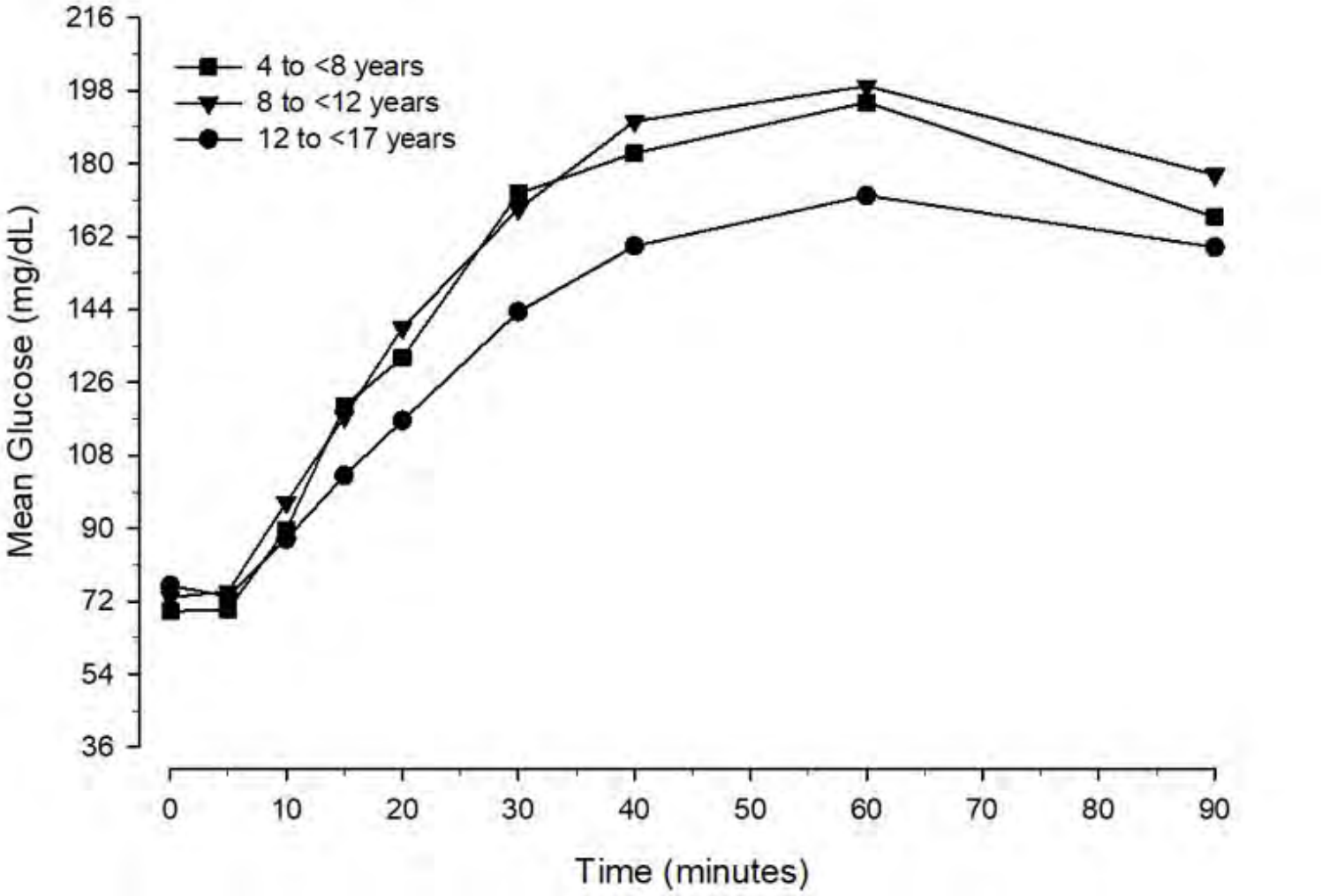


Figure 2 Mean glucose concentration over time in pediatric Type 1 Diabetes patients administered BAQSIMI

12.3 Pharmacokinetics

Absorption

Glucagon absorption via the intranasal route, achieved mean peak plasma levels of 6130 pg/mL at around 15 minutes.

Distribution

The apparent volume of distribution was approximately 885 L.

Elimination

The median half-life was approximately 35 minutes.

Metabolism

Glucagon is known to be degraded in the liver, kidneys, and plasma.

Specific Populations

Pediatrics

In pediatric patients (4 to <17 years), glucagon via the intranasal route, achieved mean peak plasma levels between 15 and 20 minutes. The median half-life was 21 to 31 minutes.

Patients with Colds

Common cold with nasal congestion did not impact the pharmacokinetics of BAQSIMI.

Drug Interaction Studies

Common cold with use of decongestant did not impact the pharmacokinetics of BAQSIMI.

Hide

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to evaluate carcinogenic potential have not been performed. Recombinant glucagon was positive in the bacterial Ames assay. It was determined that an increase in colony counts was related to technical difficulties in running this assay with peptides. Studies in rats have shown that glucagon does not cause impaired fertility.

Hide

14 CLINICAL STUDIES

14.1 Adult Patients

Study 1 (NCT03339453) was a randomized, multicenter, open-label, 2-period, crossover study in adult patients with type 1 diabetes. The efficacy of a single 3 mg dose of BAQSIMI was compared to a 1 mg dose of intramuscular glucagon (IMG). Insulin was used to reduce blood glucose levels to <60 mg/dL. Seventy patients were enrolled, with a mean age of 41.7 years and a mean diabetes duration of 20.1 years. Twenty-seven (39%) were female.

The primary efficacy outcome measure was the proportion of patients achieving treatment success, which was defined as either an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level. Glucose nadir was defined as the minimum glucose measurement at the time of, or within 10 minutes, following glucagon administration.

The mean nadir blood glucose was 54.5 mg/dL for BAQSIMI and 55.8 mg/dL for IMG. BAQSIMI demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycemia with 100% of BAQSIMI-treated patients and 100% of IMG-treated patients achieving treatment success. The mean time to treatment success was 11.6 and 9.9 minutes in the BAQSIMI and IMG 1 mg treatment groups, respectively.

Table 5: Adult Patients with Type 1 Diabetes Meeting Treatment Success and Other Glucose Criteria in Study 1

	Type 1 Diabetes (N=66)[a]	
	BAQSIMI 3 mg	**IMG 1 mg**
Treatment Success – n (%)	66 (100%)	66 (100%)
Treatment Difference (2-sided 95% confidence limit)[b, c]	0% (-2.9%, 2.9%)	
Glucose criterion met – n (%)		
(i) ≥70 mg/dL	66 (100%)	66 (100%)
(ii) Increase by ≥20 mg/dL from nadir	66 (100%)	66 (100%)
Both (i) and (ii)	66 (100%)	66 (100%)

[a] The Efficacy Analysis Population consisted of all patients who received both doses of the Study Drug with evaluable primary outcome.

[b] Difference calculated as (percentage with success in BAQSIMI) – (percentage with success in IMG).

[c] 2-sided 95% confidence interval (CI) of paired differences using a Wald-Min correction; non-inferiority margin = -10%.

Study 2 (NCT01994746) was a randomized, multicenter, open-label, 2-period, crossover study in adult patients with type 1 diabetes or type 2 diabetes. The efficacy of a single 3 mg dose of BAQSIMI was compared to a

1 mg dose of intra-muscular glucagon (IMG). Insulin was used to reduce blood glucose levels to the hypoglycemic range with a target blood glucose nadir of <50 mg/dL.

Study 2 enrolled 83 patients 18 to <65 years of age. The mean age of patients with type 1 diabetes (N=77) was 32.9 years and a mean diabetes duration of 18.1 years, and 45 (58%) patients were female. The mean age of patients with type 2 diabetes (N=6) was 47.8 years, with a mean diabetes duration of 18.8 years, and 4 (67%) patients were female.

The mean nadir blood glucose was 44.2 mg/dL for BAQSIMI and 47.2 mg/dL for IMG. BAQSIMI demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycemia with 98.8% of BAQSIMI-treated patients and 100% of IMG-treated patients achieving treatment success within 30 minutes.

The mean time to treatment success was 15.9 and 12.1 minutes in the BAQSIMI and IMG 1 mg treatment groups, respectively.

Table 6: Adult Patients with Type 1 and Type 2 Diabetes Meeting Treatment Success and Other Glucose Criteria in Study 2

	Type 1 and Type 2 Diabetes (N=80)[a]	
	BAQSIMI 3 mg	**IMG 1 mg**
Treatment Success – n (%)	79 (98.8%)	80 (100%)
Treatment Difference (2-sided 95% confidence limit) [b,c]	-1.3% (-4.6%, 2.2%)	
Glucose criterion met – n (%)[d]		
(i) ≥70 mg/dL	77 (96%)	79 (99%)
(ii) Increase by ≥20 mg/dL from nadir	79 (99%)	80 (100%)
Both (i) and (ii)	77 (96%)	79 (99%)

[a] The Efficacy Analysis Population consisted of all patients who received both doses of the Study Drug with evaluable primary outcome.

[b] Difference calculated as (percentage with success in BAQSIMI) – (percentage with success in IMG).

[c] 2-sided 95% confidence interval (CI) of paired differences using a Wald-Min correction; non-inferiority margin = -10%.

[d] Percentage based on number of patients.

14.2 Pediatric Patients

Study 3 (NCT01997411) was a randomized, multicenter, clinical study that assessed BAQSIMI compared to intra-muscular glucagon (IMG) in pediatric patients aged 4 years and older with type 1 diabetes. Insulin was used to reduce blood glucose levels, and glucagon was administered after glucose reached <80 mg/dL. Efficacy was assessed based on percentage of patients with a glucose increase of ≥20 mg/dL from glucose nadir within 30 minutes following BAQSIMI administration.

Forty-eight patients were enrolled and received at least one dose of study drug. The mean age in the Young Children cohort (4 to <8 years) was 6.5 years. In the Children cohort (8 to <12 years), mean age was 11.1 years and in the Adolescents cohort (12 to <17 years) mean age was 14.6 years. In all age cohorts, the population was predominantly male and white.

Across all age groups, all (100%) patients in both treatment arms achieved an increase in glucose ≥20 mg/dL from glucose nadir within 20 minutes of glucagon administration. The mean time to reach a glucose increase of ≥20 mg/dL for BAQSIMI and IMG for all age groups is shown in Table 7.

Table 7: Mean Time to Reach Glucose Increase of ≥20 mg/dL from Nadir in Pediatric Patients with Type 1 Diabetes in Study 3

Increase from Nadir	**Mean Time Post-Glucagon Administration (minutes)**					
	Young Children (4 to <8 years old)		**Children (8 to <12 years old)**		**Adolescents (12 to <17 years old)**	
	IMG[a] N=6	**BAQSIMI 3 mg N=12**	**IMG[a] N=6**	**BAQSIMI 3 mg N=12**	**IMG[a] N=12**	**BAQSIMI 3 mg N=12**

[a] 0.5 mg or 1 mg of IMG (based upon body weight)

Increase from Nadir	Mean Time Post-Glucagon Administration (minutes)					
	Young Children (4 to <8 years old)		Children (8 to <12 years old)		Adolescents (12 to <17 years old)	
	IMG[a] N=6	BAQSIMI 3 mg N=12	IMG[a] N=6	BAQSIMI 3 mg N=12	IMG[a] N=12	BAQSIMI 3 mg N=12
≥20 mg/dL	10.8	10.8	12.5	11.3	12.5	14.2

[a] 0.5 mg or 1 mg of IMG (based upon body weight)

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16 HOW SUPPLIED/STORAGE AND HANDLING

BAQSIMI is supplied as an intranasal device containing one 3 mg dose of glucagon as a preservative free, white powder.

- BAQSIMI One Pack™ carton contains 1 intranasal device (NDC 0002-6145-11)
- BAQSIMI Two Pack™ carton contains 2 intranasal devices (NDC 0002-6145-27)
- Store at temperatures up to 86°F (30°C) in the shrink wrapped tube provided.
- Keep BAQSIMI in the shrink wrapped tube until ready to use. If the tube has been opened, BAQSIMI may have been exposed to moisture and may not work as expected.
- Discard BAQSIMI and tube after use.

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17 PATIENT COUNSELING INFORMATION

Advise the patient and family members or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Recognition of Severe Hypoglycemia:

Inform patient and family members or caregivers on how to recognize the signs and symptoms of severe hypoglycemia and the risks of prolonged hypoglycemia.

Administration:

Review the Patient Information and Instructions for Use with the patient and family members or caregivers.

Serious Hypersensitivity:

Inform patients that allergic reactions can occur with BAQSIMI. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.3)]*.

Literature revised: October 2020

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BAQ-0002-USPI-20201027

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PATIENT PACKAGE INSERT

PATIENT INFORMATION
BAQSIMI™ (BAK-see-mee)
(glucagon) nasal powder

This Patient Information has been approved by the U.S. Food and Drug Administration
Issued: July 2019

What is BAQSIMI?
BAQSIMI is a prescription medicine used to treat very low blood sugar (severe hypoglycemia) in people with diabetes ages 4 years and above.
It is not known if BAQSIMI is safe and effective in children under 4 years of age.

Do not use BAQSIMI if you:

- have a tumor in the gland on top of your kidneys (adrenal gland) called pheochromocytoma.
- have a tumor in your pancreas called insulinoma.
- are allergic to glucagon, or any other ingredients in BAQSIMI. See the end of this Patient Information for a complete list of ingredients in BAQSIMI.

Before using BAQSIMI, tell your healthcare provider about all of your medical conditions, including if you:

- have a tumor in your pancreas.
- have not had food or water for a long time (prolonged fasting or starvation).
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if BAQSIMI passes into your breast milk. You and your healthcare provider should decide if you can use BAQSIMI while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use BAQSIMI?

- Read the detailed **Instructions for Use** that comes with BAQSIMI.
- Use BAQSIMI exactly how your healthcare provider tells you to use it.
- Make sure your caregiver knows where you keep your BAQSIMI and how to use BAQSIMI the right way before you need their help.
- Your healthcare provider will tell you how and when to use BAQSIMI.
- BAQSIMI contains only 1 dose of medicine and **cannot** be reused.
- BAQSIMI should be given in one side of your nose (nostril) but does not need to be inhaled.
- BAQSIMI will work even if you have a cold or are taking cold medicine.
- After giving BAQSIMI, the caregiver should call for emergency medical help right away.
- If the person does not respond after 15 minutes, another dose may be given, if available.
- Tell your healthcare provider each time you use BAQSIMI.

What are the possible side effects of BAQSIMI?
BAQSIMI may cause serious side effects, including:

- **High blood pressure.** BAQSIMI can cause high blood pressure in certain people with tumors in their adrenal glands.
- **Low blood sugar.** BAQSIMI can cause certain people with tumors in their pancreas to have low blood sugar.
- **Serious allergic reaction.** Call your healthcare provider or **get medical help right away** if you have a serious allergic reaction including:

- rash
- difficulty breathing
- low blood pressure

The most common side effects of BAQSIMI include:

- nausea
- vomiting
- headache
- runny nose
- discomfort in your nose
- stuffy nose
- redness in your eyes
- itchy nose, throat and eyes
- watery eyes

These are not all the possible side effects of BAQSIMI. For more information, ask your healthcare provider. Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

This Patient Information has been approved by the U.S. Food and Drug Administration
Issued: July 2019

How should I store BAQSIMI?

- Store BAQSIMI at temperatures up to 86ºF (30ºC).
- Keep BAQSIMI in the shrink wrapped tube until you are ready to use it.

Keep BAQSIMI and all medicines out of the reach of children.

General Information about the safe and effective use of BAQSIMI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BAQSIMI for a condition for which it was not prescribed. Do not give BAQSIMI to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about BAQSIMI that is written for healthcare professionals.

What are the ingredients in BAQSIMI?

Active Ingredient: glucagon

Inactive Ingredients: betadex and dodecylphosphocholine

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

www.baqsimi.com

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For more information, call 1-800-LillyRx (1-800-545-5979) or go to the following website: www.baqsimi.com.

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– **INSTRUCTIONS FOR USE**

INSTRUCTIONS FOR USE

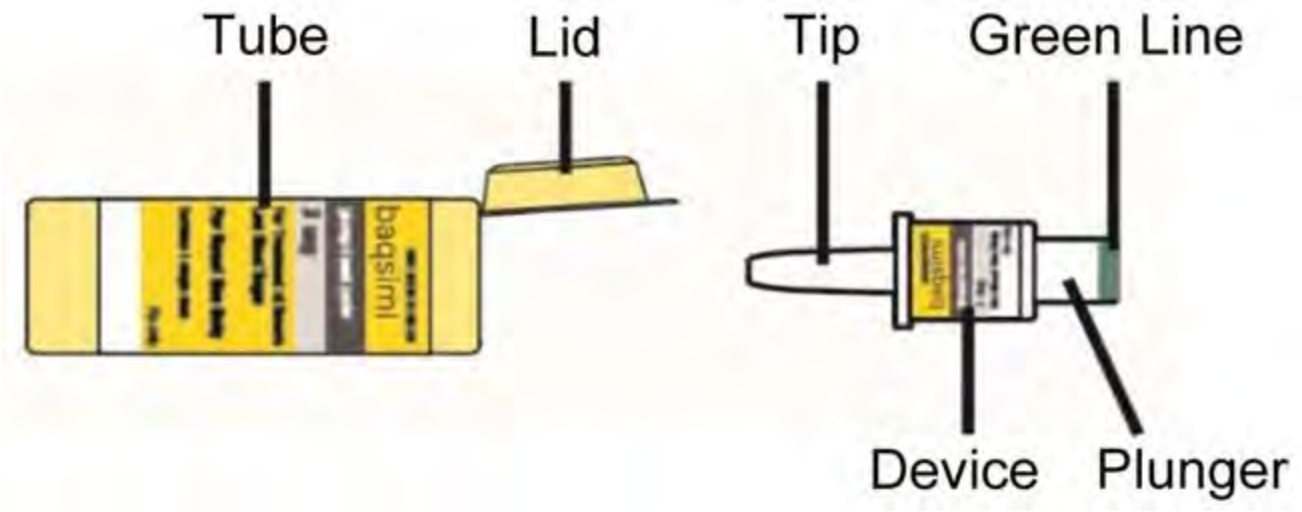
BAQSIMI™

(glucagon) nasal powder

3 mg

Read the Instructions for Use for BAQSIMI before using it. BAQSIMI is used to treat very low blood sugar (severe hypoglycemia) that may cause you to need help from others. You should make sure you show your caregivers, family and friends where you keep BAQSIMI and explain how to use it by sharing these instructions. **They need to know how to use BAQSIMI before an emergency happens.**

Tube and Device Parts

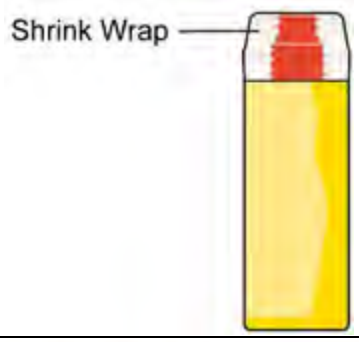


Important Information to Know

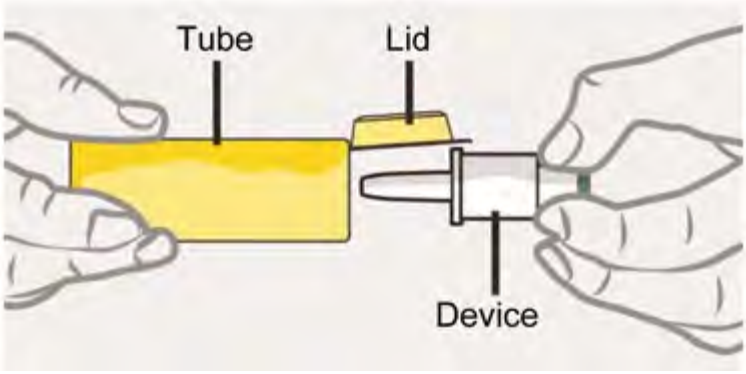
- **Do not** remove the Shrink Wrap or open the Tube until you are ready to use it.

- If the Tube has been opened, BAQSIMI could be exposed to moisture. **This could cause BAQSIMI not to work as expected.**
- Do not push the plunger or test BAQSIMI before you are ready to use it.
- BAQSIMI contains 1 dose of glucagon nasal powder and **cannot** be reused.
- BAQSIMI is for nasal (nose) use only.
- BAQSIMI will work even if you have a cold or are taking cold medicine.

Preparing the Dose

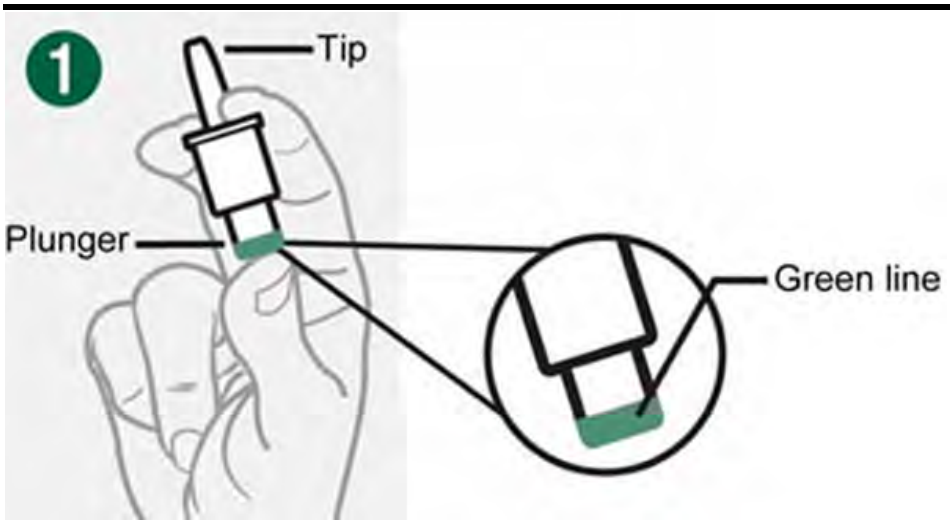


- Remove the Shrink Wrap by pulling on red stripe.



- Open the Lid and remove the Device from the Tube.
  Caution: Do not press the Plunger until ready to give the dose.

Giving the Dose



- **Hold Device** between fingers and thumb.
- **Do not** push Plunger yet.

- **Insert Tip** gently into one nostril until finger(s) touch the outside of the nose.

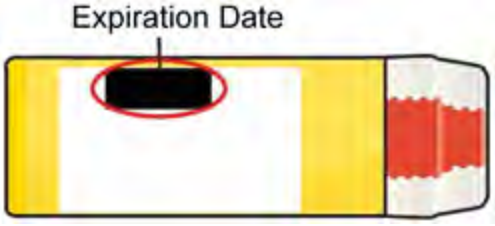
- **Push Plunger** firmly all the way in.
- **Dose is complete when the Green Line disappears.**

After giving BAQSIMI

- Call for emergency medical help right away.
- If the person is unconscious turn the person on their side.
- **Throw away the used Device and Tube.**
- Encourage the person to eat as soon as possible. When they are able to safely swallow, give the person a fast acting source of sugar, such as juice. Then encourage the person to eat a snack, such as crackers with cheese or peanut butter.
- If the person does not respond after 15 minutes, another dose may be given, if available.

Storage and Handling

- **Do not remove the Shrink Wrap or open the Tube until you are ready to use it.**
- Store BAQSIMI in the shrink wrapped Tube at temperatures up to 86º F (30ºC).
- Replace BAQSIMI before the expiration date printed on the Tube or carton.



Other Information

- **Caution: Replace the used BAQSIMI right away so you will have a new BAQSIMI in case you need it.**
- Keep BAQSIMI and all medicines out of the reach of children.

For Questions or More Information about BAQSIMI

- Call your healthcare provider
- Call Lilly at 1-800-Lilly-Rx (1-800-545-5979)
- Visit www.baqsimi.com

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BAQSIMI Device meets all applicable requirements defined in ISO 20072

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Dean Meenach
EMS in Focus

Prehospital ultrasound: Emerging technology for EMS

Review the evidence for nine clinical applications for field ultrasound to assess, treat and monitor critically ill patients

May 15, 2019

Prehospital ultrasound is a form of medical imaging that is portable, non-invasive, painless, and does not expose the patient to ionizing radiation. With proper training and education, prehospital providers can use ultrasound to obtain immediate anatomical, diagnostic, and functional information on their patients [1].

In recent years, ultrasound devices have decreased in size and cost while producing images of enhanced quality. The recent advances in bedside devices have made ultrasound more accessible to prehospital providers with the introduction of field ultrasound devices that are more affordable, smaller in size, durable, lightweight, and with high-resolution imaging quality.

Prehospital ultrasound may be beneficial in the diagnosis and management of critically ill patients [2,3,4,5,6,7]. EMS providers can apply training to interpret ultrasound scans with a high degree of accuracy in a relatively short period of time [5,8].

Point of care ultrasound has many prehospital applications. (Photo/Greg Friese)

For example, prehospital focused abdominal sonography for trauma (FAST) exams have the potential to provide valuable information in abdominal trauma with high reliability leading to more appropriate transport destination decisions [9,10,11]. In addition, field ultrasound images can be transmitted enroute to the emergency department to facilitate further evaluation by ED physicians and trauma surgeons to expedite care [12,13,14].

Prehospital ultrasound has been widely adopted in most states and around the world with a continuously growing list of diagnostic applications [5,6]. The enhanced technology enables prehospital professionals to answer focused clinical questions, which translate into faster and more accurate diagnosis and care of patients presenting with time-sensitive emergency conditions [2,3,4]. Better outcomes have been reported with the use of prehospital ultrasound [2,5,6,15,16].

Bedside ultrasound is well accepted by patients and has shown to improve patient satisfaction [17]. However, like any other nontraditional intervention, the addition of field ultrasound raises several questions in terms of potential clinical applications, feasibility, training requirements, cost, and more importantly its impact on the care process and patient outcome.

CLINICAL APPLICATIONS FOR FIELD ULTRASOUND

In EMS systems with regionalized trauma care and field triage guidelines, field ultrasound offers earlier detection of time-critical conditions that may require deliberate transport to an accredited trauma center, chest pain center, stroke center, or pediatric specialty care facility. There is an abundance of clinical applications for the use field ultrasound discussed in the literature with varying degrees of benefit:

1. CAUSES OF DYSPNEA

Field ultrasound increases the accuracy of diagnosing pulmonary edema versus chronic obstructive pulmonary disease as the cause of acute dyspnea [1,18,]. It is effective in patients with unexplained hemodynamic instability to help differentiate between cardiac and non-cardiac causes of shock [18,19]. In

some limited cases the potential of field ultrasound to detect massive pulmonary emboli in patients has been demonstrated [15,20].

2. RECOGNIZING OB EMERGENCIES

Although advanced training is necessary, some prehospital providers have shown that ectopic pregnancy, placenta previa, and placenta abruption can be identified with about 95% reliability [4,21,22].

3. CARDIAC EVALUATION AND RESUSCITATION

Specialized prehospital resuscitation protocols using ultrasound have shown that in patients undergoing CPR, ultrasound helped prehospital providers determine cardiac wall motion when the initial ECG diagnosis was identified as asystole [23]. This was associated with an increased survival to hospital admission [24].

In addition to cardiac motion, ultrasound helped differentiate between true PEA – electromechanical dissociation – and pseudo-PEA – coordinated electrical activity with no palpable pulse [23,24]. Pseudo-PEA was also associated with increased survival to hospital admission when compared with true-PEA [23,24].

In patients in a peri-resuscitation state, ultrasound improved the diagnostic accuracy for potential diagnoses of tamponade, profound hypovolemia, myocardial insufficiency (severe left and/or right ventricular dysfunction), or thromboembolism (pulmonary or cardiac) [25,26]. EMS systems with prehospital protocols that use asystole or PEA as criteria for field resuscitation termination can benefit from adding ultrasound to such protocols [23,25,26].

4. AIRWAY PLACEMENT CONFIRMATION AND MONITORING

Another diagnostic application of field ultrasound includes confirming endotracheal tube placement through high-resolution detection [27]. Although waveform capnography is considered the gold standard for successful ETT verification, this method has some limitations in specific situations such as cardiac arrest, low cardiac output, acute pulmonary embolism, and hypothermia [28].

Ultrasound offers prehospital professionals an alternative method for ETT confirmation for recognizing tube displacement or differentiating between main tracheal intubation and right mainstem intubation [27,28,29,30,31]. For example, Adi et al's (2013) study showed an impressive result of 98.1% accuracy in initial verification [30].

5. GASTRIC TUBE PLACEMENT CONFIRMATION

Gastric tube placement – nasogastric or orogastic – remains a recommended critical care intervention for all intubated patients as it decreases the risk of aspiration and improves tidal volume. Some EMS systems that place gastric tubes report that placement is easily confirmed using field ultrasound [32].

6. FRACTURE DETERMINATION

Many types of suspected long-bone fractures are managed in the prehospital setting. Growing evidence suggests that use of field ultrasound can successfully identify several types of long bone fractures [33,49,50].

7. PREHOSPITAL NEEDLE THORACOSTOMY PLACEMENT

Prehospital ultrasound use in trauma patients with suspected pneumothorax can be effective in preventing unnecessary field needle thoracostomys [34,35]. One study showed that when thoracic ultrasound was used to detect pneumothorax, only 26% of the patients were actually found to not have a pneumothorax [34,35,36,37]. Using field ultrasound could help decrease potentially unnecessary needle thoracostomys and other invasive procedures en route to hospital [38].

8. PERIPHERAL INTRAVENOUS ACCESS

Establishing vascular access is one of the most common procedures performed in the prehospital setting and on occasion is a high priority for the critically ill and unstable patient. The condition of the patient often presents challenges in attaining intravenous access. Conditions associated with difficult vascular access include very young age, obesity, chronic illness, IV drug abuse, and hypovolemia to list a few [39,40,41].

Patients with difficult IV access are often subjected to repeated attempts as in some cases time to IV placement can affect optimal resuscitation of the critically ill patient. Ultrasound guided IV access has shown to increase the success rate and decrease complications [42,43,44,45,46,47,48].

9. STROKE DIAGNOSIS

It is well discussed in the literature that improving the outcome of stroke patients requires early and rapid time-sensitive diagnosis and treatment as well as transport to an accredited stroke center. Early diagnosis using telestroke protocols with field transcranial ultrasound for stroke diagnosis has shown to decrease diagnosis-to-fibrinolytic therapy times and expand the use of special interventional radiology procedures [51,52,53].

PRACTICE CHALLENGES FOR FIELD ULTRASOUND

Widespread adoption of field ultrasound in the United States has been limited due to several factors. The most commonly reported barriers to field ultrasound implementation include, but are not limited to, cost, training deficits, short transport times, concerns about delaying time to definitive care, lack of evidence, approval by EMS administration, buy-in by medical directors and ED staff, and acceptance by veteran EMS providers [1,52,54].

In most cases initial ultrasound education and training is possible with relatively short training courses. Like any other clinical skill, ultrasound competency requires practice, ongoing education, and quality management programs with physician oversight [55,56].

FUTURE DIRECTION OF POC ULTRASOUND

Prehospital emergency ultrasound has many clinical applications that can potentially reduce patient morbidity and mortality from life-threatening emergency conditions. The potential for the evolution of field ultrasound is largely dependent upon developing a growing body of prehospital data that demonstrates its safety and effectiveness in clinical procedures and timely diagnosing medical and trauma conditions.

Above all, the value of ultrasound use in the prehospital setting must illustrate how it improves patient outcomes. This could be facilitated by enhancing the technology of telesonography for real-time assistance

with interpretation of ultrasound images by physicians [43,57]. Also, developing effective ultrasound training programs for different level providers is important to maximize its use. In addition, a cost-benefit analysis for prehospital ultrasound must be entertained.

One area of future research must include the early ultrasound diagnosis of ischemic stroke in the prehospital setting to improve time to thrombolysis. Hopefully, this research will correlate into better neurologic outcomes of stroke affected patients [53]. Considering the growing areas of mobile integrated healthcare and community paramedic programs, one cannot anticipate the endless possibilities that prehospital ultrasound could offer these diverse community healthcare services [58].

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Prehospital point-of-care ultrasound: A transformative technology

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Abstract

Point-of-care ultrasound at the bedside has evolved into an essential component of emergency patient care. Current evidence supports its use across a wide spectrum of medical and traumatic diseases in a variety of settings. The prehospital use of ultrasound has evolved from a niche technology to impending widespread adoption across emergency medical services systems internationally. Recent technological advances and a growing evidence base support this trend. However, concerns regarding feasibility, education, and quality assurance must be addressed proactively. This topical review describes the history of prehospital ultrasound, initial training needs, ongoing skill maintenance, quality assurance and improvement requirements, available devices, and indications for prehospital ultrasound.

Keywords

Critical care, emergency medicine, point-of-care ultrasound, emergency medical services, prehospital medicine

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Introduction

Clinician-performed ultrasound at the bedside of a patient has become increasingly common over the past two decades.[1,2] As the evidence base has grown supporting its use across a wide spectrum of medical and traumatic disease patterns in a variety of settings, novel applications and rapid assessment protocols have emerged.[3,4] Improvements in mortality, diagnostic accuracy, patient care metrics, and patient satisfaction have all been associated with bedside ultrasound use.[5–8] Interest in ultrasound outside of traditional practice settings such as hospitals or physician offices has also increased. Prehospital medicine in many ways is often considered an austere environment, as patients are frequently critically ill and require immediate care based on limited history and very limited advanced diagnostic tools.[9] Therefore, the use of ultrasound in prehospital emergency care to improve diagnostic accuracy and facilitate rapid treatment decisions has attracted significant interest in recent years.[10]

Methods

For this topical review, the team of authors included a critical care paramedic with training in point-of-care ultrasound (POCUS), an emergency medical technician-basic with formal training in literature analysis and a prehospital physician medical director with training and certification in emergency medicine, critical care medicine, emergency medical services (EMS), and clinical ultrasonography. We first conducted two sessions akin to focus group meetings to define the scope of prehospital ultrasound, during which we agreed on the following five aspects of prehospital ultrasound: technology, clinician training, prehospital operations, patient needs and outcomes, and medical oversight. We then conducted an extensive search in the PubMed database combining the search terms "ultrasound", "prehospital" and "emergency medical services". We selected relevant manuscripts via group consensus based on the five pre-established categories. In addition, we reviewed related articles and their list of references from the authors' personal literature libraries.

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Review

History of ultrasound

The first clinical ultrasound imaging machines were developed in the 1950s. It would take another 20 years for these machines to be refined enough for widespread clinical use.[11] By the 1980s, technological improvements led to widespread adoption across hospitals.[12] In the last two decades, ultrasound performed and interpreted by physicians at the bedside has seen widespread adoption, including in the United States.[13] These exams are often performed on critically ill patients in whom diagnostic decisions and the response to therapies provided can be assessed rapidly by ultrasound. This type of ultrasound is referred to as POCUS.[14]

Initial routine use of portable ultrasound devices in the prehospital setting dates back to the late 2000s, mostly in European physician-based EMS systems.[15] Since then, a new generation of portable ultrasound devices have emerged that are small and lightweight enough to qualify as "handheld" devices which can be easily used in the prehospital emergency care field.[16] As these ultrasound devices have also become more affordable, adoption in the prehospital setting has further increased.

Although there is much potential for PHUS performed by EMS personnel, to date, there are no universally acknowledged guidelines for prehospital ultrasound (PHUS) use, indications, educational and credentialing requirements, and quality assurance.

Training requirements

Prehospital physicians are more likely to have had formal ultrasound training during their medical education, while nursing and paramedic schools traditionally have not provided ultrasound training.[17] Nonetheless, nurses and paramedics can learn POCUS and perform select exams competently with relatively short training periods.[18–21] Prehospital POCUS programs vary widely, with training ranging from minutes to several days. In general, training programs included didactic and practical training, with some successfully implementing blended online and in-person curricula.[22] There is a paucity of literature regarding the education practicing prehospital clinicians have obtained outside of feasibility studies or pre-implementation surveys. However, in two studies, paramedics with advanced training or significant experience demonstrated higher degrees of accuracy in lung ultrasound.[19,23] Beyond formal training, additional ultrasound education is likely being obtained from unit-level in-services, courses, and conferences, as well as free open-access medical education, especially in the non-physician clinician base where formal ultrasound education may be harder to obtain because of availability and/or cost. Guy et al. describe a comprehensive prehospital POCUS curriculum for Canadian critical care paramedics spanning cardiac, thoracic, abdominal, and vascular scans. This curriculum utilized web-based, didactic, and hands-on learning sessions. Online pre-reading was followed by a 2-day in-person course. Free open-access medical education was utilized to allow for easy flow of information to potential future adopting departments. Scans performed included the extended Focused Assessment with Sonography for Trauma (eFAST), cardiac views (parasternal long axis and subxiphoid), pleural assessment, inferior vena cava (IVC) measurement, and vascular structure identification. All students passed the practical examination, and $>75\%$ of the students passed a post-course written examination.[21]

In most studies of prehospital ultrasound programs, assessment involves pre- and post-implementation knowledge checks followed by either simulation or volunteer practice and finally proctoring or expert review of exams in the clinical setting. Sensitivity, specificity, and succesful image acquisition were commonly used primary study outcome measures. EMS clinicians generally perform favorably and significantly improve on post-implementation knowledge assessment. A 2015 systematic review of paramedic ultrasound curricula found that most studies centered on paramedic-performed Focused Assessment with Sonography for Trauma (FAST) exams.[24]

While academic knowledge assists in the application and understanding of ultrasound, competency is a key factor in successful clinical application. Competency may be measured by a standardized minimum competency level, and the number of scans performed to achieve this minimum level is a frequently-used educational matric.[24] There is no current evidence for a minimum number of scans to be considered competent in paramedic-performed prehospital ultrasound. The American College of Emergency Physicians (ACEP) recommends 25 to 50 scans per assessment type as indicative of competency for emergency physicians.[25] Logically, these suggestions may seem generally extrapolatable to paramedical clinicians; however, over the international spectrum, paramedical clinicians vary widely in knowledge and skill sets.[26]

Recent work has begun to lay the framework for both initial training guidelines and minimum competency levels for prehospital ultrasound. The Air Medical Physician Association recommends the following minimum competency outcomes for initial training: (1) Identify the function of basic controls of the ultrasound machine, (2) discuss the basic physics principles of ultrasound, (3) demonstrate how to optimize ultrasound images, (4) describe normal ultrasound anatomy, (5) describe common pathological ultrasound anatomy, (6) discuss basic ultrasound artifacts and their use, and (7) describe expectations of ultrasound imaging during patient care encounter. In addition, they also include recommendations for simulation-based procedural skills prior to live human attempts and image acquisition on live humans where both normal and abnormal anatomy can be found.[17] Micheller et al. developed a theory-driven prehospital POCUS curriculum outlining basic

critical competencies for prehospital services to utilize to suit their needs. A total of five modalities (cardiac, thoracic, FAST, aorta, and procedural) were defined, with 32 measured competencies and 72 subcompetencies. This consensus was developed by a multi-institutional expert panel utilizing the Delphi technique to develop and refine the competency list.[27] It is important to note that this curriculum is yet to be validated in actual prehospital clinical practice.

Workforce

Prehospital personnel combinations vary significantly, both internationally and between ground and air transport systems. Teams may be made up of different levels of emergency medical technicians, nurses, respiratory therapists, physicians, or any combination thereof. The educational background of each individual clinician may range from no experience to significant POCUS exposure, in addition to general physics knowledge relevant to ultrasound theory. Clinician comfort and perceptions on topics such as scene time, effect on medical decision making, and clinical outcomes may also be important areas to focus on in initial education. Identification of the most prominent barriers and negative clinician perceptions to address in initial training may help to recruit a larger clinician base. There is minimal literature regarding clinician perceptions and barriers on general prehospital ultrasound use. In feasibility studies where feedback is elicited, there is a positive trend toward ease of use, interest in field application, and clinical utility.[28,29] A survey of Scottish paramedics and consultant physicians' perspectives on remotely supported prehospital ultrasound found that paramedics were enthusiastic and saw ultrasound as a logical, helpful progression in the care they provide. Physician perspectives were generally more reserved with concerns for limited clinical utility, inadequate training, misinterpretation, and deskilling. Both parties recognized the need for good interprofessional communication and potential transmission difficulties. Finally, both parties questioned the likelihood of measurable clinical benefit.[30] These studies are usually small, specific to the local system studied, and designed for feasibility, reducing their generalizability.

Beyond the end-user level, medical director endorsement is the foundation for any prehospital ultrasound program. In 2014, a survey of North American medical directors found the highest barriers to implementation were equipment, training costs, challenges in training, transport time, concerns about delaying time to definitive care, and concerns that ultrasound is beyond the current scope of EMS clinicians. Implementation was also felt to require further research in mortality/morbidity, clinical utility, time management, and indications for use, as well as position statements and practice guidelines from stakeholders.[31]

Prehospital ultrasound technology

While in theory almost any type of ultrasound machine could be mounted into an ambulance, portability, as defined by size and weight, is key to its use from a practical perspective. Current handheld devices that are widely available internationally can be dichotomized into those requiring a separate output device, such as a tablet device or smartphone, and those that have a screen included.[32] While the majority of devices on the market continues to use piezoelectric crystals, a device introduced in the market in 2018 uses capacitive micromachined ultrasound transducer technology, allowing for exams across all frequencies to be performed using a single probe, as opposed to the traditional crystal-based technology requiring multiple probes.[33]

Clinical applications and outcomes

While PHUS encompasses the full bandwidth of applications used in in-hospital settings, certain applications stand out as particularly meaningful. Trauma patients were an early focus of PHUS efforts, especially the FAST exam to evaluate for intraperitoneal free fluid and pericardial effusion, and its extension, the eFAST exam, which adds a lung assessment component to evaluate for pneumothorax.[34–36] Echocardiography is another common application of PHUS, as it allows to assess for cardiac standstill during cardiac arrest resuscitation and can help identify pericardial and myocardial disease, such as tamponade, decreased left ventricular ejection fraction, or right ventricular dysfunction.[37–39] Ultrasound can be utilized for procedural guidance, for example, peripheral or central vascular access or confirmation of endotracheal tube placement.[40] Rapid assessment protocols that combine different ultrasound exams to rapidly rule in or out life-threatening causes of hypotension or respiratory distress, such as the Rapid Ultrasound in SHock (RUSH) and Bilateral Lung Ultrasound in Emergency (BLUE) protocols and their modifications, are of particular interest for prehospital use.[1,3,4] They are especially appealing for use in this environment, as current diagnostic methods are mostly limited to physical exam, pulse oximetry, and electrocardiogram. Therefore, prehospital care often leans toward a one-size-fits-all approach of combining treatments for multiple disease processes at once (e.g. acute exacerbations of congestive heart failure and chronic obstructive pulmonary disease), and these rapid assessment protocols may help tailor treatment toward the most likely disease process. However, a sustained effect on prehospital patient outcomes has not been shown yet. Applications such as fracture diagnosis, joint dislocations, and procedural guidance for joint reductions or ocular ultrasound are of limited practical value in the majority of urban EMS systems or those with short transport times, but they can play an additional role in EMS systems that face long transport times, in remote and austere environments, or where a "treat and release" approach is commonly practiced, for example,

Table 1. Ultrasound applications commonly used in prehospital emergency care.

Exam type	Indications	Examples of clinical use
Extended Focused Assessment with Sonography for Trauma (eFAST)	Multi-system trauma	Evaluation for free intraperitoneal fluid or pneumothorax after blunt trauma with advanced notification of the receiving trauma center
Transthoracic echocardiography	Respiratory distress, chest pain, and cardiac arrest	Termination of resuscitation in a patient with cardiac arrest and no cardiac motion identified after 20 mins of resuscitative efforts
Lung ultrasound / Bilateral Lung Ultrasound in Emergency (BLUE) protocol[4]	Respiratory distress	Differentiation between pulmonary edema, suspected pulmonary infection, or pneumothorax in a patient with undifferentiated shortness of breath and a history of congestive heart failure and chronic obstructive pulmonary disease
Rapid Ultrasound in SHock (RUSH) protocol: evaluation of pericardium, left ventricular function, right ventricular size, inferior vena cava, lung ultrasound, evaluation of pleural and abdominal cavity, abdominal aorta ultrasound, proximal deep veins of the lower extremities[2]	Non-traumatic shock	Ruling in pulmonary embolism in a patient with hypotension who is found to have right ventricular enlargement and a deep venous thrombosis
Airway	Endotracheal intubation	Confirmation of endotracheal tube placement after prehospital rapid sequence intubation
Vascular access	Difficult vascular access with non-emergent need for intravenous fluids	Placement of an ultrasound-guided peripheral intravenous catheter
Musculoskeletal	Suspected fracture or dislocation	Diagnosis of radius fracture in a wilderness medical environment

to facilitate triage to a referral hospital or urgency of follow-up.[41–45] Many other applications have been described which can be of use in certain care environments or on a case-by-case basis.[10]

Table 1 provides an overview of common PHUS exam types, indications, and clinical use examples.

Medical oversight and quality assurance

Skill retention is vital for successful application of prehospital ultrasound. Therefore, continuing education and quality assurance/improvement (QA/QI) play a critical role. There is no known literature focusing on skill retention in prehospital ultrasound, and skill retention in general is poorly reported in the literature as an outcome for feasibility. Individual studies show a trend toward adequate skill retention; however, methodology and robustness of data are limited.[22,46–48]

A common theme in prehospital emergency care is difficulty to maintain proficiency with low-volume, high-risk procedures (e.g. endotracheal intubation, cricothyrotomy, and thoracostomy). While the risks of ultrasound are negligible compared to the abovementioned procedures, quality of initial education, frequency of use, continuing education, and a robust QA/QI program are key. The continuum between initial education and QA/QI is most prone to lapses in proficiency, and thus continuing education must be provided as a preventive measure. Universal recommendations regarding continuing education requirements for prehospital ultrasound do not currently exist. ACEP recommends 10 hours of continuing medical education every 2 years for emergency physicians.[25] However, this may not generalizable to the prehospital arena, most notably in the non-physician clinician base, because of differences in initial education, extent of ultrasound knowledge base, and frequency of use. The Air Medical Physician Association's position statement suggests utilizing ACEP's Ultrasound Imaging Criteria Compendium to guide QA/QI program development.[49] Clinicians should be able to obtain and capture images for review with appropriate documentation of relevant findings. Images should be reviewed by appropriately qualified experts, and feedback should be provided in a timely manner. Secure storage of QA/QI proceedings for later review and processes for communication with interested parties when missed or incidental findings are identified should be considered crucial components.[17,50]

Feasibility and implementation concerns

Despite the excitement for and potential of prehospital ultrasound, some concerns exist. These include a lack of standardized educational requirements, the implementation of sustainable quality assurance systems (and the associated cost), and the impact of physician medical oversight.[10]. Several technological issues can limit feasibility and image acquisition, such as glare from the screen when used outside, battery life, or limited one-handed operation.[1,51,52] Finally, no systematic data exist on the impact that potential incorrect ultrasound diagnoses could have on patient

outcomes and downstream care. Therefore, it is critically important that administrators, medical directors, and front-line clinicians consider any potential unintended negative effects of PHUS use, such as distracting from the basic steps of resuscitation, other important prehospital interventions, or avoidable prolongations of on-scene times in unstable patients.

Limitations of this review

As prehospital ultrasound is an emerging technology, the recommendations made in this article should be considered preliminary and must be applied within the appropriate local context. It is important to note that this topical review is not a systematic review either. In addition, EMS systems vary across different countries, legislatures, and medical care systems, and what works well for one EMS system and the patients that it serves may not be appropriate for a different EMS system.

Conclusion

PHUS has evolved from a niche technology to impending widespread adoption across EMS systems internationally. Recent technological advances and a growing evidence base support this trend; however, concerns regarding feasibility, education, and quality assurance must be addressed proactively. Additional research is needed examining the impact on patient care of widespread prehospital ultrasound use outside of focused research projects. We recommend that EMS administrators and medical directors evaluate the available evidence within the context of their local EMS infrastructure and capabilities. Adoption of this technology requires a robust assessment of the investments needed in terms of finances, training, and quality assurance, along with consideration of the local patient population, transport times, and the needs of receiving hospitals.

Author contributions

C.B.A. and D.C.R. contributed equally to this manuscript.

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REVIEW Open Access

The role of point of care ultrasound in prehospital critical care: a systematic review

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Abstract

Background: In 2011, the role of Point of Care Ultrasound (POCUS) was defined as one of the top five research priorities in physician-provided prehospital critical care and future research topics were proposed; the feasibility of prehospital POCUS, changes in patient management induced by POCUS and education of providers. This systematic review aimed to assess these three topics by including studies examining all kinds of prehospital patients undergoing all kinds of prehospital POCUS examinations and studies examining any kind of POCUS education in prehospital critical care providers.

Methods and results: By a systematic literature search in MEDLINE, EMBASE, and Cochrane databases, we identified and screened titles and abstracts of 3264 studies published from 2012 to 2017. Of these, 65 studies were read in full-text for assessment of eligibility and 27 studies were ultimately included and assessed for quality by SIGN-50 checklists. No studies compared patient outcome with and without prehospital POCUS. Four studies of acceptable quality demonstrated feasibility and changes in patient management in trauma. Two studies of acceptable quality demonstrated feasibility and changes in patient management in breathing difficulties. Four studies of acceptable quality demonstrated feasibility, outcome prediction and changes in patient management in cardiac arrest, but also that POCUS may prolong pauses in compressions. Two studies of acceptable quality demonstrated that short (few hours) teaching sessions are sufficient for obtaining simple interpretation skills, but not image acquisition skills. Three studies of acceptable quality demonstrated that longer one- or two-day courses including hands-on training are sufficient for learning simple, but not advanced, image acquisition skills. Three studies of acceptable quality demonstrated that systematic educational programs including supervised examinations are sufficient for learning advanced image acquisition skills in healthy volunteers, but that more than 50 clinical examinations are required for expertise in a clinical setting.

Conclusion: Prehospital POCUS is feasible and changes patient management in trauma, breathing difficulties and cardiac arrest, but it is unknown if this improves outcome. Expertise in POCUS requires extensive training by a combination of theory, hands-on training and a substantial amount of clinical examinations – a large part of these needs to be supervised.

Keywords: Prehospital, Ultrasound, Critical care, Trauma, Cardiac arrest, Dyspnea, Point of care, Education, Systematic review

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Background

Prehospital Point-of-care Ultrasound (POCUS) can potentially improve patient outcome and the role of POCUS was defined as one the top five research priorities in physician-provided prehospital critical care in 2011 [1]. Three key research questions were identified; 1) which ultrasound examinations can be reliably transferred to the prehospital setting? 2) how does prehospital ultrasound affect patient management and the patient pathway? and 3) how should providers achieve and maintain specific ultrasound skills.

Although previous reviews have been positive towards the feasibility of prehospital POCUS, they were unable to demonstrate improved patient outcomes with POCUS [2, 3]. This was mainly due to very limited and heterogeneous literature of low quality lacking patient centered outcome measures. Lack of evidence of improved patient outcomes, equipment costs and training difficulties are considered significant barriers to widespread use of prehospital ultrasound [4]. Prehospital patient categories with time-critical conditions as defined by the first hour quintet may benefit from improved early diagnostics (i.e. cardiac arrest, chest pain, stroke, respiratory failure, and severe trauma) [5]. Prehospital POCUS may also alter the patient pathway for other patient groups, which may be beneficial to both the patient and the health care system.

Thus, the aim of this study was to answer the three previously defined research questions by performing a systematic review on clinical use of prehospital POCUS and on prehospital POCUS education.

Methods

This was a commissioned systematic review on the role of POCUS in prehospital critical care conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. No formal registration was performed.

Eligibility criteria

We included studies examining all types of patients of all ages undergoing a prehospital ultrasound examination and studies examining all types of ultrasound education in all types of prehospital critical care providers. Only interventional studies (randomized and non-randomized), observational controlled and un-controlled studies and studies of diagnostic accuracy were included. Only studies published in full-text in English were included.

Outcome measures

The primary outcome for clinical studies was patient survival within the study period. Secondary outcomes were changes in patient management, diagnostic accuracy, feasibility of the examinations and agreement between providers and experts. The primary outcome for educational studies was image acquisition skills. Secondary outcomes were image interpretation skills and theoretical knowledge.

Information sources

As commissioned by the journal, we included studies published from January 1st, 2012. We included studies indexed in MEDLINE, EMBASE, and Cochrane Central Register of Controlled Studies. In addition, we hand-searched all included studies for references and searched the ISI Web of Science: Science Citation Index for studies citing the included studies.

Search strategy and study selection

The search was conducted on April 24, 2017 according to the search strings supplied in the Additional file 1. Papers were imported into ENDNOTE X8 (Clarivate Analytics, Philadelphia, US) and duplicates were removed. Two reviewers (MTB and LK) independently screened papers by title and abstract and agreed on papers to assess for eligibility by their full-text version. The two reviewers then independently assessed which papers to include in the review based on their full-text. Discrepancies were solved by consensus. In case of doubt, an email was sent to the corresponding author for clarification.

Data collection

One reviewer (MTB) extracted the following study characteristics information into a standardized spreadsheet; author last name, publication date, study type, number of participants (providers and/or patients), aim of the study, and main results. For clinical studies, type of POCUS and provider-type (physicians, paramedics, nurses etc.) was extracted. For educational studies, the educational program used was extracted.

Assessment of quality of evidence

We used the relevant SIGN 50 checklists to assess the quality of the included studies and their risk of bias [6]. Two reviewers (SSR, LJ) independently assessed all points on the SIGN 50 checklist. When the reviewers agreed on a point, this assessment was considered final. Disagreements between reviewers were resolved by discussion using a third reviewer (MTB) as arbiter.

Results

We identified 3264 studies (Fig. 1). Of these, 27 studies were included in the review [7–33]. See the Additional file 1 for detailed reasons for exclusion following full-text assessment. Studies exclusively examining ultrasound in one of the first hour quintet patient groups are presented in Table 1, studies examining mixed

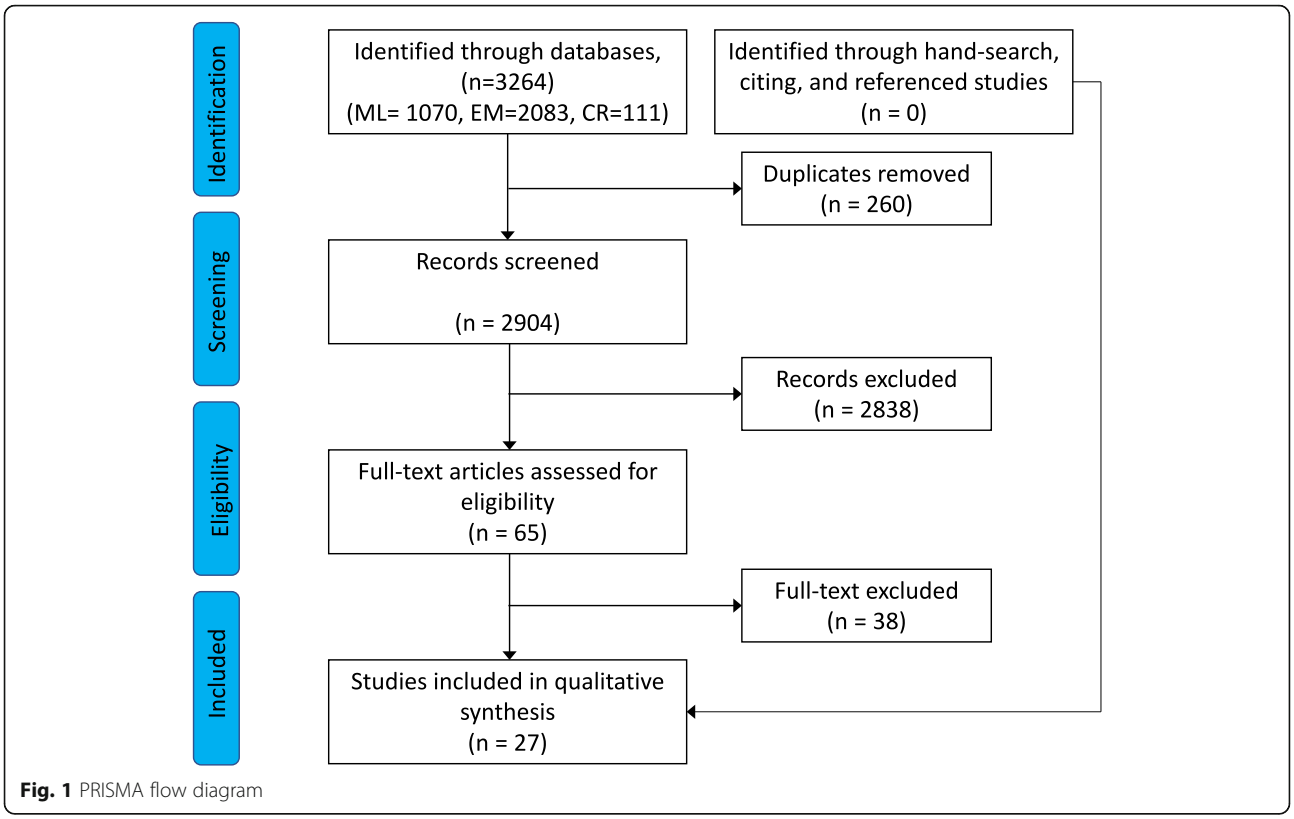

Fig. 1 PRISMA flow diagram

populations or POCUS for procedural guidance in Table 2, and studies examining the effect of education in Table 3. Details on the quality of evidence assessment can be found in the Additional file 1.

None of the included studies compared patient outcome or morbidity with and without application of POCUS.

Cardiac arrest

Three studies that were all of acceptable quality exclusively examined ultrasound in cardiac arrest patients and demonstrated feasibility of 80–100% [7, 27, 29]. One study demonstrated a high positive predictive value of cardiac standstill for death at 97.5% when assessed by physicians [7]. POCUS performed by paramedics during pulse-checks led to prolonged pauses in compressions in another study [27]. The last study demonstrated that paramedics were able to discriminate between cardiac activity and standstill [29]. Another study of acceptable quality examined physician-based POCUS in both trauma and cardiac arrest patients and demonstrated frequent changes in patient management, among others a decision to cease resuscitation in 9 of 31 (29%) of cardiac arrest patients [18].

Chest pain

None of the included studies specifically examined patients with chest pain.

Stroke

One study examined transcranial ultrasound conducted by expert neurologists and demonstrated a high specificity for major stroke, but was rejected (see details of the quality of evidence assessment in the Additional file 1) [17].

Breathing difficulties

Three studies evaluated POCUS conducted by physicians in patients with breathing difficulties [20, 21, 30]. One study of acceptable quality demonstrated 100% feasibility for simplified lung ultrasound evaluation of B-lines and a high negative predictive value of 94%, but a lower positive predictive value of 77% for congestive heart failure [20]. One study of acceptable quality demonstrated that pleural effusion is a 100% sensitive marker for congestive heart failure and that POCUS in dyspneic patients causes additional therapeutic consequences in 25% of patients [21]. The last study examining the use of B-lines by lung ultrasound to monitor the effect of treatment in heart failure patients was rejected (see details of the quality of evidence assessment in the Additional file 1) [30].

Trauma

Three studies exclusively examined trauma patients [12, 24, 32]. One study of acceptable quality examined each

Table 1 Included studies exclusively examining one of the first hour quintet patient groups

First author, year	n	Study type	Aim	US types, providers	Main results	Rating
Cardiac arrest only						
Aichinger, 2012	42	Prospective, observational (cohort)	To evaluate the ability of heart US to predict outcome in cardiac arrest	Heart (cardiac standstill y/n) Novice physicians	Feasibility 100%. 1/32 patients with cardiac standstill vs. 4/10 patients with cardiac movement survived to hospital discharge ($p = 0{,}008$). Cardiac standstill 97.1% PPV for death at scene.	+
Reed, 2017	45	Prospective, observational (cohort)	To evaluate the ability of paramedics to perform heart US during pulse check	Heart Extensively trained paramedics	Adequate view in first attempt in 80% of patients, but prolonged pauses in compressions – median 17 s (IQR 13–20).	+
Rooney, 2016	19	Cohort	To determine if paramedics could perform cardiac ultrasound in the field and correctly identify cardiac activity/standstill	Heart Novice paramedics	A total of 17/19 (89, 95% CI 67–99) exams were adequate for clinical decision-making. Correct identification of 17/17 cases of cardiac activity and 2/2 cases of cardiac standstill.	+
Chest pain						
No studies						
Suspected stroke						
Herzberg, 2014	102	Diagnostic accuracy	To evaluate the accuracy of transcranial US for neurovascular emergency diagnostics	Transcranial color-coded US in combination with clinical examination Experienced neurologists	Any stroke: sensitivity 94%, specificity 48% Major stroke: sensitivity 78%, specificity 98%	0
Breathing difficulties						
Neesse, 2012	56	Diagnostic accuracy	To evaluate the feasibility and diagnostic value of a chest ultrasound algorithm in dyspnea	Heart, anterior lungs, dorsolateral pleura Certified physicians	US helpful tool in 38/56 (68%) patients, additional therapeutic consequences drawn in 14/56 (25%). Pleural effusion found to be a 100% sensitive marker for congestive heart failure.	+
Laursen, 2016	40	Diagnostic accuracy	To assess feasibility, time-use and diagnostic accuracy of lung ultrasound for cardiogenic pulmonary edema	Anterior and lateral part of the lungs (4 regions, B-lines only) Novice physicians	Feasibility 100%. Median time used 3 min. Sensitivity 94% (CI 73–100), specificity 77% (CI 55–92), PPV 77% (CI 55–92), NPV 94% (CI 73–100)	+
Strnad, 2016	20	Prospective, observational (cohort)	To determine the usefulness of lung ultrasound		Lower total number of B-lines after than before CPAP	0

Table 1 Included studies exclusively examining one of the first hour quintet patient groups *(Continued)*

First author, year	n	Study type	Aim	US types, providers	Main results	Rating
			in treatment monitoring with CPAP vs standard treatment in CHF	Anterior and lateral part of the lungs (15 regions), B-lines only. Physicians	($p < 0.001$). Percentage of positive US lung scans significantly reduced in several regions in the CPAP group. Changes in B-lines correlated with improved vital signs.	
Trauma						
Brun, 2014	98	Cluster-randomized (controlled)	To compare the feasibility and efficiency of eFAST on-site, during transfer, or both	Lungs, heart, abdomen (PTX, tamponade, hemothorax, hemoperitoneum y/n) Physicians, heterogenous experience	On-site: feasibility 95.4%, efficiency 95% During transfer: feasibility 93.9%, efficiency 97% Both: feasibility 95.2%, efficiency 100% No difference between groups (w = 0.68)	–
Press, 2014	293	Diagnostic accuracy	To determine the accuracy of each component of trauma ultrasound performed by HEMS providers	Lungs, heart, abdomen (PTX, tamponade, hemothorax, hemoperitoneum y/n) Flight nurses/paramedics	Hemoperitoneum: sensitivity 46% (CI 27–94), specificity 94% (CI 89–97). Laparotomy: sensitivity 65% (CI 39–85), specificity 94%(CI 89–97). Pneumothorax: sensitivity 19% (CI 9–34), specificity 99.5% (CI 98.2–99.9). Thoracostomy: sensitivity 50% (CI 22–59), specificity 99.8% (CI 98.6–100)	+
Yates, 2017	190	Observational, controlled	To correlate prehospital trauma ultrasound findings to inhospital trauma team findings	Lungs, heart, abdomen (PTX, tamponade, hemothorax, hemoperitoneum y/n). Flight nurses/paramedics	PPV 100% NPV 98.3% Equivalent to in-hospital trauma team ultrasound	0

Abbreviations: *US* ultrasound, *PPV* positive predictive value, *IQR* interquartile range, *CI* confidence interval, *NPV* negative predictive value, *CPAP* continuous positive airway pressure ventilation, *PTX* pneumothorax
Rating scale: ++ High quality, + Acceptable, – Low quality/unacceptable, 0 Rejected

Table 2 Included studies examining mixed patient populations or ultrasound for procedural guidance

First author, year	n	Study type	Aim	US types, providers	Main results	Rating
Mixed populations						
Quick, 2016	149 patients	Controlled (prehospital paramedics vs in-hospital physicians)	To evaluate the ability of ability of in-flight thoracic US to identify pneumothorax (trauma and medical patients)	Lung (PTX), paramedics compared to ED physicians	Gold standard chest CT ($n = 116$). Prehospital sensitivity of 68% (95% CI 46–85), specificity 96% (95% CI 90–98), accuracy 91% (95% CI 85–95). Physician-based ED US; sensitivity 84% (95% CI 62–94), specificity 98% (95% CI 93–99), accuracy 96% (95% CI 90–98).	+
O'Dochertaigh, 2017	455 missions	Cohort	To describe the use of US to support interventions when used by physicians and non-physicians (trauma and medical patients)	Trauma ultrasound and IVC, highly trained physicians and non-physicians (paramedics)	Interventions was supported in US in 26% (95% CI 18–34) of cases when used by non-physicians, and in 45% (95% CI 34–56) when used by physicians ($p < 0.006$)	0
Roline, 2013	71 (41 scans)	Cohort	To evaluate the feasibility of bedside thoracic US (trauma and medical patients)	Lung (PTX), prehospital care providers (paramedics?)	In 71 eligible patients, 41 (58%) scans were completed. Level of agreement between flight crew and expert substantial with a kappa of 0.67, (95% CI 0.44–0.90). 54% of images were rated "good". Causes for not completing US were lack of time or space limitation in aircraft.	+
Ketelaars, 2013	281 patients, 326 exams	Cohort	To evaluate the impact of US chest examinations on the care of patients in a HEMS service (trauma and cardiac arrest patients)	Heart, lung (PTX), abdomen, experienced physicians	PTX sensitivity 38%, specificity 97%, PPV 90%, NPV 69%. Treatment plan changed in 60 (21%) patients; in 10 (4%) a chest tube was abandoned; in 10 (4%) the destination for definitive care was changed, in 9 (3%) cardiopulmonary resuscitation was stopped	+

Table 2 Included studies examining mixed patient populations or ultrasound for procedural guidance *(Continued)*

First author, year	n	Study type	Aim	US types, providers	Main results	Rating
					and in 31 (11%) there were other changes.	
Procedural guidance						
Chenaita, 2012	130 patients	Diagnostic accuracy	To estimate the diagnostic accuracy of US confirmation of gastric tube placement	Abdominal (gastric), experienced physicians	Sensitivity 98.3% (95% CI 94–99.5), specificity 100% (95% CI 75.7–100). PPV 100%, NPV 85.7%. Correlation between gastric tube size and visualization (larger tubes easier to see)	+
Brun, 2014	32	Controlled study (2-point US vs syringe test)	To estimate the diagnostic accuracy of 2-point US to confirm gastric tube placement	Esophageal, abdominal, physicians	100% visualization of gastric tube in the esophagus, 62.5% in the stomach. X-ray confirmed 28/32 in correct position. US higher diagnostic accuracy than syringe test.	0
Zadel, 2015	124 patients	Diagnostic accuracy	To assess the sensitivity and specificity of US for confirming endotracheal intubation	Lung (lung sliding and diaphragm excursion), certified physicians	Gold standard, capnography. US sensitivity 100%, specificity 100%, PPV 100%, NPV 100%. Median US time 30 s.	0

Abbreviations: *US* ultrasound, *PTX* pneumothorax, *CI* confidence interval, *ED* emergency department, *CT* computed tomography, *IVC* inferior vena cava, *PPV* positive predictive value, *NPV* negative predictive value
Rating scale: ++ High quality, + Acceptable, − Low quality/unacceptable, 0 Rejected

component of the trauma ultrasound examination and demonstrated a positive predictive value of 90% and a negative predictive value of 98% for a required intervention due to pneumothorax, a positive predictive value of 50% with a negative predictive value of 96% for a need for laparotomy due to intraabdominal free fluid, but had an insufficient amount of pericardial effusions for reliability on this part [24]. The last two studies exclusively in trauma patients were either rejected or assessed to be of low quality (see details of the quality of evidence assessment in the Additional file 1) [12, 32]. Three studies of acceptable quality examined both trauma and medical patients and demonstrated a high level of agreement between prehospital examinations and in-hospital ultrasound assessment by expert sonographers and a change in treatment in 20% of trauma patients [18, 26, 28]. A study comparing intervention support in both trauma and medical patients when ultrasound was used by physicians and non-physicians was rejected (see details of the quality of evidence assessment in the Additional file 1) [22].

Education

Eleven studies examined POCUS education in prehospital critical care providers [8–11, 14, 16, 19, 23, 25, 29, 31]. Three of these were either rejected or assessed to be of low quality (see details of the quality of evidence assessment in the Additional file 1) [10, 16, 31].

Two studies examining short courses were of acceptable quality [8, 29]. One demonstrated that a simple one-hour lecture improves theoretical knowledge among paramedics [8]. The other demonstrated that 2 h theory and 1 h hands-on training in paramedics with no prior ultrasound experience lead to images useful for clinical interpretation in 89% of cardiac arrest patients and correct identification of cardiac activity and cardiac standstill [29].

Three studies examining 1- or 2 day courses were of acceptable quality [14, 19, 23]. One demonstrated that theoretical knowledge, image interpretation skills and a structured observation of ultrasound examination skills in lung, heart, and abdominal ultrasound, could be improved by 2 h e-learning and 4 h hands-on course [19]. One demonstrated that after completing a two-day course, cardiac image acquisition skills were only moderate and agreement with experts was weak for left ventricular function, right ventricular size, and pericardial effusion and very weak for inferior vena cava assessment [14]. The last demonstrated that there was no difference in neither image acquisition skills nor theoretical knowledge scores when comparing traditional trauma ultrasound training to simulator-based training or both [23].

Three studies of acceptable quality examined the effect of longer educational programs [9, 11, 25]. One study examined a program comprising 1-day course with 2 h lectures and 4 h hands-on followed by at least four supervised examinations in real-life patients, 60–120 min e-learning and a number of unsupervised real-life examinations and demonstrated that 27 and 28 of 33 paramedics were able to pass a structured clinical exam and a theoretical exam, respectively [25]. Another study examined the effect of a program comprising 4 h e-learning, 1-day hands-on course, 10 supervised examinations in real-life patients and a number of unsupervised examinations and demonstrated 98% image acquisition ability after the program and that 21/21 (100%) physicians used ultrasound in the prehospital setting after the program [11]. The last study compared image acquisition skills among experienced and inexperienced physician providers (defined as more or less than 50 examinations after initial training) and demonstrated a highly significant difference for all evaluated items [9].

Procedural guidance

Two studies evaluated the use of ultrasound to confirm gastric tube placement [13, 15]. One was rejected [13]. The other demonstrated high sensitivity and specificity of gastric ultrasound [15]. One study evaluating the effect of lung ultrasound to confirm endotracheal intubation was rejected (see details of the quality of evidence assessment in the Additional file 1) [33].

Discussion

The main finding of this review is that considerable amounts of literature on both clinical use of prehospital POCUS and POCUS education for prehospital providers has been published since 2011, indicating a growing interest in prehospital POCUS. The most recent literature does not provide evidence of outcome improvement, but supports the use of POCUS in trauma and breathing difficulties, calls for caution in cardiac arrest, and indicates that extensive training efforts are needed for providers to obtain the necessary skills.

Previous reviews on prehospital ultrasound have pointed to a high risk of bias in the published studies and to the lack of evidence for outcome improvements [2, 3]. The authors of this review still share this concern, but consider the quality of studies included in this review as improved. Nevertheless, studies are still very heterogeneous and of variable scientific quality and the literature lacks patient centered outcome measures.

Which ultrasound examinations can be reliably transferred to the prehospital setting?

Prehospital POCUS of the lungs for the diagnosis of pneumothorax has a moderate diagnostic accuracy and shows good agreement with experts [18, 24, 26, 28]. Positive predictive values ranges from 80 to 90% and

Table 3 Included studies examining the effect of ultrasound education

First author, year	n	Study type	Aim	Education program	Main results	Rating
Short course						
Chin, 2012	20 paramedics	Cohort	To determine if paramedics can acquire and interpret US for pneumothorax, pericardial effusion and cardiac activity	2-h session – 1 h lecture and 1 h hands-on session	After-test only: All subjects could identify the pleural line and 19/20 could obtain a cardiac view suitable for interpretation. Test score results were 9.1 out of a possible 10 (95% CI 8.6–9.6).	0
West, 2014	10 paramedics	Diagnostic accuracy	Not specified, but tested diagnostic accuracy for free fluid in abdominal trauma ultrasound	4 h course with lectures and hands-on training	Detecting of free fluid after course (peritoneal dialysis patients). Sensitivity 67%, specificity 56%. Higher false-positive rate than false-negative rate (59% vs 41%, $p < 0.01$)	0
Bhat, 2015	57 EMTs, paramedics and students	Controlled (before-and-after)	To assess the ability of EMS providers and students to accurately interpret heart and lung US images	1 h lecture on PTX, pericardial effusion and cardiac standstill	Theoretical test before and after: Test score 62.7% vs 91.1%. 95% CI for change 22–30%, $p < 0.001$). New post test in 19 subjects after one week: 93.1%.	+
Rooney, 2016	4 paramedics, 19 patients	Cohort	To determine if paramedics could perform cardiac ultrasound in the field and correctly identify cardiac activity/standstill	3 h course with 2 h theory and 1 h hands-on training	A total of 17/19 (89, 95% CI 67–99) exams were adequate for clinical decision-making. Correct identification of 17/17 cases of cardiac activity and 2/2 cases of cardiac standstill.	+
1- or 2-day course						
Charron, 2015	100 exams	Diagnostic accuracy	To assess the ability of emergency physicians to obtain and interpret heart and inferior vena cava views using portable US	2-day course	Parasternal short axis, long axis and subcostal views were adequate in 44, 46 and 46%, respectively. Apical 4-chamber was adequate in 67%. Agreement with experts was weak for LVF, RV size and pericardial effusion and very weak for IVC.	+
Paddock, 2015	36 paramedics, nurses and physicians	Randomized controlled study	To compare the effectiveness of training using an ultrasound simulator to traditional trauma ultrasound training	Group A: Traditional training. Group B: US simulator training. Group C: Both	No difference between groups on neither image acquisition	+

Table 3 Included studies examining the effect of ultrasound education *(Continued)*

First author, year	n	Study type	Aim	Education program	Main results	Rating
					skills nor theoretical knowledge scores.	
Booth, 2015	11 paramedics (4 long-term)	Controlled (before-and-after)	To determine if paramedics can be trained to perform and interpret US of the heart in cardiac arrest	1-day course with 2 h theory and 4 h hands-on training.	Theoretical test before and after: Improved theoretical knowledge (test score 54% before vs 89% after, $p < 0.001$). Practical test only after: 88% success in image acquisition during 10-min pulse-check window. Reduced to 75% (3/4) after 10 weeks.	–
Krogh, 2016	40 physicians	Controlled (before-and-after)	To evaluate the effect of e-learning and a hands-on US course of the lungs, heart, and abdomen	1-day course with 120 min e-learning + 4 h hands-on course	Improvement in theoretical knowledge after e-learning compared to before (51.3 (SD 5.9) vs 37.5 (SD 10.0), $p < 0.001$). Improvement in practical US performance and image interpretation after hands-on compared to before ($p < 0.001$).	+
Longer program						
Press, 2013	33 paramedics and nurses	Controlled (before-and after)	To evaluate the effectiveness of a trauma US training curriculum and to determine if demographic factors predicted successful completion	1-day course with 2 h lectures, 4 h hands-on training + proctored session (4 exams) during 6 weeks + 60–120 min e-learning + unsupervised real-life exams	Theoretical test: none passed pre-test, 28/33 passed post-test with 78% score ($p > 0.001$ for difference). 27/33 passed structured clinical examination – only demographic factor predicting passing structured clinical exam was passing theoretical post-test.	+
Bobbia, 2015	14 physicians, 85 patients	Controlled (on experience-level)	To evaluate the interpretability of prehospital heart US based on physician experience	Experienced and non-experienced physicians defined by more or less than 50 exams after initial training (theory, 25 supervised exams)	Eight (57%) experienced physicians performed 51 (60%) exams and 6 (43%) novice physicians performed 34 (40%) exams. In multivariate analysis, only physicians experience was associated with the number of interpretable items (96% vs 56% for LVF, 98% vs 29% for PE, 92% vs 26% for RVD, and 67% vs 21% for IVC)	+

Table 3 Included studies examining the effect of ultrasound education *(Continued)*

First author, year	n	Study type	Aim	Education program	Main results	Rating
Botker, 2017	24 physicians	Controlled (before-and-after)	To evaluate the effect of a systematical education program in US of the heart and pleura on image acquisition skills, use and barriers	4 h e-learning + 1-day hands-on course + 10 supervised examinations + 3 months unsupervised exams	Proportion of images useful for interpretation increased from 0.70 (95% CI 0.65–0.75) to 0.98 (95% CI 0.95–0.99), $p < 0.001$. Used by 21/21 (100%) of prehospital providers after 4 years. Barriers for prehospital use comprised image quality in difficult patients and equipment	+

Abbreviations: *US* ultrasound, *CI* confidence interval, *EMT* emergency medical technician, *EMS* emergency medical services, *PTX* pneumothorax, *M-mode* motion mode, *2D-mode* 2-dimensional mode, *LVF* left ventricular function, *RV* right ventricle, *IVC* inferior vena cava, *SD* standard deviation, *PE* pericardial effusion, *RVD* right ventricular dilation
Rating scale: ++ High quality, + Acceptable, − Low quality/unacceptable, 0 Rejected

negative predictive values from 69 to 90%. The same patterns apply to prehospital trauma ultrasound, although positive predictive value is generally lower for hemoperitoneum (around 50%) than for pneumothorax [24]. A positive POCUS finding is highly predictive of a need for intervention and seems useful for prehospital triage [18, 24]. The negative predictive values are not sufficiently high to recommend POCUS-based rule-out of serious injuries.

Prehospital POCUS of the lungs to diagnose congestive heart failure in patients with breathing difficulties displays high negative predictive value but lower positive predictive value and is reliable for rule-out, but not rule-in of congestive heart failure [20]. The addition of POCUS of the pleura may improve the positive predictive value for the diagnosis of congestive heart failure [21]. Recent studies conducted in in-hospital settings suggest that supplementing POCUS of the lungs with POCUS of the heart may further improve the positive predictive value and reduce the time to correct diagnosis [34, 35].

Prehospital POCUS of the heart is feasible and reliable for assessing simple dichotomous questions in cardiac arrest like "cardiac activity yes/no", but may cause prolonged pauses in compressions during cardiopulmonary resuscitation [7, 27, 29]. The ability to assess more complex measures like pericardial effusion, left ventricular function, and right ventricular dilation requires extensive training and clinical ultrasound experience [9, 14]. There were no studies examining prehospital ultrasound in chest pain patients during the study period, but a recently published study demonstrated that ultrasound may also be used for early diagnosis of non-ST-elevation myocardial infarction in patients suspected of acute coronary syndrome [36].

How does prehospital ultrasound affect patient management and the patient pathway?

Prehospital POCUS predicts the need for interventions and causes changes in patient management in both trauma, cardiac arrest, and breathing difficulties [18, 21, 24]. But, it is unknown if these changes improve patient outcomes. Since the inclusion period of this review, a secondary analysis of an included study was published [37, 22]. This study demonstrated that interventions were more likely to be supported with ultrasound in patients with markers of high acuity than in patients with presumed low-grade disease [37]. We do however question the practice of ceasing resuscitation based on cardiac standstill used in one study [18]. Early studies on this were promising [38, 39]. Yet, there are survivors following cardiac standstill in both recent and previous studies, indicating that this decision should not be based on POCUS alone [7, 40, 39].

How should providers achieve and maintain specific ultrasound skills?

Lectures seem efficient for obtaining the simplest of image interpretation skills, while image acquisition skills require hands-on training [8, 19, 29]. The type of training used (i.e. traditional or simulation training) seems less important [23]. Systematic educational programs comprising some sort of theory (e-learning and/or lectures), hands-on training, supervised examinations, and unsupervised clinical use makes it possible to consistently produce images useful for interpretation in healthy volunteers [11, 25]. Physician experience seems to affect especially the interpretability of POCUS images of the heart after initial hands-on training and 50 examinations greatly improves image acquisition skills in real-life patients [9]. This is in accordance with a recent in-hospital study demonstrating that for most examination types, between 50 and 75 results in both excellent interpretation and good image quality in actual patients [41].

Future research questions

Future research should address the gap in the literature demonstrating a beneficial effect of POCUS on patient centered outcome measures (improved triage, improved treatment, length-of-stay, and when possible mortality). But, to translate diagnostic accuracy into clinical utility we need to take one step back from the protocols. POCUS protocols have been defined a priori, and there is a tendency in the literature to promote specific ultrasound protocols. This is research in reverse order. When dealing with a specific patient with a specific medical history, symptoms and objective findings, some clinical questions (or differential diagnoses) arise – some of these may be answered by ultrasound. Thus, more studies on the diagnostic accuracy on specific components of a POCUS examination (such as B-lines, pleural effusion, impaired LV function) in patients with specific symptomatology (like chest pain, dyspnea, cardiac arrest, etc.) are needed to clarify which findings are key and which examinations are a waste of valuable time [42]. Only then can good controlled trials examining decision-making with and without ultrasound be planned. The Press et al. study examining sensitivity and specificity for each of the components in the trauma ultrasound examination in relation to both the relevant pathology and the associated intervention is a good example of the types of studies needed for other patient categories [24].

There is an ethical dilemma in educating prehospital critical care providers in ultrasound and randomize patients to either have the examination or not. This may be overcome by examining outcome in specific patient groups (such as abdominal aortic aneurism) in case-control studies where patients triaged directly to a specialized center by prehospital ultrasound is compared

to patients admitted to local hospital and secondarily transferred, although this type of studies carries inherent risks of bias. Another way of overcoming this could be to perform cluster-randomized studies in emergency medical services where ultrasound is not already implemented. In addition, the distance to nearest hospital (and/or specialized center) may affect the value of prehospital ultrasound. Which examinations can effectively change patient management depends highly upon the local setting and organization of both prehospital and hospital care. Thus, distance and time in the emergency medical services are relevant issues for future POCUS research.

There is still a paucity of literature aiming at determining the number of examinations needed for clinical proficiency. This may be addressed by linking individual level experience to the quality of images and the correctness of clinical interpretations when compared to expert assessment.

Limitations

Publication bias may have led to studies with neutral findings not being included – this may have been exaggerated by the choice to only include studies published in English. Especially the educational section may suffer from publication bias and conclusions must be interpreted with caution. Although the use of checklists for study quality assessment is generally recommended, the studies included in this review were very heterogeneous and we had difficulties deciding which checklists to use. Many educational studies were "before-and-after" studies. The results of this kind of study generally must be interpreted with caution due to a high risk of confounding and bias in favor of the intervention.

Conclusion

Prehospital POCUS remains unexamined in a wide range of patient groups. Prehospital POCUS seems feasible and changes patient management in trauma and breathing difficulties. POCUS is also feasible in cardiac arrest but may cause prolonged pauses in compressions. It is unknown how prehospital POCUS affects patient outcome. The best available evidence suggests that specific POCUS skills can be achieved by a combination of theoretical education, hands-on teaching, and more than 50 clinical examinations of which a large part are supervised.

Additional file

Additional file 1: Search strings **Table S1**. Studies excluded based on full text **Table S2**. SIGN 50 checklist of cohort studies included in the review **Table S3**. SIGN 50 checklist of controlled studies included in the review 5 **Table S4**. SIGN 50 checklist of diagnostic accuracy studies included in the review references. (PDF 229 kb)

Abbreviations

POCUS: Point of Care Ultrasound; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Authors' contributions

MTB, LK, SSR, and LJ made the study protocol. MTB and LK conducted the literature search. SSR and LJ performed the assessment of study quality with MTB as third reviewer. MTB drafted the manuscript and SSR, LJ and LK revised the manuscript and approved it before submission.

Ethics approval and consent to participate

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Consent for publication

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Competing interests

MTB receives royalties for e-learning produced for USabcd.org. LK is co-owner of USabcd.org. SR and LJ reported no competing interests.

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